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Striatin Genotype-Based, Mineralocorticoid Receptor Antagonist-Driven Clinical Trial (StiMRAD): Study Rationale and Design

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Abstract

Objectives—Hypertension (HTN) is a major risk factor for cardiovascular disease (CV) injury particularly in association with increased dietary sodium. Genetic factors contribute to HTN risk and specifically salt sensitive blood pressure (SSBP). In human observational studies and genetically altered mouse studies, variants in the striatin gene (*STRN*) are associated with increased blood pressure (BP) and increased aldosterone on a liberal salt diet. Thus, this proof-of-concept clinical trial is based on the presumed mechanism for striatin-associated HTN -- increased aldosterone. It is designed to determine if participants with the *STRN* risk alleles will have a greater BP reduction on a liberal salt diet with a specific, mechanism-based therapy — a mineralocorticoid receptor antagonist (MRA), eplerenone — as compared with a non-specific anti-hypertensive therapy — amlodipine.

Methods—105 hypertensive adults who carry the *STRN* risk alleles (SNP rs2540923 carriers or rs888083 homozygotes) will be enrolled in a 12-week, double blind, dose escalation, clinical trial. After a minimum of a 2-week washout period and a baseline assessment of BP on a liberal salt diet, participants will be randomized to either daily eplerenone or amlodipine. Participants will take daily at-home BP recordings as a safety check. After 4 and 8 weeks of drug therapy, BP will be measured by the study team and medication will be increased, if needed, to achieve a participant goal BP of <140/90 mmHg.

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Conflict of interest

None declared.

Anticipated Results—We anticipate that *STRN* risk allele carriers will demonstrate a greater reduction in BP on a liberal salt diet with eplerenone and will require a lower dose of eplerenone to reach goal BP as compared with amlodipine.

Conclusions—This is a proof-of-concept clinical trial. If the results are positive, they support the feasibility of performing genetically-defined, mechanistically-driven trials in HTN. Clinically, it would suggest that genetic biomarkers can identify individuals highly responsive to specific treatment.

Keywords

Amlodipine; Cardiovascular Health; Eplerenone; Genotype; Hypertension; Mineralocorticoid receptor; Personalized Medicine; Striatin

Introduction

Cardiovascular disease (CV) is the leading cause of mortality in the United States and is a major focus of medical studies, specifically regarding reduction of risk factors. As a major CV risk factor, hypertension (HTN) is a target for first line treatment [1]. Studies exploring the underlying causes of HTN have identified a relationship between heightened dietary sodium intake and increased blood pressure (BP) [2]. This relationship may indicate primary dysfunction of two key regulators of renal sodium handling; the degree of renal artery constriction, and secretion of aldosterone. In some cases, these traits are associated with polymorphic variants in the striatin (*STRN*) gene [2-4].

The STRN protein modulates vascular function by mediating the non-genomic effects of steroids, specifically aldosterone via interactions with the mineralocorticoid receptor (MR) and estrogen via the estrogen receptor-α [3,9,10]. Genetically-modified mice with STRN deficiency have increased aldosterone levels and salt sensitive BP (SSBP). Human carriers of *STRN* risk alleles for HTN exhibit the same phenotypic characteristics [4,10].

Based on these clinical and preclinical studies, we hypothesize that individuals with the *STRN* risk allele for HTN will be particularly responsive to a MR antagonist (MRA). We, therefore, designed a two-limb, double blind, proof-of-concept study enrolling individuals with the *STRN* risk alleles (rs2540923 minor allele carriers or rs888083 major allele homozygotes) — **Striatin Genotype-Based, Mineralocorticoid Receptor Antagonist-Driven Clinical Trial (StiMRAD).** Participants will be randomized to treatment with an MRA blocker (eplerenone) or a non-specific anti-hypertensive agent (the calcium channel blocker, amlodipine) for 12 weeks. We anticipate that participants with the *STRN* risk allele will have a greater anti-hypertensive response to eplerenone than to amlodipine. If correct, these data will support a specific, genetically driven, and mechanistically based therapy for a subset of patients with HTN.

Methods/Design

Study Population and Recruitment

The StiMRAD study will enroll 105 adults between the ages of 18 and 70 years who are *STRN* risk allele carriers (SNP rs2540923 or SNP rs888083) and have been diagnosed with HTN. Eligibility will be assessed at two separate, in person screening visits. The first screening visit will involve a cheek swab to determine genotype eligibility, and the second screening visit will involve a detailed history, physical examination, and laboratory assessment.

Participants will primarily be recruited through Brigham & Women's Hospital (BWH) Partners Healthcare's Research Patient Data Registry and the Partners Biobank Portal. Additional participants will be recruited from clinical research websites, online advertisements, and posted fliers. Finally, eligible participants who previously consented to be contacted by our group about future research studies will be contacted.

Inclusion criteria will require presence of minor allele at rs2540923 or being homozygous for the major allele at rs888083. Participants will have a diagnosis of HTN that is controlled with no more than two anti-hypertensive medications; normal renal, metabolic, electrolyte, complete blood cell count, and lipid profile laboratory tests. Exclusion criteria will include known cardiac disease other than HTN; renal, circulatory, pulmonary, or neurologic diseases; diabetes; cancer; smoking; secondary HTN as indicated by history, physical examination, screening blood and urine tests; any drug therapy except for anti-hypertensives and replacement thyroid medication.

All participants will give informed, written consent, and all study procedures have been approved by the Brigham & Women's Hospital Institutional Review Board. Recruitment began in June 2019 and is expected to be completed by June 2023. The study was registered with ClinicalTrials.gov (NCT03683069).

Study Protocol

Overview—StiMRAD's detailed study schema is shown in Figure 1. All study visits will occur in the Center for Clinical Investigations (CCI) at BWH. Participants will complete a medication washout if they are taking antihypertensive therapy before enrollment. Next, subjects will enter a three-part protocol. First, to more completely phenotype the subjects before randomization, their BP sensitivity to salt intake will be assessed. BP will be measured on low and liberal salt diets (Visits 1 & 2). For parts two and three, BP will be measured after six days of a liberal salt diet with the resulting BP at Visit 2 being their baseline BP used for the rest of the trial. Second, after randomization, participants will return to the CCI 4 weeks later to assess BP response to the lowest dose of eplerenone or amlodipine (Visit 3). This assessment is one of two primary endpoints. Third, for this Visit and Visit 4 four weeks later, dose titration will occur, if the subject has not reached goal BP (<140/90 mmHg). A final BP will be obtained at the completion of the trial (Visit 5) four weeks after Visit 4. During this part of the protocol, BP measurements will be tightly controlled: 1) after six days on a liberal salt diet; 2) between 7-10 AM; 3) fasting; 4) after remaining supine for at least 60-minutes; and 5) measured every two minutes for twenty

minutes using an automated sphygmomanometer (Dinamap, General Electric Healthcare, Chicago IL). The highest and lowest BP readings will be discarded and the remaining values will be averaged. Using this approach to obtain an accurate BP measurement, there will be co-primary endpoints: BP response to lowest treatment dose and the dose required to achieve goal BP.

Study Diets—To measure BP on a liberal salt diet in *STRN* risk allele carriers, StiMRAD assesses BP at the end of two separate diets: liberal salt and restricted salt diets. The restricted salt daily intake contains 10 mEq sodium, 100 mEq potassium, 800 mg calcium and the liberal salt daily intake has the same composition except the sodium content is 200 mEq. The restricted salt diet meals will be prepared and provided to participants by the CCI Nutrition and Metabolic Core. Each diet is ingested for 6 days prior to a visit when the participant's BP is measured. A 24-hour urine collection is utilized to assess compliance with the diets. A 24-hour urine Na+ excretion >160 mEq on the liberal salt diet and <30 mEq on the restricted salt diet indicate compliance with the liberal and restricted salt intakes, respectively. Creatinine levels are used to assess completeness of urine collections.

Washout—To ensure that the results we see are due to our study interventions and not the participant's previous HTN treatment, all participants who are on anti-hypertensive medications prior to the study will enter a washout phase that lasts at least 2 weeks as we have previously described [11]. If the participant is on an angiotensin converting enzyme inhibitor, angiotensin receptor blocker or MRA, these medications are stopped for 4 weeks prior to starting the baseline assessment of BP. During the medication washout phase and throughout the entire protocol, participants are monitored by study staff. Participants are trained on how to use an automatic sphygmomanometer, so they can take daily morning BP recordings at home and report them to study staff three times a week.

Visits 1 and 2—Study Visits 1 and 2 are designed to assess baseline SSBP We will determine whether BP responses to treatment are associated with baseline SSBP. This will be accomplished by measuring the participant's BP response to a restricted followed by a liberal salt diet. After completing a restricted salt diet for 6 days, participants will arrive fasting to the CCI for Visit 1 and bring a completed 24-hour urine collection for creatinine and sodium analysis to verify dietary adherence. After remaining supine for at least 60 minutes, participants will have blood samples obtained and BP will be assessed as described above.

After completing Visit 1, participants will be counselled regarding consumption of a liberal salt diet. After completing a liberal salt diet for 6 days, participants will arrive on the CCI for Visit 2 with a completed 24-hour urine collection and repeat the study procedures from Visit 1. The difference in BP obtained during Visits 1 and 2 (BP on liberal salt minus BP on restricted salt diet) will be used to assess SSBP The Visit 2 BP will serve as the baseline BP on a liberal salt diet for the rest of the study.

Randomization to Study Drug—Following Visit 2, participants will be randomized to either amlodipine or eplerenone by the Investigational Drug Service at BWH Central Pharmacy. Both participant and study team members will be blinded to drug assignment.

The starting treatment doses will be 2.5 mg/day for amlodipine and 50 mg/day for eplerenone since these doses were shown to have approximately equivalent effects on BP in a general hypertensive population [11]. After randomization, participants will begin taking the study drug daily and continue taking at-home daily BP recordings for the duration of the study. Participants will send at-home daily BP measurements to study staff at weekly intervals. Study staff will perform weekly check-ins to assess medication compliance, review BP, and inquire if the participants are experiencing side effects.

Visit 3—Four weeks after the initial dose of study drug, BP will be assessed during Visit 3 after participants have consumed 6 days of a liberal salt diet. Study procedures, including 24-hour urine collection, are as described for Visit 2. Study drug dose will be doubled to 5 mg amlodipine or 100mg eplerenone if BP is ≥ 140/90 mmHg. Following the completion of Visit 3, participants will continue to take the study drug and record at-home BP for an additional four weeks.

Visit 4—Study Visit 4 occurs eight weeks after initiation of study drug and four weeks after Visit 3. As occurred with Visit 3, participants will consume a liberal salt diet run-in for 6 days followed by collection of a 24-hour urine for sodium and creatinine, and assessment of BP during a CCI Visit. The same procedures for BP assessment will be conducted as described above. If BP is ≥ 140/90 mm Hg then the study drug dose will be doubled a final time to 10mg amlodipine or 200mg eplerenone.

Visit 5—The final study visit occurs 12 weeks after study drug initiation and four weeks after Visit 4. The protocol is identical to Visit 3 and 4. Following Visit 5, participants will have completed the study and will resume their prior BP medications.

Safety and Monitoring

Blood Pressure—Throughout the study, participants will monitor their BP daily and report readings to the study staff once per week. However, the participant is instructed to remeasure his/her BP in an hour if it is >160/105 mmHg. If the BP remains >160/105 mmHg, the participant is to report this to the study staff. If BP is greater than 170/109 mmHg on two consecutive occasions 24 hours apart or the participant develops cardiovascular symptoms, then they will be removed from the study and instructed to resume their prior antihypertensive program.

Serum Potassium—Because eplerenone may increase serum potassium levels, potassium will be assessed at Visits 3 and 4, which is 4 and 8 weeks after study drug initiation. If study drug is doubled, the serum potassium will be obtained one week later. If serum potassium is greater than 5.5 mM, it will be rechecked. If serum potassium is greater than 5.5 mM on two consecutive occasions 24 hours apart, the participant will be removed from the study.

Adverse Events—Treatment with amlodipine is well-tolerated at doses up to 10 mg daily. The most common side effects are headache, edema, fatigue, nausea, and abdominal pain. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) rarely have been described. We will discontinue amlodipine if this side effect occurs.

Eplerenone's most serious side effect is hyperkalemia in individuals with renal insufficiency with or without diabetes. More common side effects include dizziness, diarrhea, coughing, flu-like symptoms, tiredness, muscle weakness, irregular heartbeat, tingling, nausea, feeling dehydrated, swelling in legs, confusion. If symptoms suggest possible side effects, an additional study visit, including lab work, may be required to further evaluate the participant. Depending on this evaluation, participants may be discontinued from the study and appropriate clinical follow-up arranged.

Data Safety Monitoring Plan—Data and safety will be monitored by the Cardiovascular Endocrinology Research Group, which includes more than 5 patient-oriented clinical investigators who are endocrinologists with detailed knowledge of human subjects research and the medications used in this study as well as lay individuals. At each meeting, recruitment status, adverse events or safety issues, protocol deviations, and other pertinent study-related issues are reviewed. The Cardiovascular Endocrinology Research Group reviews each adverse event and formulates a plan for how to address it.

Laboratory Measurements

Plasma renin activity (PRA) and aldosterone (Immuno-Biological Laboratories Inc., Minneapolis, MN, USA), and cortisol (Beckman Coulter, Brea, CA, USA) will be measured in blood samples collected the mornings of each visit after participants were lying supine for at least 60-minutes. Sodium and potassium levels in urine will be measured by flame photometry (Cole-Parmer, Vernon Hill, IL, USA).

Statistics and Power Calculation

Participants (n=105) will be randomized, after screening, with equal probability to eplerenone or amlodipine, using random block sizes in this double-blind study. It is anticipated that at least 45 participants in each arm will have complete data for analysis. We previously documented that in a general hypertensive population, the starting doses of eplerenone (50 mg) and amlodipine (2.5 mg) had approximately equivalent effects on BP [11]. We hypothesize that individuals with the *STRN* risk alleles have aldosterone-dependent hypertension and thus will have a greater BP response with an MRA as compared with a calcium channel blocker. We will use two analytical approaches as co-primary endpoints. For the **first** approach, we anticipate that in participants with the *STRN* risk alleles, the mean change in systolic BP (SBP) from baseline (Visit 2) to after 4 weeks of study drug treatment (Visit 3) will be 4 mmHg in those receiving 2.5 mg amlodipine daily and 10 mmHg in those receiving 50 mg eplerenone daily. As previously reported, the within-group standard deviation for the change in mean SBP is expected to be 8 mmHg [12]. With 45 participants in each arm of the study, we will have greater than 90% power, with a 2-sided alpha of 0.05 to see a 6 mmHg difference in SBP (Table 1). Group differences in the BP lowering effects of the two drugs will be tested through covariance analysis [13].

The **second** approach will compare the maximum dose needed to achieve goal BP (≤140/90 mmHg). For the anticipated effect size, we used the rank of the drug dose. We equated eplerenone and amlodipine dosing, with rankings of 1, 2, and 3 for the ordered maximum dose for each drug, and a ranking of 4 for the failure to reach BP goal by the end of

the study. Table 2 shows the anticipated percentage of participants with each ranking in each group. Ordinal logistic regression will be used assuming a proportional odds model. The odds ratio and 95% confidence interval for eplerenone relative to amlodipine will be determined, i.e., the relative cumulative odds of needing a lower (or higher) maximum drug dose to achieve goal BP. This anticipated percentage (Table 2) of participants in each arm with each ranking will have an arm comparison power greater than 90%. Body mass index, sex, race, baseline SBP and age will be covariates for both analyses. Exploratory analysis will include: the difference in diastolic BP calculated at baseline and at the end of the study; correlation between the baseline SSBP and BP response at 4 weeks to initial dose of each study drug; and the correlation between the baseline SSBP and the dose needed to achieve goal BP. Effect sizes will be determined to improve the design of a future confirmatory study.

Discussion

The StiMRAD trial is a randomized, proof of concept, double-blind study designed to explore the specificity of MRA in treating a subset of hypertensive individuals. Participants with the *STRN* risk alleles will be the only enrollees. If the results are positive, then a larger study could be performed including non-risk allele carriers and using the results of the present study to develop a more specific power calculation. If the results are negative, there will be little need to pursue this line of research. However, we anticipate that *STRN* risk allele carriers will have a significantly greater reduction of BP in response to 50 mg eplerenone compared to 2.5 mg amlodipine. In addition, we anticipate that BP goals will be achieved with lower doses of eplerenone than with amlodipine.

This study design and anticipated results are based on results from a series of translational research studies relating genetics, salt intake and aldosterone secretion. When salt intake is varied in wild type (WT) rodents, tissue levels of STRN vary; restriction of sodium intake reduces STRN levels. The opposite results are observed with aldosterone: restricting sodium intake increases aldosterone levels. When a mouse is deficient in STRN, sodium intake no longer modulates STRN levels. The heterozygote knock out (HET-KO) mouse, who is deficient in STRN, has inappropriately increased aldosterone and BP on a liberal sodium diet [3,4,6-8]. Humans who have the risk alleles for *STRN* also have increased BP on a liberal salt diet compared to non-risk allele carriers. These human and mouse data provide the rationale for the StiMRAD trial.

Activation of the MR results in two activities: genomic and non-genomic [3,4,8]. Classically MR activation has been documented to induce changes in gene transcription with a time course of hours. Stimulation of MR activates a non-genomic, rapid pathway with a time course of seconds/minutes. STRN plays a central role in modulating MR's non-genomic activity. In a humanized endothelial cell line, STRN was shown to co-localize with the MR. When the cells were stimulated with aldosterone, phosphorylation of ERK1/2 and AKT rapidly occurred, which was prevented when *STRN* was knocked down with siRNA. Furthermore, in primary cultures of mouse aortic endothelial cells aldosterone increased STRN levels via MR activation. Thus, STRN and aldosterone are associated in a negative feedback relationship. Knocking down *STRN* with siRNA does not alter MR's gene

transcription effects; thus documenting STRN's specificity in aldosterone's mechanism of action [3,4,8]. A defect in MR's non-genomic actions when STRN levels are reduced may explain the increased aldosterone levels and increased BP in HET-KO mouse on a liberal salt diet. Similar mechanisms could lead to hypertension in individuals with the *STRN* rs2540923 or rs888083 risk alleles.

The results of this study will, 1) enhance clinical understanding of the mechanisms by which *STRN* functions as a modulator of cardiovascular damage, and 2) potentially offer a more precise approach to treat hypertensive *STRN* risk allele carriers than the currently available one-size-fits-all algorithms to treat hypertension. StiMRAD's study design is based on the concept that essential hypertension, in part, is a collection of separate subsets that have unique pathophysiologic mechanisms that will allow more specific treatment. We propose that genotype can identify a unique subset of hypertensives and thus can be used to direct anti-hypertensive therapy [14]. Furthermore, pre-clinical studies have shown that aldosterone and excess MR activation can lead to hypertension and CV damage. But the CV damage is not necessarily mediated by the elevated BP as CV damage can be completely prevented through use of an MRA despite persistently elevated BP [15,16]. These data support the need to identify specific therapeutic responses beyond BP control. The StiMRAD looks to find the most effective treatment for *STRN* risk allele carriers by directing treatment at the likely underlying pathophysiologic mechanisms causing the hypertension. If the results of StiMRAD are positive, it's study design may provide a novel, two-step, cost effective, genetic approach to predicting precise treatment for hypertension, and potentially extend as a model for the study of other chronic diseases.

StiMRAD's study design has several limitations. First, although participants in the amlodipine limb will be utilized as an active control group, the StiMRAD does not have a true control group of non-risk allele homozygotes. Thus, in the future, a more comprehensive four-limb study will be needed to confirm a positive outcome from this study. Second, the study length might pose limitations by producing a false positive, as initial observed differences could disappear with longer therapeutic exposure. While this is a concern, most clinical trials using these agents achieve stable BP responses during the proposed time interval. Finally, it is important to acknowledge that a treatment failure leading to a negative outcome could be secondary to an aldosterone mediated effect that is not blocked by eplerenone, or to an aldosterone mediated effect whose mechanism is exacerbated by the MR blockade.

For the past two decades, there has been an increasing drive to take advantage of molecular tools to more precisely identify the mechanisms underlying the pathophysiology of subsets of complex diseases. StiMRAD is an example of this approach. It is designed to illuminate the relationship between STRN, aldosterone, and BP in hypertensive carriers of the *STRN* risk alleles using a novel, cost effective study design. Furthermore, it is one of the first clinical trials in hypertension using genotype to identify participants with an underlying mechanism that is uniquely responsive to a specific form of therapy. Importantly, the human phenotype associated with the underlying mechanism would be expensive to determine, while it is anticipated that the genotype approach is cheap and precise.

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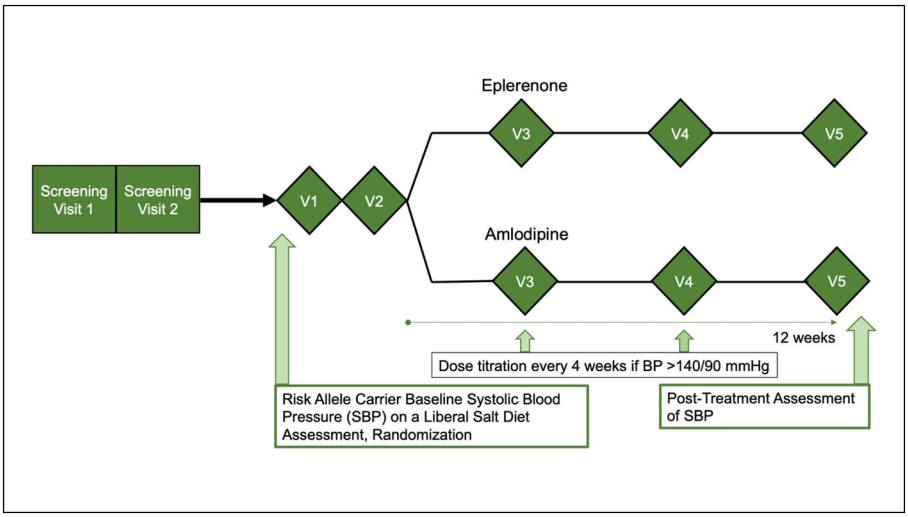

Figure 1: StiMRAD's Schema.

V1-V5 represent Study Visits one through five.

TABLE 1:

Scenarios providing sufficient power, 5% 2-sided alpha.

Baseline SBP minus SBP at first dose (mmHg)		Within-group standard deviation of the changes (mmHg)	Power
Amlodipine (n=45)	Eplerenone (n=45)		
4.0	10.0	8.0	0.94
4.0	10.0	9.0	0.88
4.0	10.0	10.0	0.80
4.0	9.0	8.0	0.84
3.0	9.0	8.0	0.94
3.0	9.0	9.0	0.88
3.0	9.0	10.0	0.80

TABLE 2:

Anticipated proportions of participants reaching maximum dose at each successive ranked dose.

	Maximum dose rank			
	1	**2**	**3**	**4**
Amlodipine (n=45)	0.10	0.30	0.35	0.25
Eplerenone (n=45)	0.30	0.50	0.15	0.05