BMJ open

Hypertension Analysis of stress Reduction using Mindfulness meditatiON and Yoga (The HARMONY Study): study protocol of a randomized control trial [ClinicalTrials.gov Identifier: NCT00825526]

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-000848
Article Type:	Protocol
Date Submitted by the Author:	09-Jan-2012
Complete List of Authors:	Blom, Kimberly; Sunnybrook Health Sciences Center, Medicine How, Maxine; Sunnybrook Health Sciences Centre, Medicine Dai, Monica; Queen's University, Baker, Brian; University Health Network, Psychiatry Irvine, Jane; York University, Psychology Abbey, Susan; University Health Network, Medicine Abramson, Beth; St Michael's Hospital, Medicine Myers, Martin; Sunnybrook Health Sciences Centre, Medicine Perkins, Nancy; Sunnybrook Health Sciences Centre, Medicine Tobe, Sheldon; Sunnybrook Health Sciences Centre, Medicine
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Cardiovascular medicine, Complementary medicine
Keywords:	Hypertension < CARDIOLOGY, COMPLEMENTARY MEDICINE, Clinical trials < THERAPEUTICS

Hypertension Analysis of stress Reduction using Mindfulness meditatiON and Yoga (The HARMONY Study): study protocol of a randomized control trial [ClinicalTrials.gov Identifier: NCT00825526]

Corresponding Author: Kimberly Blom

Sunnybrook Health Sciences Centre

2075 Bayview Avenue, room A140

Toronto ON

M5N 3M5

Email: kimberly.blom@sunnybrook.ca

Telephone: 416 480 6100 x 6861

Fax: 416 480 5164

Co-Authors: How, M. (1), Dai, M. (2), Baker, B. (3), Irvine, J. (4), Abbey, S. (5), Abramson, B.L. (6), Myers, M. (1), Perkins, N. (1) and Tobe, S. (1).

Institutions and Affiliations:

(1). Sunnybrook Health Sciences Centre, Department of Medicine, Toronto Ontario, Canada.

(2). Queen's University, Department: N/A (current medical student), Kingston Ontario, Canada.

(3). University Health Network, Department of Psychiatry, Toronto Ontario, Canada.

(4). York University, Department of Psychology, Toronto Ontario, Canada.

(5). University Health Network, Department of Medicine, Toronto Ontario, Canada.

(6). St. Michael's Hospital, Department of Medicine, Toronto Ontario, Canada.

Key words: hypertension, blood pressure, ambulatory blood pressure monitoring, complementary medicine, meditation.

Word Count: 3,427

ABSTRACT

Hypertension (HTN) is a leading risk factor for preventable cardiovascular disease with over 1 in 5 adults affected worldwide. Lifestyle modification is a key strategy for the prevention and treatment of HTN. Stress has been associated with greater cardiovascular risk and stress management is a recommended intervention for hypertensives. Stress reduction through relaxation therapies have been shown to have an effect on human physiology including lowering blood pressure (BP). However, individualized behavioural interventions are resource intensive and group stress management approaches have not been validated for reducing HTN. The HARMONY study is a pilot randomized controlled trial designed to determine if mindfulness based stress reduction (MBSR), a standardized group therapy, is an effective intervention for lowering BP in stage-1 unmedicated hypertensives. Men and women unmedicated for HTN with mean daytime ambulatory blood pressure (ABP) =/> 135/85 mmHg or 24 hour ABP =/>130/80 mmHg were included in the study. Subjects were randomized to receive MBSR immediately or after a wait-list control period. The primary outcome measure is mean awake and 24 hour ABP. The primary objective of the HARMONY study is to compare ABP between the treatment and wait-list control arm at the 12 week post-baseline primary assessment period. Results from this study will determine if MBSR is an effective intervention for lowering BP in early unmedicated hypertensives. This research project was approved by the Sunnybrook Research Ethics Board (Toronto, Canada) and the University Health Network Research Ethics Board (Toronto, Canada). Planned analyses are in full compliance with the principles of the Declaration of Helsinki. Data collection will be completed by early spring 2012. Primary and secondary analysis will commence immediately after data monitoring is completed; dissemination plans include preparing publications for submission during the summer of 2012. This study is registered with

clinicaltrials.gov (NCT00825526).

INTRODUCTION

Based on an annual consensus conference reviewing the world literature including the Cochrane Collaboration databases, the Canadian Hypertension Education Program recommends lifestyle modification as a key strategy for the prevention and treatment of hypertension[1]. Over 5 million Canadians, part of a worldwide epidemic, are hypertensive[2].[3] Data extrapolated from large population surveys and prospective studies[4,5] show that approximately 250,000 Canadians with high-normal blood pressure (SBP 120-139 or DBP 80-89 mmHg) will develop full-blown high blood pressure every year (BP ≥ 140/90 mmHg) – putting them at higher risk for heart attack and stroke, necessitating the use of medications in most of them. Preventing and controlling hypertension is one of the most cost effective strategies for reducing the global burden of premature cardiovascular disease and death[6]. Reducing systolic blood pressure by just 3 mmHg in the general population has the potential to reduce stroke mortality by 8% and coronary artery disease mortality by 5%[7,8]. The published findings of the *InterStroke* study, one of the largest studies of its type in the world, concluded definitively that uncontrolled hypertension is the single most influential risk factor for stroke[9].

Stress has been associated with greater cardiovascular risk and consideration of stress management is a recommended intervention for hypertensives[1]. However, specific stress management approaches are not well validated for reducing hypertension[10-12]. Stress management therapies can be differentiated based on their approach and delivery: single- or multi-component approach and individualized or group delivery. Certain therapeutic approaches have been efficacious for reducing blood pressure in hypertensive subjects: transcendental meditation (a single-component, individualized therapy), cognitive behavioral therapy (a multi-

component, individualized therapy) and, more recently, contemplative meditation[13] (a multi-component, group therapy).

Transcendental meditation (TM) is a standardized form of meditation where an individual repeats a mantra to move the mind towards a state of greater relaxation and bliss[10]. Evidence indicates that single-component interventions like TM are efficacious in some conditions[14-19] including hypertension[20], with possible long term effects[17]. The blood pressure lowering effect of TM has been further supported by two meta-analyses, each suggesting TM can reduce both systolic and diastolic blood pressure[21,22]. However, other meta-analyses have suggested that the available clinical trials had significant "methodological weaknesses and [were] potentially biased by the affiliation of authors to the TM organization"[10]; thus, one must proceed with caution when evaluating if TM has a cumulative positive effect on lowering blood pressure[10]. Cognitive behavioral therapy (CBT) teaches subjects to be aware of stressors, to re-evaluate negative life events and to decrease sympathetic arousal. In a carefully controlled trial, Linden et al demonstrated that CBT decreased blood pressure in hypertensive participants[23]. While CBT, a multi-component individualized therapy, has demonstrated efficacy in treating hypertension the cost of administering this one-on-one therapy presents a significant barrier to its widespread use. Contemplative meditation has demonstrated promising results however the limited research on the topic indicates that more work must be done before final conclusions can be drawn[13].

Mindfulness Based Stress Reduction (MBSR), like CBT, is a multi-component therapy that encourages participants to achieve results by changing their thought patterns[24]. However, unlike CBT, MBSR is a standardized group therapy which can be delivered to a heterogeneous population. It is now available for stress reduction through some community and hospital

alternative medicine programs and in Ontario it is covered in part by the Ontario Health Insurance Plan. While CBT can be viewed as an acute treatment option, MBSR works as both an acute and preventative treatment as it provides participants with a new method of thinking and functioning[24]. MBSR teaches participants to use mindfulness meditation as a strategy to adapt to stress, pain and illness. In both clinical and non-clinical populations, MBSR has demonstrated benefits for: chronic pain[25-28], anxiety[29-33], depression[29,32-36], fibromyalgia[37-39], binge-eating[40], psoriasis[41], psychological wellbeing, immune function and cortisol levels in cancer subjects[3,42-52], psychological well-being of cancer patient's partners[53] and glycemic control in diabetic populations[54]. Three meta-analyses[55-57] support the efficacy of MBSR for improving both physical and mental well-being in groups of subjects with mixed medical illness. Through its cognitive restructuring format, MBSR improves participants' resistance to stress. It changes the participant's cognitive appraisals, reduces anxiety and enables the participant to cope with future stressful situations more effectively[31].

Preliminary information suggests that participating in an MBSR program also lowers blood pressure[23,42,54] and improves certain components of cardiovascular functioning[58]. Barnes et al initiated one of the earliest studies investigating MBSR and blood pressure; compared to control, those who participated in a two month meditation intervention based on MBSR techniques demonstrated lower systolic blood pressure as measured by an automated device: -4 mmHg (intervention) compared to +2 mmHg (control)[59]. A follow-up study using ambulatory blood pressure monitoring (ABPM) also found significant differences in blood pressure reduction for the meditation group at specific time periods (e.g. after school)[60]. In an abstract, Van Wielingen reported that breast cancer patients who participated in MBSR had lower automated home blood pressure compared to those on wait list control[61]. Examining the

treatment group alone, those with higher blood pressure at baseline demonstrated a greater decrease in systolic blood pressure compared to those with lower systolic blood pressure at baseline[61]. A similar treatment effect was described by Linden in subjects also starting with higher blood pressure levels[62]. Two studies by Carlson et al demonstrated high rates of MBSR class attendance, compliance and home meditation[43,44], with the follow-up study reporting consistent drops in clinic blood pressure persisting up to one year[42]. A randomized controlled trial of an abbreviated 6 week program using MBSR principles for pain tolerance in normotensive university students found improved pain tolerance and lower diastolic blood pressure in both the treatment and control groups[63]. These early studies point towards a blood pressure lowering effect from MBSR. However, more rigorous methodology and larger sample sizes are required to demonstrate whether MBSR can truly lower blood pressure.

Before a large outcome study of MBSR for hypertension can be conducted, it is necessary to collect data documenting efficacy and treatment effect. The HARMONY study, a randomized controlled pilot trial investigating the use MBSR for unmedicated stage 1 hypertension, will test whether MBSR can significantly lower blood pressure. If found effective, the HARMONY study will provide evidence to support a larger randomized controlled trial by evaluating the feasibility and safety of MBSR as a complementary or alternative treatment for hypertension.

METHODS

Study Design

The HARMONY study is a randomized, prospective, two-armed, wait-list controlled pilot trial. The intervention is a standard 8 week MBSR program. The main outcome measure is mean awake and 24 hour systolic and diastolic ambulatory blood pressure. The study population

consists of unmedicated men and women with stage 1 hypertension. Based on the power analysis the established recruitment goal was one hundred subjects. Baseline ambulatory blood pressure monitoring determined hypertensive eligibility. Screening and follow-up visits take place at Sunnybrook Health Sciences Centre, Toronto Ontario. All MBSR therapy was conducted at the University Health Network's Toronto General Hospital, Toronto Ontario.

Study Participants

Eligible participants were adults aged 20 to 75 years old who had a mean awake systolic or diastolic ambulatory blood pressure equal to or greater than 135 mmHg or 85 mmHg, or mean 24 hour ambulatory blood pressure equal to or greater than 130 mmHg or 80 mmHg. Study participants consist of those who met the screening criteria, were willing and able to participate in the MBSR program, could attend all necessary study visits and complete all safety blood pressure evaluations. Further details regarding inclusion and exclusion criteria can be found in Table 1.

Table 1: Study inclusion and exclusion criteria.

Inclusion criteria:
1. Age 20 to 75 years. 2. Hypertension by ABPM at baseline (daytime ≥ 135/85 mmHg or 24-hour ABPM ≥ 130/80 mmHg). 3. Willing and able to participate in the MBSR program. 4. Willing to be followed for safety BP checks during the primary outcome period. 5. Willing to accept a possible waiting period of 12-weeks for MBSR. 6. Written informed consent.

7. Able to participate in mindfulness meditation program following screening ABPM.
Exclusion criteria:
1. Use of antihypertensive within 6 months of the screening ABPM. 2. Screening office BP > 180/100 mmHg and ABPM ≥ 160/100 mmHg. 3. Diabetes. 4. Secondary hypertension. 5. Renal disease (GFR < 60 ml/min or overt nephropathy). 6. History of heart attack. 7. Stroke or TIA or 8. Re-vascularization procedure. 9. Active malignant disease (except non-melanoma skin cancer). 10. Epileptic seizure 6 months before the screening visit. 11. Congestive heart failure. 12. Severe liver disease. 13. Pregnancy or lactation period. 14. Participation in a clinical trail or receipt of investigational compound or treatment in the 3 months prior to the initial screening visit. 15. Planned elective surgery during the study period except for cataract surgery. 16. Inability or unwillingness to perform 3 ABPM over 6 months.

Study Recruitment

The planned recruitment rate was 25 subjects every 6 months for a total of 100 subjects. Potential participants were identified through the clinical practices and referral bases of Dr's Abramson, Myers and Tobe. Additional successful screening strategies included public information sessions, advertisements in local news papers and hospital posters. Screening was performed using a validated automated blood pressure device, the BpTRU (VSM MedTech Ltd Coquitlam, Canada). Those with unmedicated office blood pressure $\geq$ 135/85 mmHg were invited to the next step of screening of 24 hour ABPM.

Randomization and Study Blinding

Randomization to one of two study arms was done by sealed envelope method using the permuted block design, with blocks of 2 and 4 subjects to maintain the adequacy of randomization. A computer program generated a random number sequence which was used to allocate subjects to the treatment or wait-list control group. The randomization schedule and sealed envelopes were prepared by an individual who worked closely with the Centre for Statistical Design and Analysis and was not directly involved in the study. Upon review of the screening/baseline ABPM results, consenting subjects who met study inclusion criteria were randomized. Those randomized to the treatment arm began the MBSR program within 4 weeks of their baseline visit and had ABPM repeated 12 weeks after starting MBSR. Those randomized to the wait-list control arm were wait-listed for 12 weeks and subsequently began MBSR within 4 weeks of their 12 week post baseline ABPM (Figure 1).

Primary Outcome

The primary outcome measure is mean awake and 24 hour ambulatory blood pressure (ABP). The primary objective of the HARMONY study is to compare mean awake and 24 hour

ABP between the treatment and control arms at the 12 week post-baseline primary assessment period (Figure 1)

Secondary Outcomes

Secondary outcomes include evaluating a within-group effect of MBSR on ABP from pre- to post- MBSR intervention. Persistence of effect 12 weeks after completing the therapy will also be investigated (Figure 1). Between and within-group comparisons of the effect of MBSR on nighttime ABP will also be assessed. The proportion of subjects achieving blood pressure targets (24 hour ABP < 130/80, daytime ABP < 135/85 mmHg), those requiring the initiation of medical therapy during the study and adverse events will also be examined. The amount of MBSR practiced outside the classroom will be analyzed (via participant diaries and homework logs) with respect to change in blood pressure to evaluate any dose-response interactions. Associations between the effect of MBSR on ABP and individual participant characteristics will also be explored. This will be achieved by examining covariates and incorporating them into a model with blood pressure. See Table 2 for further details regarding data collected at study visits.

Table 2. Baseline and ongoing data collection. All listed measurements were collected baseline. Measurements 1-5 are repeated at subsequent study visits (before MBSR, following MBSR and at the 12-week study close-out).

1. Ambulatory blood pressure monitoring (ABPM):
▪ Participants wear an ambulatory blood pressure monitor (model 90207, Spacelabs Medical Inc., Redmond, WA). ▪ Blood pressure recorded every 15 minutes during a typical day and every 30 minutes between 11 pm and 7 am.

▪ Mean values calculated for systolic and diastolic blood pressure
2. Anthropometric measurements:
▪ Body weight and height measured to calculate Body Mass Index. ▪ Waist circumference measured at the top of the iliac crest.
3. Office blood pressure:
▪ Seated office systolic and diastolic blood pressure measured by BpTRU (VSM MedTech Ltd., Vancouver, BC, Canada). ▪ Device takes 6 measurements every 2 minutes. Averages the last 5 to determine the average seated blood pressure.
4. Fasting serum samples:
▪ Plasma glucose, HbA1c, total cholesterol, HDL- cholesterol, LDL-cholesterol, triglycerides, creatinine, electrolytes and liver enzyme levels.
5. Urine samples:
▪ Urine creatinine levels and microalbuminuria levels.
6. Electrocardiogram (ECG)
▪ ECG to detect any abnormal heart rhythms and left ventricular hypertrophy.

The following questionnaires were included in the study protocol to account for external confounders: 1) Demographics and Lifestyle Questionnaire, 2) State-Trait Anger Expression Inventory-2[64], 3) Hospital Anxiety and Depression Scale[65], 4) Perceived Stress Scale[66], 5) Psychosocial Stress Questionnaire[67], 6) Exercise questionnaire, 7) Job Content Questionnaire[68], 8) Five-Facet Mindfulness Questionnaire[69], 9) Clinical Outcome Routine

Evaluation Outcome Measure[70], 10) Toronto Mindfulness Scale[71]. All questionnaires administered at baseline with questionnaires 2, 4, 5, and 6 repeated at each study visit (ie. Pre MBSR, post MBSR, and study close out). The Toronto Mindfulness Scale was administered after the 2nd and 7th MBSR class. Planned future analyses include evaluating the relationships between blood pressure, gender and responses from the questionnaires.

Intervention

Mindfulness Based Stress Reduction (MBSR) is a multi-component group therapy that provides systematic training in mindfulness meditation as a self-regulation approach to stress reduction and emotion management. The primary goal of MBSR is to provide participants with training meditation techniques that will cultivate psychological resilience and resistance to stress through cognitive restructuring. This is achieved through fostering the quality of "mindfulness"[29-31,34,42,51,72,72,73]. MBSR teaches attendees to approach stressful situations "mindfully"; allowing them to step back from thoughts and feelings during stressful situations and avoid engaging in anxious worry that may otherwise escalate into a cycle of stress reactivity and contribute to more emotional distress[74-77].

The standard MBSR program is delivered by trained therapists to groups of 25 - 30 individuals and consists of 10 sessions: an introductory session, eight weekly sessions of 2.5 hours, and a 6 hour intensive session/silent retreat held between week six and seven of the course on a Saturday or Sunday. The MBSR program incorporates four major therapeutic elements: formal meditation, informal mindfulness practice, psycho-educational activities, and self monitoring / reflection exercises. Each session also includes guided imagery, progressive muscle relaxation, breathing exercises and yoga, as well as didactic teaching and discussion. The development of mindfulness depends heavily upon regular and repeated practice; thus participants commit to

carry out daily 15-45 minute homework assignments. Daily meditation practice is encouraged; homework includes both formal and informal meditation practices, as well as self-observation questions. CDs are included to guide attendees in daily formal meditation practice.

Adherence to MBSR was tracked by participant diary and homework log. Together, these capture the amount of time participants spent on various learned meditation practices each week. As the MBSR program is standardized and can be offered to both heterogeneous and homogeneous groups, subjects were accommodated in other MBSR classes if necessary for scheduling.

Data Collection

All study related information is maintained in individual subjects charts as well as electronically in a Microscoft Access Database file.

Safety

Lifestyle therapy is indicated for people who have stage 1 hypertension (140-159/90-99 mmHg) with no underlying risk factors[1]. Linden has previously demonstrated the role and safety of the wait-list control methodology and determined it to be appropriate in studies with stage 1 and 2 hypertensives (140-179/90-109 mmHg)[23,62]. In accordance with the Canadian standard of care for blood pressure management, all participants received standard recommendations of suggested lifestyle modifications for blood pressure management at study entry.

With participant consent, primary care physician(s) are informed of their patient's participation in the study. Physicians are asked to delay the start of their patient's antihypertensive therapy until after they have completed the study. If physicians believe that antihypertensive should be initiated, they are asked to communicate their decision to study staff

before doing so. A letter updating their patient's progress, along with laboratory and ABPM results are sent to the primary care physician after each study visit.

Automated office blood pressure safety assessments are included to closely monitor subjects' blood pressure and the primary investigator is notified if subjects exceed blood pressure safety limits. If any of the following conditions are discovered during study enrollment participants are withdrawn and treated: 1) increases in ambulatory blood pressure of 20/10 mmHg or greater, 2) accelerated hypertension with an office reading of 160/100 mmHg or greater, 3) macrovascular target organ damage, 4) diabetes mellitus or 5) chronic kidney disease (GFR<60 ml/min). Any subject started on antihypertensive therapy during the study remains in the study and the initiation of medical therapy is recorded.

Sample Size Considerations

The main objective of this study is to assess the difference in mean awake and 24 hour systolic and diastolic ambulatory blood pressure 12 weeks post baseline between the treatment and wait-list control arm. The following calculations/analyses are based on Linden's work and the difference in mean systolic blood pressure between treatment groups measured as by ABPM. Linden found a 6.1 mmHg systolic blood pressure drop from baseline to the end of the primary assessment period for participants in the immediate intervention group, whereas the wait-list control group showed a 0.9 mmHg increase in the same time interval[23] This resulted in a 7.0 mmHg difference between the two groups[23], a relatively large treatment effect, due in part to the use of subjects with higher blood pressure.

Unlike Linden who found blood pressure rising in the control group, more recent results from the Double Exposure study in a hypertensive cohort found that blood pressure tends to fall over time, even in unmedicated hypertensives, possibly due to adoption of lifestyle

changes[78,79]. Baseline data from the unmedicated hypertensive cohort in the Double Exposure study demonstrated mean awake ABP equal to 137/85 ± 8/5 mmHg. After one year, mean awake ABP had fallen to 133/83 ± 8/7 mmHg. Based on these results, it is reasonable to assume that blood pressure will fall in the HARMONY wait-list control arm.

Very conservative assumptions were made for the HARMONY power analysis. A reduction of 2.0 mmHg for mean systolic ambulatory blood pressure (half the change observed in the Double Exposure study) was assumed for the control group (compared to the rise that Linden found[23]). The variance recorded in Linden's study (9 mmHg) was used for the HARMONY power analysis; a variance higher than that recorded in the Double Exposure cohort (8 mmHg in only 35 subjects). Linden found a blood pressure difference of 7.0 mmHg between the treatment and control group. In the power analysis, the difference between treatment and control groups was reduced from Linden's result to a more conservative value, 6mmHg. This value was chosen as it was closer to findings from Dickinson's meta-analysis[12]and because participants' overall blood pressure is anticipated to be lower in the HARMONY study (stage 1 hypertensives) compared to Linden's study (stage 1 and stage 2 hypertensives)[23]. Using a two-tailed two-sample t-test, an estimated group standard deviation of 9.0 mmHg and a significance level of 0.05 it was determined that a sample size of 37 subjects in each group would provide sufficient power (81%) to detect a systolic blood pressure difference of 6.0 mmHg between the null hypothesis (both groups start with equal means and have an equal a drop in systolic blood pressure of 8.0 mmHg) and the alternative hypothesis (control group systolic blood pressure will fall by only 2.0 mmHg). To account for potential drop-outs and subjects lost to analysis (25% lost in Linden's study[23]), the number of subjects was increased to 50 subjects per group (Figure 2).

Statistical Analysis

The primary outcome will be examined using an intent-to-treat analysis. An intent-to-treat population is defined as all subjects entered into the study that completed at least one session of MBSR. The primary outcome measure is mean awake and 24 hour systolic and diastolic ambulatory blood pressure. Ambulatory blood pressure between treatment and control will be compared by two-tailed two-sample t-test at the end of the 12 week primary outcome period. Within subject analysis of the effect of MBSR on ambulatory blood pressure will be performed by a paired t-test. Persistence of effect of MBSR on blood pressure will be assessed using repeated ANOVA measures, comparing group differences between subsequent study visits (baseline, pre MBSR, post MBSR, and study close out). The proportion of subjects achieving blood pressure targets will be analyzed using chi-squared tests. Multiple regression analyses will be employed to assess differences in blood pressure between subjects while adjusting for covariates. Subjects may be started on antihypertensive therapy during the study. If this leads to imbalance between the study arms, a per-protocol analysis may be performed to take this variable into account. All analyses will be carried out using SAS version 9.1 (SAS Institute, Cary North Carolina, USA).

Ethical Considerations

This research project was approved by the Research Ethics Board at Sunnybrook Research Institute (Toronto, Canada) and the University Health Network Research Ethics Board (Toronto, Canada). Planned data analyses are in full conformance with the principles of the "*Declaration of Helsinki*"[80]. Conduct of the HARMONY study is fully adherent to the principles outlined in the "*Guideline for Good Clinical Practice*" ICH Tripartite Guideline

[January 1997][81] and in the 2nd edition of Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans[82].

Dissemination Plans

Data collection will be completed by early spring 2012. Primary and secondary analysis will commence immediately after data monitoring is completed; publications will be prepared for submission in summer of 2012. Study findings are also planned to be presented at the following conferences: October 2012: Hypertension Canada, May 2013: American Society of Hypertension, June 2013: European Society of Hypertension, September 2013: International Society of Hypertension.

Authors' Contributions

ST conceptualized the study and MD, BB, MM, SA, BA, NP and JI assisted with the study design. KB, MH and MD collected data which was overseen by NP. KB and MH cleaned the collected data, preformed interim analyses and interpreted interim results. ST is the guarantor. KB, MD, MH, and ST wrote and revised the article, as well as designed figures. NP, BB, MM, SA, BA and JI critically revised the draft for important intellectual content. All authors approved this final version to be published.

Funding Statement

This work was supported by Heart and Stroke Foundation of Ontario (#NA 6349). The Heart & Stroke Foundation of Ontario played no role in the study design, data collection, analysis and interpretation of data, writing of the article or the decision to submit it for publication.

Competing Interests Statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

REFERENCES

1 Rabi DM, Daskalopoulou SS, Padwal RS, et al. *The 2011 Canadian Hypertension Education Program Recommendations for the Management of Hypertension: Blood Pressure Measurement, Diagnosis, Assessment of Risk, and Therapy.* Can J Cardiol 2011;**27**:415-433.

2 Chockalingam A, Campbell NR, Fodor JG. *Worldwide epidemic of hypertension.* Can J Cardiol 2006;**22**:553-555.

3 Lengacher CA, Johnson-Mallard V, Barta M, et al. *Feasibility of a mindfulness-based stress reduction program for early-stage breast cancer survivors.* Journal of Holistic Nursing 2011;**29**:107-117.

4 Vasan RS, Larson MG, Leip EP, et al. *Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study.* Lancet 2001;**358**:1682-1686.

5 Julius S, Nesbitt S, Egan B, et al. *Feasibility of treating prehypertension with an angiotensin-receptor blocker.* N Engl J Med 2006;**354**:1685-1697.

6World Health Organization. Preventing chronic diseases: a vital investment. Available at: www.who.int/chp/chronic_disease_report/contents/en/index.html. Accessed 04/27, 2007.

7 Stamler J, Rose G, Stamler R, et al. *INTERSALT study findings. Public health and medical care implications.* Hypertension 1989;**14**:570-577.

8 Appel LJ. *Lifestyle modification as a means to prevent and treat high blood pressure.* Journal of the American Society of Nephrology 2003;**14**:S99-S102.

9 O'Donnell MJ, Xavier D, Liu L, et al. *Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study.* Lancet 2010;**376**:112-123.

10 Canter PH, Ernst E. *Insufficient evidence to conclude whether or not Transcendental Meditation decreases blood pressure: results of a systematic review of randomized clinical trials.* J Hypertens 2004;**22**:2049-2054.

11 Parati G, Steptoe A. *Stress reduction and blood pressure control in hypertension: a role for transcendental meditation?* J Hypertens 2004;**22**:2057-2060.

12 Dickinson HO, Mason JM, Nicolson DJ, et al. *Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials.* J Hypertens 2006;**24**:215-233.

13 Manikonda JP, Stork S, Togel S, et al. *Contemplative meditation reduces ambulatory blood pressure and stress-induced hypertension: a randomized pilot trial.* J Hum Hypertens 2008;**22**:138-140.

14 Wenneberg SR, Schneider RH, Walton KG, et al. *A controlled study of the effects of the Transcendental Meditation program on cardiovascular reactivity and ambulatory blood pressure.* Int J Neurosci 1997;**89**:15-28.

15 Castillo-Richmond A, Schneider RH, Alexander CN, et al. *Effects of stress reduction on carotid atherosclerosis in hypertensive African Americans.* Stroke 2000;**31**:568-573.

16 Schneider RH, Staggers F, Alxander CN, et al. *A randomised controlled trial of stress reduction for hypertension in older African Americans.* Hypertension 1995;**26**:820-827.

17 Schneider RH, Alexander CN, Staggers F, et al. *Long-term effects of stress reduction on mortality in persons > or = 55 years of age with systemic hypertension.* Am J Cardiol 2005;**95**:1060-1064.

18 Paul-Labrador M, Polk D, Dwyer JH, et al. *Effects of a randomized controlled trial of transcendental meditation on components of the metabolic syndrome in subjects with coronary heart disease.* Arch Intern Med 2006;**166**:1218-1224.

19 Schneider RH, Alexander CN, Staggers F, et al. *A randomized controlled trial of stress reduction in African Americans treated for hypertension for over one year.* American Journal of Hypertension 2005;**18**:88-98.

20 Nidich SI, Rainforth MV, Haaga DA, et al. *A randomized controlled trial on effects of the Transcendental Meditation program on blood pressure, psychological distress, and coping in young adults.* American Journal of Hypertension 2009;**22**:1326-1331.

21 Anderson JW, Liu C, Kryscio RJ. *Blood pressure response to transcendental meditation: a meta-analysis.* American Journal of Hypertension 2008;**21**:310-316.

22 Rainforth MV, Schneider RH, Nidich SI, et al. *Stress reduction programs in patients with elevated blood pressure: a systematic review and meta-analysis.* Curr Hypertens Rep 2007;**9**:520-528.

23 Linden W, Lenz JW, Con AH. *Individualized stress management for primary hypertension: a randomized trial.* Arch Intern Med 2001;**161**:1071-1080.

24 Praissman S. *Mindfulness-based stress reduction: a literature review and clinician's guide.* J Am Acad Nurse Pract 2008;**20**:212-216.

25 Plews-Ogan M, Owens JE, Goodman M, et al. *A pilot study evaluating mindfulness-based stress reduction and massage for the management of chronic pain.* Journal of General Internal Medicine 2005;**20**:1136-1138.

26 Morone NE, Greco CM, Weiner DK. *Mindfulness meditation for the treatment of chronic low back pain in older adults: a randomized controlled pilot study.* Pain 2008;**134**:310-319.

27 Esmer G, Blum J, Rulf J, et al. *Mindfulness-based stress reduction for failed back surgery syndrome: a randomized controlled trial.* J Am Osteopath Assoc 2010;**110**:646-652.

28 Rosenzweig S, Greeson JM, Reibel DK, et al. *Mindfulness-based stress reduction for chronic pain conditions: variation in treatment outcomes and role of home meditation practice.* J Psychosom Res 2010;**68**:29-36.

29 Shapiro SL, Schwartz GE, Bonner G. *Effects of mindfulness-based stress reduction on medical and premedical students.* J Behav Med 1998;**21**:581-599.

30 Astin JA. *Stress reduction through mindfulness meditation. Effects on psychological symptomatology, sense of control, and spiritual experiences.* Psychotherapy & Psychosomatics 1997;**66**:97-106.

31 Kabat-Zinn J, Massion AO, Kristeller J, et al. *Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders.* Am J Psychiatry 1992;**149**:936-943.

32 Vieten C, Astin J. *Effects of a mindfulness-based intervention during pregnancy on prenatal stress and mood: results of a pilot study.* Archives of Women's Mental Health 2008;**11**:67-74.

33 Vollestad J, Sivertsen B, Nielsen GH. *Mindfulness-based stress reduction for patients with anxiety disorders: evaluation in a randomized controlled trial.* Behaviour Research & Therapy 2011;**49**:281-288.

34 Barnhofer T, Duggan D, Crane C, et al. *Effects of meditation on frontal alpha-asymmetry in previously suicidal individuals.* Neuroreport 2007;**18**:709-712.

35 Kenny MA, Williams JM. *Treatment-resistant depressed patients show a good response to Mindfulness-based Cognitive Therapy.* Behaviour Research & Therapy 2007;**45**:617-625.

36 Kingston J, Chadwick P, Meron D, et al. *A pilot randomized control trial investigating the effect of mindfulness practice on pain tolerance, psychological well-being, and physiological activity.* J Psychosom Res 2007;**62**:297-300.

37 Grossman P, Tiefenthaler-Gilmer U, Raysz A, et al. *Mindfulness training as an intervention for fibromyalgia: evidence of postintervention and 3-year follow-up benefits in well-being.* Psychotherapy & Psychosomatics 2007;**76**:226-233.

38 Sephton SE, Salmon P, Weissbecker I, et al. *Mindfulness meditation alleviates depressive symptoms in women with fibromyalgia: results of a randomized clinical trial.* Arthritis & Rheumatism 2007;**57**:77-85.

39 Schmidt S, Grossman P, Schwarzer B, et al. *Treating fibromyalgia with mindfulness-based stress reduction: results from a 3-armed randomized controlled trial.* Pain 2011;**152**:361-369.

40 Kristeller JL, Hallett CB. *An Exploratory Study of a Meditation-based Intervention for Binge Eating Disorder.* Journal of Health Psychology 1999;**4**:357-363.

41 Kabat-Zinn J, Wheeler E, Light T, et al. *Influence of a mindfulness meditation-based stress reduction intervention on rates of skin clearing in patients with moderate to severe psoriasis undergoing phototherapy (UVB) and photochemotherapy (PUVA).* Psychosom Med 1998;**60**:625-632.

42 Carlson LE, Speca M, Faris P, et al. *One year pre-post intervention follow-up of psychological, immune, endocrine and blood pressure outcomes of mindfulness-based stress reduction (MBSR) in breast and prostate cancer outpatients.* Brain, Behavior, & Immunity 2007;**21**:1038-1049.

43 Carlson LE, Speca M, Patel KD, et al. *Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress and levels of cortisol, dehydroepiandrosterone sulfate*

(DHEAS) and melatonin in breast and prostate cancer outpatients. Psychoneuroendocrinology 2004;**29**:448-474.

44 Carlson LE, Speca M, Patel KD, et al. *Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress, and immune parameters in breast and prostate cancer outpatients.* Psychosom Med 2003;**65**:571-581.

45 Henderson VP, Clemow L, Massion AO, et al. *The effects of mindfulness-based stress reduction on psychosocial outcomes and quality of life in early-stage breast cancer patients: a randomized trial.* Breast Cancer Research & Treatment 2012;**131**:99-109.

46 Lengacher CA, Johnson-Mallard V, Post-White J, et al. *Randomized controlled trial of mindfulness-based stress reduction (MBSR) for survivors of breast cancer.* Psychooncology 2009;**18**:1261-1272.

47 Ledesma D, Kumano H. *Mindfulness-based stress reduction and cancer: a meta-analysis.* Psychooncology 2009;**18**:571-579.

48 Matchim Y, Armer JM, Stewart BR. *Mindfulness-based stress reduction among breast cancer survivors: a literature review and discussion.* Oncol Nurs Forum 2011;**38**:E61-71.

49 Matchim Y, Armer JM, Stewart BR. *Effects of mindfulness-based stress reduction (MBSR) on health among breast cancer survivors.* West J Nurs Res 2011;**33**:996-1016.

50 Matousek RH, Dobkin PL. *Weathering storms: a cohort study of how participation in a mindfulness-based stress reduction program benefits women after breast cancer treatment.* Current Oncology 2010;**17**:62-70.

51 Smith JE, Richardson J, Hoffman C, et al. *Mindfulness-Based Stress Reduction as supportive therapy in cancer care: systematic review.* J Adv Nurs 2005;**52**:315-327.

52 Witek-Janusek L, Albuquerque K, Chroniak KR, et al. *Effect of mindfulness based stress reduction on immune function, quality of life and coping in women newly diagnosed with early stage breast cancer.* Brain, Behavior, & Immunity 2008;**22**:969-981.

53 Birnie K, Garland SN, Carlson LE. *Psychological benefits for cancer patients and their partners participating in mindfulness-based stress reduction (MBSR).* Psychooncology 2010;**19**:1004-1009.

54 Rosenzweig S, Reibel DK, Greeson JM, et al. *Mindfulness-based stress reduction is associated with improved glycemic control in type 2 diabetes mellitus: a pilot study.* Alternative Therapies in Health & Medicine 2007;**13**:36-38.

55 Baer RA. *Mindfulness Training as a Clinical Intervention: A Conceptual and Empirical Review.* Clinical Psychology: Science and Practice 2003;**10**:125-143.

56 Grossman P, Niemann L, Schmidt S, et al. *Mindfulness-based stress reduction and health benefits. A meta-analysis.* J Psychosom Res 2004;**57**:35-43.

57 Bohlmeijer E, Prenger R, Taal E, et al. *The effects of mindfulness-based stress reduction therapy on mental health of adults with a chronic medical disease: a meta-analysis.* J Psychosom Res 2010;**68**:539-544.

58 Ditto B, Eclache M, Goldman N. *Short-term autonomic and cardiovascular effects of mindfulness body scan meditation.* Annals of Behavioral Medicine 2006;**32**:227-234.

59 Barnes VA, Treiber FA, Davis H. *Impact of Transcendental Meditation on cardiovascular function at rest and during acute stress in adolescents with high normal blood pressure.* J Psychosom Res 2001;**51**:597-605.

60 Barnes VA, Davis HC, Murzynowski JB, et al. *Impact of meditation on resting and ambulatory blood pressure and heart rate in youth.* Psychosom Med 2004;**66**:909-914.

61 LE Van Wielingen, LE Carlson and TS Campbell. *Mindfulness-based stress reduction (MBSR), blood pressure and psychological functioning in women with cancer.* [abstract]. Psychosom.Med. 2007;69:A43.

62 Linden W, Moseley JV. *The efficacy of behavioral treatments for hypertension.* Applied Psychophysiology & Biofeedback 2006;**31**:51-63.

63 Kingston T, Dooley B, Bates A, et al. *Mindfulness-based cognitive therapy for residual depressive symptoms.* Psychology & Psychotherapy: Theory, Research & Practice 2007;**80**:193-203.

64 Spielberger C, Jacobs G, Russel S, Crane R. Assessment of Anger: The State-Trait Anger Scale. In: Butcher J, Spielberger C, eds. Advances in Personality Assesment. Hillsdale, NJ: Lawrence Erlbaum Associates 1983:112-189.

65 Bjelland I, Dahl AA, Haug TT, et al. *The validity of the Hospital Anxiety and Depression Scale. An updated literature review.* J Psychosom Res 2002;**52**:69-77.

66 Cohen S, Kamarck T, Mermelstein R. *A global measure of perceived stress.* Journal of Health & Social Behavior 1983;**24**:385-396.

67 Rosengren A, Hawken S, Ounpuu S, et al. *Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study.* Lancet 2004;**364**:953-962.

68 Karasek R, Brisson C, Kawakami N, et al. *The Job Content Questionnaire (JCQ): an instrument for internationally comparative assessments of psychosocial job characteristics.* J Occup Health Psychol 1998;**3**:322-355.

69 Baer RA, Smith GT, Lykins E, et al. *Construct validity of the five facet mindfulness questionnaire in meditating and nonmeditating samples.* Assessment 2008;**15**:329-342.

70 Evans C, Connell J, Barkham M, et al. *Towards a standardised brief outcome measure: psychometric properties and utility of the CORE-OM.* British Journal of Psychiatry 2002;**180**:51-60.

71 Lau MA, Bishop SR, Segal ZV, et al. *The Toronto Mindfulness Scale: development and validation.* J Clin Psychol 2006;**62**:1445-1467.

72 Shapiro SL, Brown KW, Thoresen C, et al. *The moderation of Mindfulness-based stress reduction effects by trait mindfulness: results from a randomized controlled trial.* J Clin Psychol 2011;**67**:267-277.

73 Reibel DK, Greeson JM, Brainard GC, et al. *Mindfulness-based stress reduction and health-related quality of life in a heterogeneous patient population.* Gen Hosp Psychiatry 2001;**23**:183-192.

74 Kabat-Zinn J, Lipworth L, Burney R. *The clinical use of mindfulness meditation for the self-regulation of chronic pain.* J Behav Med 1985;**8**:163-190.

75 Bishop SR. *What do we really know about mindfulness-based stress reduction?* Psychosom Med 2002;**64**:71-83.

76 Kabat-Zinn J. *An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results.* Gen Hosp Psychiatry 1982;**4**:33-47.

77Kabat-Zinn J. Full catastrophe living: using the wisdom of your body and mind to face stress, pain and illness. New York: Delta 1990:.

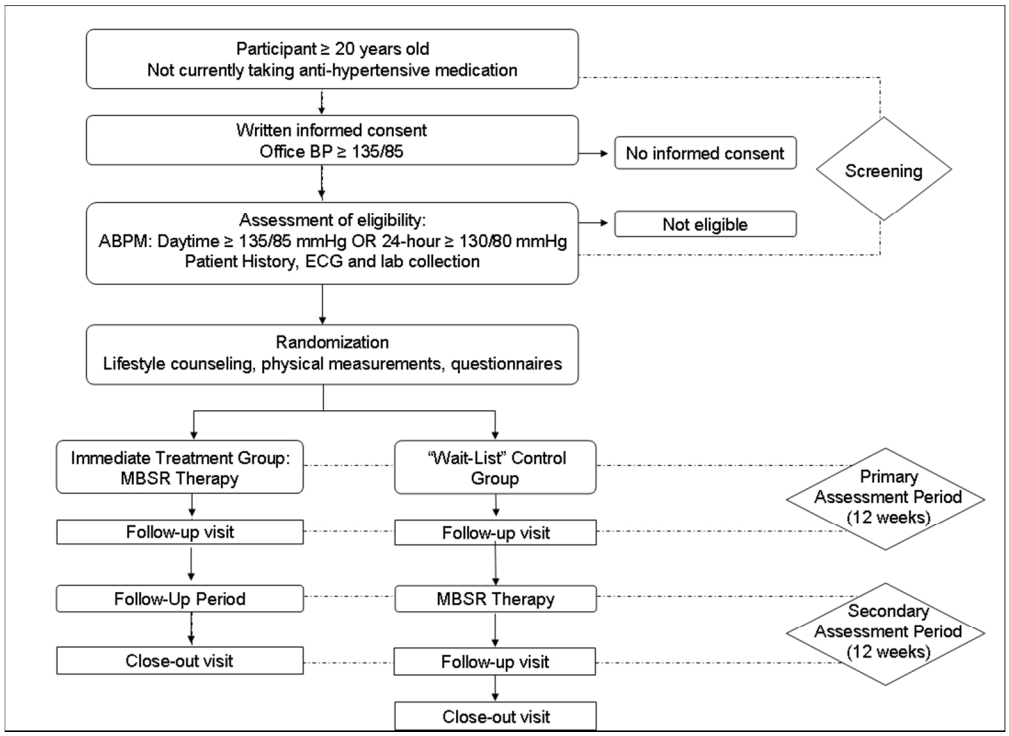
78 Baker B, Paquette M, Szalai JP, et al. *The influence of marital adjustment on 3-year left ventricular mass and ambulatory blood pressure in mild hypertension.* Arch Intern Med 2000;**160**:3453-3458.

79 Tobe SW, Kiss A, Sainsbury S, et al. *The impact of job strain and marital cohesion on ambulatory blood pressure during 1 year: the double exposure study.* American Journal of Hypertension 2007;**20**:148-153.

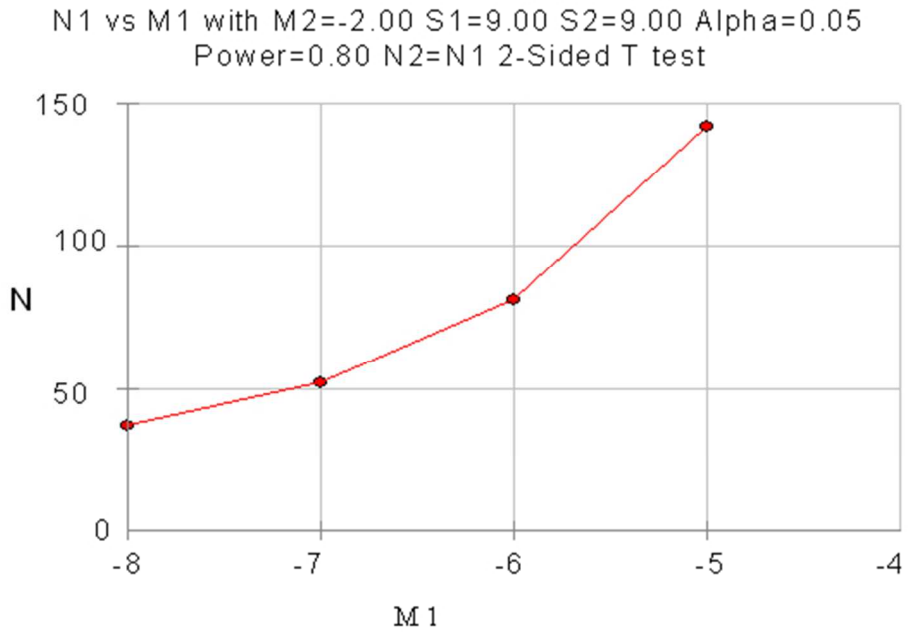
80World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. From the 59th World Medical Association Assembly, Seoul. 2008; Available at: http://www.wma.net/en/30publications/10policies/b3/17c.pdf. Accessed 12/29, 2011.

81Health Canada. International Conference on Harmonization (ICH) Guidance E6: Good Clinical Practice: Consolidated Guidelines. 1997; Available at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e6-eng.php. Accessed 12/29, 2011.

82Goverment of Canada: Panel of Research Ethics. 2nd Edition of Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. 2010; Available at: http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/. Accessed 12/29, 2011.



HARMONY study design.



Power analysis graph illustrating necessary sample size.

BMJ open

Hypertension Analysis of stress Reduction using Mindfulness meditatiON and Yoga (The HARMONY Study): study protocol of a randomized control trial.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-000848.R1
Article Type:	Protocol
Date Submitted by the Author:	10-Feb-2012
Complete List of Authors:	Blom, Kimberly; Sunnybrook Health Sciences Center, Medicine How, Maxine; Sunnybrook Health Sciences Centre, Medicine Dai, Monica; Queen's University, Baker, Brian; University Health Network, Psychiatry Irvine, Jane; York University, Psychology Abbey, Susan; University Health Network & University of Toronto, Psychiatry Abramson, Beth; St. Michael's Hospital, Medicine Myers, Martin; Sunnybrook Health Sciences Centre, Medicine Perkins, Nancy; Sunnybrook Health Sciences Centre, Medicine Tobe, Sheldon; Sunnybrook Health Sciences Centre, Medicine
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Cardiovascular medicine, Complementary medicine
Keywords:	Hypertension < CARDIOLOGY, COMPLEMENTARY MEDICINE, Clinical trials < THERAPEUTICS

Hypertension Analysis of stress Reduction using Mindfulness meditatiON and Yoga (The HARMONY Study): study protocol of a randomized control trial.

Corresponding Author: Kimberly Blom

Sunnybrook Health Sciences Centre

2075 Bayview Avenue, room A140

Toronto ON

M5N 3M5

Email: kimberly.blom@sunnybrook.ca

Telephone: 416 480 6100 x 6861

Fax: 416 480 5164

Co-Authors: How, M. (1), Dai, M. (2), Baker, B. (3), Irvine, J. (4), Abbey, S. (3), Abramson, B.L. (5), Myers, M. (1), Perkins, N. (1) and Tobe, S.W. (1).

Institutions and Affiliations:

(1). Sunnybrook Health Sciences Centre, Department of Medicine, Toronto Ontario, Canada.

(2). Queen's University, Department: N/A (current medical student), Kingston Ontario, Canada.

(3). University Health Network, Department of Psychiatry & University of Toronto, Department of Psychiatry, Toronto Ontario, Canada.

(4). York University, Department of Psychology, Toronto Ontario, Canada.

(5). St. Michael's Hospital, Department of Medicine, Toronto Ontario, Canada.

Key words: hypertension, blood pressure, ambulatory blood pressure monitoring, complementary medicine, meditation.

Word Count: 4094

ABSTRACT

Introduction

Hypertension (HTN) is a leading risk factor for preventable cardiovascular disease with over 1 in 5 adults affected worldwide. Lifestyle modification is a key strategy for the prevention and treatment of HTN. Stress has been associated with greater cardiovascular risk and stress management is a recommended intervention for hypertensives. Stress reduction through relaxation therapies have been shown to have an effect on human physiology including lowering blood pressure (BP). However, individualized behavioural interventions are resource intensive and group stress management approaches have not been validated for reducing HTN. The HARMONY study is a pilot randomized controlled trial designed to determine if mindfulness based stress reduction (MBSR), a standardized group therapy, is an effective intervention for lowering BP in stage-1 unmedicated hypertensives.

Methods and Analysis

Men and women unmedicated for HTN with mean daytime ambulatory blood pressure (ABP) =/> 135/85 mmHg or 24 hour ABP =/>130/80 mmHg were included in the study. Subjects were randomized to receive MBSR immediately or after a wait-list control period. The primary outcome measure is mean awake and 24 hour ABP. The primary objective of the HARMONY study is to compare ABP between the treatment and wait-list control arm at the 12 week primary assessment period. Results from this study will determine if MBSR is an effective intervention for lowering BP in early unmedicated hypertensives.

Ethics and Dissemination

This research project was approved by the Sunnybrook Research Ethics Board and the University Health Network Research Ethics Board (Toronto, Canada). Planned analyses are in

full compliance with the principles of the Declaration of Helsinki. Data collection will be completed by early spring 2012. Primary and secondary analysis will commence immediately after data monitoring is completed; dissemination plans include preparing publications for submission during the summer of 2012.

Registration Details

This study is registered with clinicaltrials.gov (NCT00825526).

INTRODUCTION

Based on an annual consensus conference reviewing the world literature including the Cochrane Collaboration databases, the Canadian Hypertension Education Program recommends lifestyle modification as a key strategy for the prevention and treatment of hypertension[1]. Over 5 million Canadians, part of a worldwide epidemic, are hypertensive[2]. Data extrapolated from large population surveys and prospective studies[3,4] show that approximately 250,000 Canadians with high-normal blood pressure (SBP 120-139 or DBP 80-89 mmHg) will develop full-blown high blood pressure every year (BP ≥ 140/90 mmHg) – putting them at higher risk for heart attack and stroke, necessitating the use of medications in most of them. Preventing and controlling hypertension is one of the most cost effective strategies for reducing the global burden of premature cardiovascular disease and death[5]. Reducing systolic blood pressure by just 3 mmHg in the general population has the potential to reduce stroke mortality by 8% and coronary artery disease mortality by 5%[6,7]. The published findings of the *InterStroke* study, one of the largest studies of its type in the world, concluded definitively that uncontrolled hypertension is the single most influential risk factor for stroke[8].

Stress has been associated with greater cardiovascular risk and consideration of stress management is a recommended intervention for hypertensives[1]. However, specific stress management approaches are not well validated for reducing hypertension[9-11]. Stress management therapies can be differentiated based on their approach and delivery: single- or multi-component approach and individualized or group delivery. Certain therapeutic approaches have been efficacious for reducing blood pressure in hypertensive subjects: transcendental meditation (a single-component, individualized therapy), cognitive behavioral therapy (a multi-

component, individualized therapy) and, more recently, contemplative meditation[12] (a multi-component, group therapy).

Transcendental meditation (TM) is a standardized form of meditation where an individual repeats a mantra to move the mind towards a higher state of concentration; this in turn leads to a greater sense of relaxation and physiological calming[9]. Evidence indicates that single-component interventions like TM are efficacious in some conditions[13-18,18] including hypertension[19], with possible long term effects[16]. The blood pressure lowering effect of TM has been further supported by two meta-analyses, each suggesting TM can reduce both systolic and diastolic blood pressure[20,21]. However, other meta-analyses have suggested that the available clinical trials had significant "methodological weaknesses and [were] potentially biased by the affiliation of authors to the TM organization"[9]; thus, one must proceed with caution when evaluating if TM has a cumulative positive effect on lowering blood pressure[9]. Cognitive behavioral therapy (CBT) teaches subjects to be aware of stressors and to re-evaluate negative life events[22]. In a carefully controlled trial, Linden et al demonstrated that CBT decreased blood pressure in unmedicated hypertensive participants[23]. While CBT, a multi-component individualized therapy, has demonstrated efficacy in treating hypertension the cost of administering this one-on-one therapy presents a significant barrier to its widespread use. Contemplative meditation has demonstrated promising results however limited research on the topic indicates that more work must be done before final conclusions can be drawn[12].

Mindfulness Based Stress Reduction (MBSR), like CBT, is a multi-component therapy that encourages participants to modify their thought pattern through changing their relationship and approach to stressors in their lives[24]. However, unlike CBT, MBSR is a standardized group therapy which can be delivered to a heterogeneous population. It is now available for

stress reduction through some community and hospital alternative medicine programs and in Ontario it is covered in part by the Ontario Health Insurance Plan. While CBT can be viewed as an acute treatment option, MBSR works as both an acute and preventative treatment as it provides participants with strategies for working with the challenges and stressors in their lives[25]. MBSR teaches participants to use mindfulness as an approach to adapt to stress, pain and illness. In both clinical and non-clinical populations, MBSR and related mindfulness based therapeutic practices have demonstrated benefits for: chronic pain[26-29], anxiety[30-34], depression[30,33-37], fibromyalgia[38-40], binge-eating[41] and psoriasis[42], as well as improved psychological wellbeing, immune function and cortisol levels of cancer subjects[43-54], psychological well-being of cancer patient's partners[55] and glycemic control in diabetic populations[56]. Three meta-analyses[57-59] support the efficacy of MBSR for improving both physical and mental well-being in groups of subjects with mixed medical illness. By bringing mindfulness to life stressors MBSR participants may more clearly see the full context of a situation, have access to a broader range of emotional responses and therefore cope with stressful situations more effectively[32].

Preliminary information suggests that participating in an MBSR program also lowers blood pressure[23,43,56] and improves certain components of cardiovascular functioning[60]. Barnes et al initiated one of the earliest studies investigating MBSR and blood pressure; compared to control, those who participated in a two month meditation intervention based on MBSR techniques demonstrated lower systolic blood pressure as measured by an automated device: -4 mmHg (intervention) compared to +2 mmHg (control)[61]. A follow-up study using ambulatory blood pressure monitoring (ABPM) also found significant differences in blood pressure reduction for the meditation group at specific time periods (e.g. after school)[62]. In an

abstract, Van Wielingen reported that breast cancer patients who participated in MBSR had lower automated home blood pressure compared to those on wait list control[63]. Examining the treatment group alone, those with higher blood pressure at baseline demonstrated a greater decrease in systolic blood pressure compared to those with lower systolic blood pressure at baseline[63]. A similar treatment effect was described by Linden in subjects also starting with higher blood pressure levels[64]. Two studies by Carlson et al demonstrated high rates of MBSR class attendance, compliance and home meditation[44,45], with the follow-up study reporting consistent drops in clinic blood pressure persisting up to one year[43]. A randomized controlled trial of an abbreviated 6 week program using MBSR principles for pain tolerance in normotensive university students found improved pain tolerance and lower diastolic blood pressure in both the treatment and control groups[65]. These early studies point towards a blood pressure lowering effect from MBSR. However, more rigorous methodology and larger sample sizes are required to demonstrate whether MBSR can truly lower blood pressure.

Before a large outcome study can evaluate the use of MBSR for the treatment of hypertension, it is necessary to collect data documenting efficacy and treatment effect. The HARMONY study, a randomized controlled pilot trial investigating the use MBSR for unmedicated stage 1 hypertension, will test whether MBSR can significantly lower blood pressure in unmedicated hypertensives. If found effective, the HARMONY study will provide evidence to support a larger randomized controlled trial by evaluating the feasibility and safety of MBSR as a complementary or alternative treatment for hypertension.

METHODS

Study Design

The HARMONY study is a randomized, prospective, two-armed, wait-list controlled pilot trial. The intervention is a standard 8 week MBSR program. A wait-list controlled trial design was chosen in order to model our methodology after Linden[23]. The main outcome measure is mean awake and 24 hour systolic and diastolic ambulatory blood pressure. The study population consists of unmedicated men and women with stage 1 hypertension. Based on the power analysis the established recruitment goal was one hundred subjects. Screening baseline ambulatory blood pressure monitoring determines hypertensive eligibility. Screening and follow-up visits take place at Sunnybrook Health Sciences Centre, Toronto Ontario. All MBSR therapy is conducted at the University Health Network's Toronto General Hospital, Toronto Ontario.

Study Participants

Eligible participants include adults aged 20 to 75 years old with mean awake systolic or diastolic ambulatory blood pressure equal to or greater than 135 mmHg or 85 mmHg, or mean 24 hour ambulatory blood pressure equal to or greater than 130 mmHg or 80 mmHg. There must be no antihypertensive use within six months of the screening/baseline ABPM visit. We recognize the possibility that an individual may choose to go off antihypertensive therapy when they should not, and may potentially base this decision on wanting to be in the HARMONY Study. In these events, screening with the BPTru and ABPM should capture those individuals whose blood pressure is too high and who should be on active antihypertensive therapy. In a situation where screening blood pressure is too high, individuals are counselled one-on-one with the primary investigator, Dr Sheldon Tobe, about their blood pressure, antihypertensive therapy and why they could not be in the study. Using this methodology we hope to only recruit those who have moderately elevated blood pressure (Stage 1) and do not require anti-hypertensive therapy at the time of enrollment.

Study participants consist of those who meet the screening criteria, are willing and able to participate in the MBSR program, can attend all necessary study visits and complete all safety blood pressure evaluations. Further details regarding inclusion and exclusion criteria can be found in Table 1.

Table 1: Study inclusion and exclusion criteria.

Inclusion criteria:
1. Age 20 to 75 years. 2. Hypertensive as determined by ABPM at baseline (daytime ≥ 135/85 mmHg or 24-hour ABPM ≥ 130/80 mmHg). 3. Willing and able to participate in the MBSR program. 4. Willing to be followed for safety BP checks during the primary outcome period. 5. Willing to accept a possible waiting period of 12-weeks for MBSR. 6. Written informed consent. 7. Able to participate in mindfulness meditation program following screening ABPM.
Exclusion criteria:
1. Use of antihypertensive within 6 months of the screening ABPM. 2. Screening office BP > 180/100 mmHg and ABPM ≥ 160/100 mmHg. 3. Diabetes. 4. Secondary hypertension. 5. Renal disease (GFR < 60 ml/min or overt nephropathy). 6. History of heart attack. 7. Stroke or TIA or

8. Re-vascularization procedure.
9. Active malignant disease (except non-melanoma skin cancer).
10. Epileptic seizure 6 months before the screening visit.
11. Congestive heart failure.
12. Severe liver disease.
13. Pregnancy or lactation period.
14. Participation in a clinical trail or receipt of investigational compound or treatment in the 3 months prior to the initial screening visit.
15. Planned elective surgery during the study period except for cataract surgery.
16. Inability or unwillingness to perform 3 ABPM over 6 months.

Study Recruitment

The original planned recruitment rate was 25 subjects every 6 months for a total of 100 subjects. Potential participants have been identified through the clinical practices and referral bases of Dr's Abramson, Myers and Tobe. Additional successful screening strategies have included public information sessions, advertisements in local news papers and hospital posters. Screening is performed using a validated automated blood pressure device, the BpTRU (VSM MedTech Ltd Coquitlam, Canada). Individuals with unmedicated office blood pressure $\geq$ 135/85 mmHg are invited to the next step of screening using 24 hour ABPM.

Randomization and Study Blinding

Randomization to one of two study arms is done by sealed envelope method using the permuted block design, with blocks of 2 and 4 subjects to maintain the adequacy of randomization. A computer program generated a random number sequence which was used to

allocate subjects to the treatment or wait-list control group. The randomization schedule and sealed envelopes were prepared by an individual who worked closely with the Centre for Statistical Design and Analysis and was not directly involved in the study. Blinding is not possible for HARMONY study due to the wait-list control design of the study. However, those teaching the MBSR course are not informed which arm subjects are randomized to.

Upon review of the screening ABPM results, consenting subjects who meet study inclusion criteria are randomized. Screening ABP is then used as the baseline ABP for those enrolled in the study. Subjects are randomized to either 'early' or 'delayed'. Those randomized to 'early' begin MBSR within 4 weeks of their screening/baseline visit and repeat ABPM 12 weeks after the baseline/screening visit (coinciding with completion of the MBSR course). Those randomized to "delayed" are wait-listed for 12 weeks, repeat ABPM after that wait list period and subsequently begin MBSR within 4 weeks of that ABPM (Figure 1).

Primary Outcome

The primary outcome measure is mean awake and 24 hour ambulatory blood pressure (ABP). The primary objective of the HARMONY study is to compare mean awake and 24 hour ABP between the treatment and control arms at the 12 week post-baseline primary assessment period (Figure 1)

Secondary Outcomes

Secondary outcomes include evaluating a within-group effect of MBSR on ABP from pre- to post- MBSR intervention. Persistence of effect 12 weeks after completing the therapy will also be investigated (Figure 1). Between and within-group comparisons of the effect of MBSR on nighttime ABP will also be assessed. The proportion of subjects achieving blood pressure targets (24 hour ABP < 130/80, daytime ABP < 135/85 mmHg), those requiring the initiation of

medical therapy during the study and adverse events will also be examined. The amount of MBSR practiced outside the classroom will be analyzed (via participant diaries and homework logs) with respect to change in blood pressure to evaluate any dose-response interactions. Associations between the effect of MBSR on ABP and individual participant characteristics will also be explored. This will be achieved by examining covariates and incorporating them into a model with blood pressure. See Table 2 for further details regarding data collected at study visits.

Table 2. Baseline and ongoing data collection. All listed measurements were collected baseline. Measurements 1-5 are repeated at subsequent study visits (before MBSR, following MBSR and at the 12-week study close-out).

1. Ambulatory blood pressure monitoring (ABPM):
▪ Participants wear an ambulatory blood pressure monitor (model 90207, Spacelabs Medical Inc., Redmond, WA). ▪ Blood pressure is recorded every 15 minutes during a typical day and every 30 minutes between 11 pm and 7 am. ▪ Mean values calculated for systolic and diastolic blood pressure
2. Anthropometric measurements:
▪ Body weight and height measured to calculate Body Mass Index. ▪ Waist circumference measured at the top of the iliac crest.
3. Office blood pressure:
▪ Seated office systolic and diastolic blood pressure measured by BpTRU (VSM MedTech Ltd., Vancouver, BC, Canada). ▪ Device takes 6 measurements every 2 minutes. Last 5 measurements are averaged

to determine the average seated blood pressure.
4. Fasting serum samples:
▪ Plasma glucose, HbA1c, total cholesterol, HDL- cholesterol, LDL-cholesterol, triglycerides, creatinine, electrolytes and liver enzyme levels.
5. Urine samples:
▪ Urine creatinine levels and microalbuminuria levels.
6. Electrocardiogram (ECG)
▪ ECG to detect any abnormal heart rhythms and left ventricular hypertrophy.

The following questionnaires were included in the study protocol to account for external confounders: 1) Demographics and Lifestyle Questionnaire, 2) State-Trait Anger Expression Inventory-2[66], 3) Hospital Anxiety and Depression Scale[67], 4) Perceived Stress Scale[68], 5) Psychosocial Stress Questionnaire[69], 6) Exercise questionnaire, 7) Job Content Questionnaire[70], 8) Five-Facet Mindfulness Questionnaire[71], 9) Clinical Outcome Routine Evaluation Outcome Measure[72], 10) Toronto Mindfulness Scale[73]. All questionnaires are administered at baseline with questionnaires 2, 4, 5, and 6 repeated at each study visit (ie. Pre MBSR, post MBSR, and study close out). The Toronto Mindfulness Scale is administered after a period of meditation during the 2nd and 7th MBSR class. Planned future analyses include evaluating the relationships between blood pressure, gender and responses from the questionnaires.

Intervention

Mindfulness Based Stress Reduction (MBSR) is a multi-component group therapy that provides systematic training in mindfulness meditation as a self-regulation approach to stress

reduction and emotion management. MBSR provides training in formal meditation approaches with the primary goal of cultivating psychological resilience and resistance to stress. This is achieved through fostering the quality of "mindfulness", defined as the capacity to intentionally be in the present moment without judgment[24]. MBSR teaches attendees to approach stressful situations "mindfully"; allowing them to identify what is occurring in their bodies and minds and to step back from thoughts and feelings during stressful situations. This affords participants the opportunity to make wise choices with respect to managing stressful situations, such as choosing to avoid engaging in anxious worry that may otherwise escalate into a cycle of stress reactivity and contribute to more emotional distress[24,74-76].

The standard MBSR program is delivered by trained therapists to groups of 25 - 30 individuals and consists of 10 sessions: an introductory session, eight weekly sessions of 2.5 hours, and a 6 hour intensive session/silent retreat held between week six and seven of the course on a Saturday or Sunday. The MBSR program incorporates four major therapeutic elements: formal meditation, informal mindfulness practice (such as bringing mindfulness to daily activities), psycho-educational activities, and self monitoring / reflection exercises. Each session also includes group discussion. The development of mindfulness depends heavily upon regular and repeated practice; thus participants commit to daily 45 minute homework meditation practice. Homework includes both formal and informal meditation practices, as well as self-observation questions. CDs are included to guide attendees in daily formal meditation practice.

Participants learn new mindfulness practices each week, as well as strategies to incorporate mindfulness perspectives and approaches into daily activities. Some examples of mindfulness practices include the body scan, sitting meditation, mindful yoga, mindful walking, mindful eating and loving kindness meditation. Participants are asked to complete a weekly

homework log which tracks the number of minutes spent on formal meditation practice and whether informal mindfulness was practiced that day. Subjects are given new homework logs each week when they return for class. Both adherence to MBSR and class attendance is captured via the homework logs. Homework logs are faxed weekly from Toronto General Hospital to Sunnybrook Health Sciences Centre where they are entered into the electronic database. HARMONY research staff are asked to contact participants if more than two classes are missed without explanation; this also affords study staff and participants an opportunity to discuss causes for poor class attendance. As the MBSR program is standardized, subjects can be accommodated in other MBSR classes throughout the course if necessary for scheduling. If too many classes are missed due to unforeseen personal circumstances (and not due to lack of commitment/interest by the study subject) then attempts are made to accommodate them to another MBSR course if possible

Data Collection

Study subject information is organized into individual subject charts and uploaded electronically into a Microsoft Access Database file. All data of enrolled participants is collected on denominated data collection forms, with the Contact Information page and homework logs being the only exceptions. Data from potential study participants/screen fail participants are kept in a screening log binder and a screen fail binder respectively. Coding of enrolled study participants is done by study ID, executed in sequential in order (first participant = study ID 001). Data entry is completed by a research assistant; future plans include auditing all study charts and the study database at the end of the trial to ensure data was entered accurately. All study data is maintained in a secure location only accessible to study related personnel; this includes lab computers which are accessible only through authentication with ID and password.

Study data is only shared with family physicians or the Nephrology Research group at Sunnybrook Health Sciences Center with the participant's consent. All source information collected is retained under the primary investigator (Dr Sheldon Tobe) as custodian. After all data entry/data auditing is completed, paper copies of study data will be stored at Iron Mountain and destroyed after 25 years as per Health Canada guidelines. Electronic study data will be kept in the Microsoft Access Database until data analysis is completed. Maintenance of study data and study confidentiality is done in full conformance with requirements from the Sunnybrook Research Ethics Board, the University Health Network Research Ethics Board and Health Canada. **Safety**

Lifestyle therapy is indicated for people who have stage 1 hypertension (140-159/90-99 mmHg) with no underlying risk factors[1]. Linden has previously demonstrated the role and safety of the wait-list control methodology and determined it to be appropriate in studies with stage 1 and 2 hypertensives (140-179/90-109 mmHg)[23,64]. In accordance with the Canadian standard of care for blood pressure management, all participants receive standard recommendations of suggested lifestyle modifications for blood pressure management at study entry.

With participant consent, primary care physician(s) are informed of their patient's participation in the study. Physicians are asked to delay the start of their patient's antihypertensive therapy until after they have completed the study. If physicians believe that antihypertensive should be initiated, they are asked to communicate their decision to study staff before doing so. A letter updating their patient's progress, along with laboratory and ABPM results are sent to the primary care physician after each study visit.

Automated office blood pressure safety assessments are included to closely monitor subjects' blood pressure. The primary investigator is notified if subjects exceed blood pressure safety limits. If any of the following conditions are discovered during study enrollment participants are withdrawn and treated: 1) increases in ambulatory blood pressure of 20/10 mmHg or greater, 2) accelerated hypertension with an office reading of 160/100 mmHg or greater, 3) macrovascular target organ damage, 4) diabetes mellitus or 5) chronic kidney disease (GFR<60 ml/min). Any subject started on antihypertensive therapy during the study remains in the study and the initiation of medical therapy is recorded.

Sample Size Considerations

The main objective of this study is to assess the difference in mean awake and 24 hour systolic and diastolic ambulatory blood pressure 12 weeks post baseline between the treatment and wait-list control arm. The following calculations/analyses are based on Linden's work and the difference in mean systolic blood pressure between treatment groups measured as by ABPM. Linden found a 6.1 mmHg systolic blood pressure drop from baseline to the end of the primary assessment period for participants in the immediate intervention group; the wait-list control group showed a 0.9 mmHg increase in the same time interval[23] This resulted in a 7.0 mmHg difference between the two groups[23], a relatively large treatment effect, due in part to the use of subjects with higher blood pressure.

Unlike Linden who found blood pressure rising in the control group, more recent results from the Double Exposure study found that blood pressure tended to fall over time, even in unmedicated hypertensives. This may have been due in part to an adoption of lifestyle changes[77,78]. Baseline data from the unmedicated hypertensive cohort in the Double Exposure study demonstrated mean awake ABP equal to 137/85 ± 8/5 mmHg. After one year, mean awake

ABP had fallen to 133/83 ± 8/7 mmHg. Based on these results, it is reasonable to assume that blood pressure will fall in the HARMONY wait-list control arm.

Very conservative assumptions were made for the HARMONY power analysis. A reduction of 2.0 mmHg for mean systolic ambulatory blood pressure (half the change observed in the Double Exposure study) was assumed for the control group (compared to the rise that Linden found[23]). The variance recorded in Linden's study (9 mmHg) was used for the HARMONY power analysis; variance higher than that recorded in the Double Exposure cohort (8 mmHg in only 35 subjects). Linden found a blood pressure difference of 7.0 mmHg between the treatment and control group. In our power analysis, the difference between treatment and control groups was reduced from Linden's result to a more conservative value, 6mmHg. This value was chosen for two reasons: 1) It was closer to findings from Dickinson's meta-analysis[11]and 2) Participants' overall blood pressure is anticipated to be lower in the HARMONY study (stage 1 hypertensives) compared to Linden's study (stage 1 and stage 2 hypertensives)[23]. Using a two-tailed two-sample t-test, an estimated group standard deviation of 9.0 mmHg and a significance level of 0.05 it was determined that a sample size of 37 subjects in each group would provide sufficient power (81%) to detect a systolic blood pressure difference of 6.0 mmHg between the null hypothesis (both groups start with equal means and have an equal a drop in systolic blood pressure of 8.0 mmHg) and the alternative hypothesis (control group systolic blood pressure will fall by only 2.0 mmHg). To account for potential drop-outs and subjects lost to analysis (25% lost in Linden's study[23]), the number of subjects was increased to 50 subjects per group (Figure 2).

Statistical Analysis

The primary outcome will be examined using an intent-to-treat analysis. An intent-to-treat population is defined as all subjects in the study who completed at least one session of MBSR. The primary outcome measure is mean awake and 24 hour systolic and diastolic ambulatory blood pressure. Ambulatory blood pressure between treatment and control will be compared by two-tailed two-sample t-test at the end of the 12 week primary outcome period. Within subject analysis of the effect of MBSR on ambulatory blood pressure will be performed by a paired t-test. Persistence of effect of MBSR on blood pressure will be assessed using repeated ANOVA measures, comparing group differences between subsequent study visits (baseline, pre MBSR, post MBSR, and study close out). The proportion of subjects achieving blood pressure targets will be analyzed using chi-squared tests. Multiple regression analyses will be employed to assess differences in blood pressure between subjects while adjusting for covariates. Subjects may be started on antihypertensive therapy during the study. If this leads to imbalance between the study arms, a per-protocol analysis may be performed to take this variable into account. All analyses will be carried out using SAS version 9.1 (SAS Institute, Cary North Carolina, USA).

Ethical Considerations

This research project is approved by the Research Ethics Board at Sunnybrook Research Institute (Toronto, Canada) and the University Health Network Research Ethics Board (Toronto, Canada). Planned data analyses are in full conformance with the principles of the "*Declaration of Helsinki*"[79]. Conduct of the HARMONY study is fully adherent to the principles outlined in the "*Guideline for Good Clinical Practice*" ICH Tripartite Guideline [January 1997][80] and in the 2nd edition of Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans[81].

Dissemination Plans

Data collection will be completed by early spring 2012. Primary and secondary analysis will commence immediately after data monitoring is completed; publications will be prepared for submission in summer 2012. Study findings are also planned to be presented at the following conferences: October 2012: Hypertension Canada, May 2013: American Society of Hypertension, June 2013: European Society of Hypertension, September 2013: International Society of Hypertension.

Authors' Contributions

ST and BB conceptualized the study and MD, MM, SA, BA, NP and JI assisted with the study design. KB, MH and MD collected data which was overseen by NP. KB and MH cleaned the collected data, preformed interim analyses and interpreted interim results. ST is the guarantor. KB, MD, MH, and ST wrote and revised the article, as well as designed figures. NP, BB, MM, SA, BA and JI critically revised the draft for important intellectual content. All authors approved this final version to be published.

Funding Statement

This work was supported by Heart and Stroke Foundation of Ontario (#NA 6349). The Heart & Stroke Foundation of Ontario played no role in the study design, data collection, analysis and interpretation of data, writing of the article or the decision to submit it for publication.

Competing Interests Statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with

any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

REFERENCES

1 Rabi DM, Daskalopoulou SS, Padwal RS, et al. *The 2011 Canadian Hypertension Education Program Recommendations for the Management of Hypertension: Blood Pressure Measurement, Diagnosis, Assessment of Risk, and Therapy.* Can J Cardiol 2011;**27**:415-433.

2 Chockalingam A, Campbell NR, Fodor JG. *Worldwide epidemic of hypertension.* Can J Cardiol 2006;**22**:553-555.

3 Vasan RS, Larson MG, Leip EP, et al. *Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study.* Lancet 2001;**358**:1682-1686.

4 Julius S, Nesbitt S, Egan B, et al. *Feasibility of treating prehypertension with an angiotensin-receptor blocker.* N Engl J Med 2006;**354**:1685-1697.

5World Health Organization. Preventing chronic diseases: a vital investment. Available at: www.who.int/chp/chronic_disease_report/contents/en/index.html. Accessed 04/27, 2007.

6 Stamler J, Rose G, Stamler R, et al. *INTERSALT study findings. Public health and medical care implications.* Hypertension 1989;**14**:570-577.

7 Appel LJ. *Lifestyle modification as a means to prevent and treat high blood pressure.* Journal of the American Society of Nephrology 2003;**14**:S99-S102.

8 O'Donnell MJ, Xavier D, Liu L, et al. *Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study.* Lancet 2010;**376**:112-123.

9 Canter PH, Ernst E. *Insufficient evidence to conclude whether or not Transcendental Meditation decreases blood pressure: results of a systematic review of randomized clinical trials.* J Hypertens 2004;**22**:2049-2054.

10 Parati G, Steptoe A. *Stress reduction and blood pressure control in hypertension: a role for transcendental meditation?* J Hypertens 2004;**22**:2057-2060.

11 Dickinson HO, Mason JM, Nicolson DJ, et al. *Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials.* J Hypertens 2006;**24**:215-233.

12 Manikonda JP, Stork S, Togel S, et al. *Contemplative meditation reduces ambulatory blood pressure and stress-induced hypertension: a randomized pilot trial.* J Hum Hypertens 2008;**22**:138-140.

13 Wenneberg SR, Schneider RH, Walton KG, et al. *A controlled study of the effects of the Transcendental Meditation program on cardiovascular reactivity and ambulatory blood pressure.* Int J Neurosci 1997;**89**:15-28.

14 Castillo-Richmond A, Schneider RH, Alexander CN, et al. *Effects of stress reduction on carotid atherosclerosis in hypertensive African Americans.* Stroke 2000;**31**:568-573.

15 Schneider RH, Staggers F, Alxander CN, et al. *A randomised controlled trial of stress reduction for hypertension in older African Americans.* Hypertension 1995;**26**:820-827.

16 Schneider RH, Alexander CN, Staggers F, et al. *Long-term effects of stress reduction on mortality in persons > or = 55 years of age with systemic hypertension.* Am J Cardiol 2005;**95**:1060-1064.

17 Paul-Labrador M, Polk D, Dwyer JH, et al. *Effects of a randomized controlled trial of transcendental meditation on components of the metabolic syndrome in subjects with coronary heart disease.* Arch Intern Med 2006;**166**:1218-1224.

18 Schneider RH, Alexander CN, Staggers F, et al. *A randomized controlled trial of stress reduction in African Americans treated for hypertension for over one year.* American Journal of Hypertension 2005;**18**:88-98.

19 Nidich SI, Rainforth MV, Haaga DA, et al. *A randomized controlled trial on effects of the Transcendental Meditation program on blood pressure, psychological distress, and coping in young adults.* American Journal of Hypertension 2009;**22**:1326-1331.

20 Anderson JW, Liu C, Kryscio RJ. *Blood pressure response to transcendental meditation: a meta-analysis.* American Journal of Hypertension 2008;**21**:310-316.

21 Rainforth MV, Schneider RH, Nidich SI, et al. *Stress reduction programs in patients with elevated blood pressure: a systematic review and meta-analysis.* Curr Hypertens Rep 2007;**9**:520-528.

22 Beck AT. *The current state of cognitive therapy: a 40-year retrospective.* Arch Gen Psychiatry 2005;**62**:953-959.

23 Linden W, Lenz JW, Con AH. *Individualized stress management for primary hypertension: a randomized trial.* Arch Intern Med 2001;**161**:1071-1080.

24Kabat-Zinn J. Full catastrophe living: using the wisdom of your body and mind to face stress, pain and illness. New York: Delta 1990:.

25 Praissman S. *Mindfulness-based stress reduction: a literature review and clinician's guide.* J Am Acad Nurse Pract 2008;**20**:212-216.

26 Plews-Ogan M, Owens JE, Goodman M, et al. *A pilot study evaluating mindfulness-based stress reduction and massage for the management of chronic pain.* Journal of General Internal Medicine 2005;**20**:1136-1138.

27 Morone NE, Greco CM, Weiner DK. *Mindfulness meditation for the treatment of chronic low back pain in older adults: a randomized controlled pilot study.* Pain 2008;**134**:310-319.

28 Esmer G, Blum J, Rulf J, et al. *Mindfulness-based stress reduction for failed back surgery syndrome: a randomized controlled trial.* J Am Osteopath Assoc 2010;**110**:646-652.

29 Rosenzweig S, Greeson JM, Reibel DK, et al. *Mindfulness-based stress reduction for chronic pain conditions: variation in treatment outcomes and role of home meditation practice.* J Psychosom Res 2010;**68**:29-36.

30 Shapiro SL, Schwartz GE, Bonner G. *Effects of mindfulness-based stress reduction on medical and premedical students.* J Behav Med 1998;**21**:581-599.

31 Astin JA. *Stress reduction through mindfulness meditation. Effects on psychological symptomatology, sense of control, and spiritual experiences.* Psychotherapy & Psychosomatics 1997;**66**:97-106.

32 Kabat-Zinn J, Massion AO, Kristeller J, et al. *Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders.* Am J Psychiatry 1992;**149**:936-943.

33 Vieten C, Astin J. *Effects of a mindfulness-based intervention during pregnancy on prenatal stress and mood: results of a pilot study.* Archives of Women's Mental Health 2008;**11**:67-74.

34 Vollestad J, Sivertsen B, Nielsen GH. *Mindfulness-based stress reduction for patients with anxiety disorders: evaluation in a randomized controlled trial.* Behaviour Research & Therapy 2011;**49**:281-288.

35 Barnhofer T, Duggan D, Crane C, et al. *Effects of meditation on frontal alpha-asymmetry in previously suicidal individuals.* Neuroreport 2007;**18**:709-712.

36 Kenny MA, Williams JM. *Treatment-resistant depressed patients show a good response to Mindfulness-based Cognitive Therapy.* Behaviour Research & Therapy 2007;**45**:617-625.

37 Kingston J, Chadwick P, Meron D, et al. *A pilot randomized control trial investigating the effect of mindfulness practice on pain tolerance, psychological well-being, and physiological activity.* J Psychosom Res 2007;**62**:297-300.

38 Grossman P, Tiefenthaler-Gilmer U, Raysz A, et al. *Mindfulness training as an intervention for fibromyalgia: evidence of postintervention and 3-year follow-up benefits in well-being.* Psychotherapy & Psychosomatics 2007;**76**:226-233.

39 Sephton SE, Salmon P, Weissbecker I, et al. *Mindfulness meditation alleviates depressive symptoms in women with fibromyalgia: results of a randomized clinical trial.* Arthritis & Rheumatism 2007;**57**:77-85.

40 Schmidt S, Grossman P, Schwarzer B, et al. *Treating fibromyalgia with mindfulness-based stress reduction: results from a 3-armed randomized controlled trial.* Pain 2011;**152**:361-369.

41 Kristeller JL, Hallett CB. *An Exploratory Study of a Meditation-based Intervention for Binge Eating Disorder.* Journal of Health Psychology 1999;**4**:357-363.

42 Kabat-Zinn J, Wheeler E, Light T, et al. *Influence of a mindfulness meditation-based stress reduction intervention on rates of skin clearing in patients with moderate to severe psoriasis undergoing phototherapy (UVB) and photochemotherapy (PUVA).* Psychosom Med 1998;**60**:625-632.

43 Carlson LE, Speca M, Faris P, et al. *One year pre-post intervention follow-up of psychological, immune, endocrine and blood pressure outcomes of mindfulness-based stress reduction (MBSR) in breast and prostate cancer outpatients.* Brain, Behavior, & Immunity 2007;**21**:1038-1049.

44 Carlson LE, Speca M, Patel KD, et al. *Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress and levels of cortisol, dehydroepiandrosterone sulfate (DHEAS) and melatonin in breast and prostate cancer outpatients.* Psychoneuroendocrinology 2004;**29**:448-474.

45 Carlson LE, Speca M, Patel KD, et al. *Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress, and immune parameters in breast and prostate cancer outpatients.* Psychosom Med 2003;**65**:571-581.

46 Henderson VP, Clemow L, Massion AO, et al. *The effects of mindfulness-based stress reduction on psychosocial outcomes and quality of life in early-stage breast cancer patients: a randomized trial.* Breast Cancer Research & Treatment 2012;**131**:99-109.

47 Lengacher CA, Johnson-Mallard V, Barta M, et al. *Feasibility of a mindfulness-based stress reduction program for early-stage breast cancer survivors.* Journal of Holistic Nursing 2011;**29**:107-117.

48 Lengacher CA, Johnson-Mallard V, Post-White J, et al. *Randomized controlled trial of mindfulness-based stress reduction (MBSR) for survivors of breast cancer.* Psychooncology 2009;**18**:1261-1272.

49 Ledesma D, Kumano H. *Mindfulness-based stress reduction and cancer: a meta-analysis.* Psychooncology 2009;**18**:571-579.

50 Matchim Y, Armer JM, Stewart BR. *Mindfulness-based stress reduction among breast cancer survivors: a literature review and discussion.* Oncol Nurs Forum 2011;**38**:E61-71.

51 Matchim Y, Armer JM, Stewart BR. *Effects of mindfulness-based stress reduction (MBSR) on health among breast cancer survivors.* West J Nurs Res 2011;**33**:996-1016.

52 Matousek RH, Dobkin PL. *Weathering storms: a cohort study of how participation in a mindfulness-based stress reduction program benefits women after breast cancer treatment.* Current Oncology 2010;**17**:62-70.

53 Smith JE, Richardson J, Hoffman C, et al. *Mindfulness-Based Stress Reduction as supportive therapy in cancer care: systematic review.* J Adv Nurs 2005;**52**:315-327.

54 Witek-Janusek L, Albuquerque K, Chroniak KR, et al. *Effect of mindfulness based stress reduction on immune function, quality of life and coping in women newly diagnosed with early stage breast cancer.* Brain, Behavior, & Immunity 2008;**22**:969-981.

55 Birnie K, Garland SN, Carlson LE. *Psychological benefits for cancer patients and their partners participating in mindfulness-based stress reduction (MBSR).* Psychooncology 2010;**19**:1004-1009.

56 Rosenzweig S, Reibel DK, Greeson JM, et al. *Mindfulness-based stress reduction is associated with improved glycemic control in type 2 diabetes mellitus: a pilot study.* Alternative Therapies in Health & Medicine 2007;**13**:36-38.

57 Baer RA. *Mindfulness Training as a Clinical Intervention: A Conceptual and Empirical Review.* Clinical Psychology: Science and Practice 2003;**10**:125-143.

58 Grossman P, Niemann L, Schmidt S, et al. *Mindfulness-based stress reduction and health benefits. A meta-analysis.* J Psychosom Res 2004;**57**:35-43.

59 Bohlmeijer E, Prenger R, Taal E, et al. *The effects of mindfulness-based stress reduction therapy on mental health of adults with a chronic medical disease: a meta-analysis.* J Psychosom Res 2010;**68**:539-544.

60 Ditto B, Eclache M, Goldman N. *Short-term autonomic and cardiovascular effects of mindfulness body scan meditation.* Annals of Behavioral Medicine 2006;**32**:227-234.

61 Barnes VA, Treiber FA, Davis H. *Impact of Transcendental Meditation on cardiovascular function at rest and during acute stress in adolescents with high normal blood pressure.* J Psychosom Res 2001;**51**:597-605.

62 Barnes VA, Davis HC, Murzynowski JB, et al. *Impact of meditation on resting and ambulatory blood pressure and heart rate in youth.* Psychosom Med 2004;**66**:909-914.

63 LE Van Wielingen, LE Carlson and TS Campbell. *Mindfulness-based stress reduction (MBSR), blood pressure and psychological functioning in women with cancer.* [abstract]. Psychosom.Med. 2007;69:A43.

64 Linden W, Moseley JV. *The efficacy of behavioral treatments for hypertension.* Applied Psychophysiology & Biofeedback 2006;**31**:51-63.

65 Kingston T, Dooley B, Bates A, et al. *Mindfulness-based cognitive therapy for residual depressive symptoms.* Psychology & Psychotherapy: Theory, Research & Practice 2007;**80**:193-203.

66 Spielberger C, Jacobs G, Russel S, Crane R. Assessment of Anger: The State-Trait Anger Scale. In: Butcher J, Spielberger C, eds. Advances in Personality Assesment. Hillsdale, NJ: Lawrence Erlbaum Associates 1983:112-189.

67 Bjelland I, Dahl AA, Haug TT, et al. *The validity of the Hospital Anxiety and Depression Scale. An updated literature review.* J Psychosom Res 2002;**52**:69-77.

68 Cohen S, Kamarck T, Mermelstein R. *A global measure of perceived stress.* Journal of Health & Social Behavior 1983;**24**:385-396.

69 Rosengren A, Hawken S, Ounpuu S, et al. *Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study.* Lancet 2004;**364**:953-962.

70 Karasek R, Brisson C, Kawakami N, et al. *The Job Content Questionnaire (JCQ): an instrument for internationally comparative assessments of psychosocial job characteristics.* J Occup Health Psychol 1998;**3**:322-355.

71 Baer RA, Smith GT, Lykins E, et al. *Construct validity of the five facet mindfulness questionnaire in meditating and nonmeditating samples.* Assessment 2008;**15**:329-342.

72 Evans C, Connell J, Barkham M, et al. *Towards a standardised brief outcome measure: psychometric properties and utility of the CORE-OM.* British Journal of Psychiatry 2002;**180**:51-60.

73 Lau MA, Bishop SR, Segal ZV, et al. *The Toronto Mindfulness Scale: development and validation.* J Clin Psychol 2006;**62**:1445-1467.

74 Kabat-Zinn J, Lipworth L, Burney R. *The clinical use of mindfulness meditation for the self-regulation of chronic pain.* J Behav Med 1985;**8**:163-190.

75 Bishop SR. *What do we really know about mindfulness-based stress reduction?* Psychosom Med 2002;**64**:71-83.

76 Kabat-Zinn J. *An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results.* Gen Hosp Psychiatry 1982;**4**:33-47.

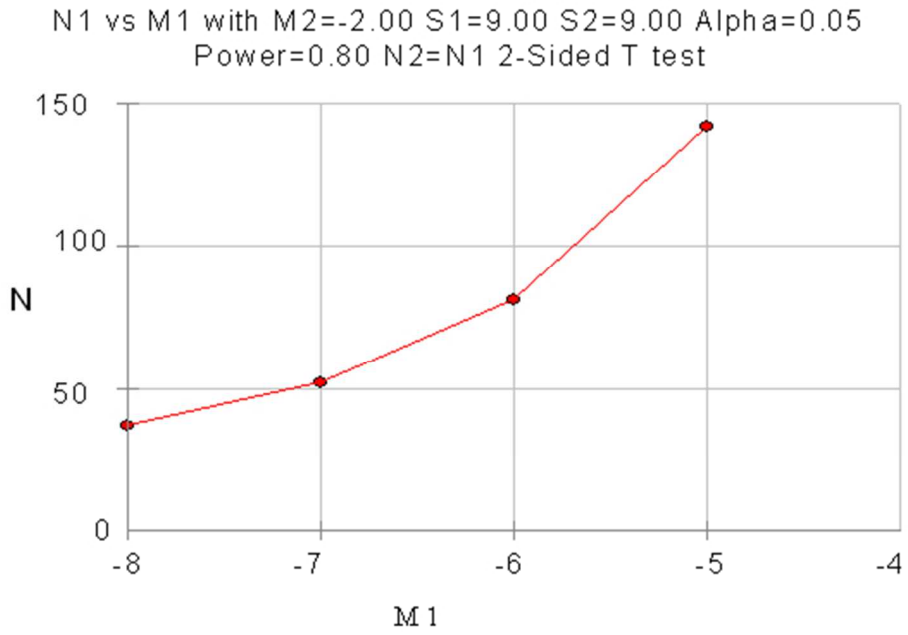
77 Baker B, Paquette M, Szalai JP, et al. *The influence of marital adjustment on 3-year left ventricular mass and ambulatory blood pressure in mild hypertension.* Arch Intern Med 2000;**160**:3453-3458.

78 Tobe SW, Kiss A, Sainsbury S, et al. *The impact of job strain and marital cohesion on ambulatory blood pressure during 1 year: the double exposure study.* American Journal of Hypertension 2007;**20**:148-153.

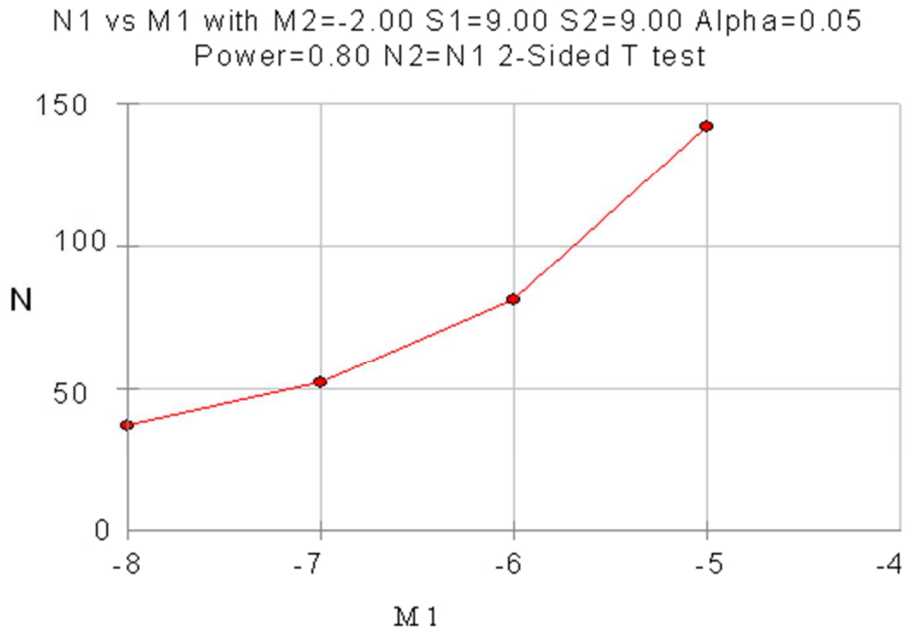
79World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. From the 59th World Medical Association Assembly, Seoul. 2008; Available at: http://www.wma.net/en/30publications/10policies/b3/17c.pdf. Accessed 12/29, 2011.

80Health Canada. International Conference on Harmonization (ICH) Guidance E6: Good Clinical Practice: Consolidated Guidelines. 1997; Available at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e6-eng.php. Accessed 12/29, 2011.

81Goverment of Canada: Panel of Research Ethics. 2nd Edition of Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. 2010; Available at: http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/. Accessed 12/29, 2011.



Power analysis graph illustrating necessary sample size.



Power analysis graph illustrating necessary sample size.

Hypertension Analysis of stress Reduction using Mindfulness meditatiON and Yoga (The HARMONY Study): study protocol of a randomized control trial. ~~[ClinicalTrials.gov Identifier: NCT00825526]~~

Corresponding Author: Kimberly Blom

Sunnybrook Health Sciences Centre

2075 Bayview Avenue, room A140

Toronto ON

M5N 3M5

Email: kimberly.blom@sunnybrook.ca

Telephone: 416 480 6100 x 6861

Fax: 416 480 5164

Co-Authors: How, M. (1), Dai, M. (2), Baker, B. (3), Irvine, J. (4), Abbey, S. (3~~5~~), Abramson, B.L. (5~~6~~), Myers, M. (1), Perkins, N. (1) and Tobe, S.W. (1).

Institutions and Affiliations:

(1). Sunnybrook Health Sciences Centre, Department of Medicine, Toronto Ontario, Canada.

(2). Queen's University, Department: N/A (current medical student), Kingston Ontario, Canada.

(3). University Health Network, Department of Psychiatry & University of Toronto, Department of Psychiatry, Toronto Ontario, Canada.

(4). York University, Department of Psychology, Toronto Ontario, Canada.

~~(5). University Health Network, Department of Medicine, Toronto Ontario, Canada.~~

(5~~6~~). St. Michael's Hospital, Department of Medicine, Toronto Ontario, Canada.

Key words: hypertension, blood pressure, ambulatory blood pressure monitoring, complementary medicine, meditation.

Word Count: 3,427

ABSTRACT

Introduction

Hypertension (HTN) is a leading risk factor for preventable cardiovascular disease with over 1 in 5 adults affected worldwide. Lifestyle modification is a key strategy for the prevention and treatment of HTN. Stress has been associated with greater cardiovascular risk and stress management is a recommended intervention for hypertensives. Stress reduction through relaxation therapies have been shown to have an effect on human physiology including lowering blood pressure (BP). However, individualized behavioural interventions are resource intensive and group stress management approaches have not been validated for reducing HTN. The HARMONY study is a pilot randomized controlled trial designed to determine if mindfulness based stress reduction (MBSR), a standardized group therapy, is an effective intervention for lowering BP in stage-1 unmedicated hypertensives.

Methods and Analysis

Men and women unmedicated for HTN with mean daytime ambulatory blood pressure (ABP) =/> 135/85 mmHg or 24 hour ABP =/>130/80 mmHg were included in the study. Subjects were randomized to receive MBSR immediately or after a wait-list control period. The primary outcome measure is mean awake and 24 hour ABP. The primary objective of the HARMONY study is to compare ABP between the treatment and wait-list control arm at the 12 week primary assessment period. Results from this study will determine if MBSR is an effective intervention for lowering BP in early unmedicated hypertensives.

Ethics and Dissemination

This research project was approved by the Sunnybrook Research Ethics Board and the University Health Network Research Ethics Board (Toronto, Canada). Planned analyses are in

Formatted: Font: Bold

Formatted: Font: Bold

Formatted: Font: Bold

Formatted: Font: Bold

full compliance with the principles of the Declaration of Helsinki. Data collection will be completed by early spring 2012. Primary and secondary analysis will commence immediately after data monitoring is completed; dissemination plans include preparing publications for submission during the summer of 2012.

Registration Details

This study is registered with clinicaltrials.gov (NCT00825526).

Formatted: Font: Bold

INTRODUCTION

Based on an annual consensus conference reviewing the world literature including the Cochrane Collaboration databases, the Canadian Hypertension Education Program recommends lifestyle modification as a key strategy for the prevention and treatment of hypertension[1]. Over 5 million Canadians, part of a worldwide epidemic, are hypertensive[2]. Data extrapolated from large population surveys and prospective studies[3,4] show that approximately 250,000 Canadians with high-normal blood pressure (SBP 120-139 or DBP 80-89 mmHg) will develop full-blown high blood pressure every year (BP $\geq$ 140/90 mmHg) – putting them at higher risk for heart attack and stroke, necessitating the use of medications in most of them. Preventing and controlling hypertension is one of the most cost effective strategies for reducing the global burden of premature cardiovascular disease and death[5]. Reducing systolic blood pressure by just 3 mmHg in the general population has the potential to reduce stroke mortality by 8% and coronary artery disease mortality by 5%[6,7]. The published findings of the *InterStroke* study, one of the largest studies of its type in the world, concluded definitively that uncontrolled hypertension is the single most influential risk factor for stroke[8].

Stress has been associated with greater cardiovascular risk and consideration of stress management is a recommended intervention for hypertensives[1]. However, specific stress management approaches are not well validated for reducing hypertension[9-11]. Stress management therapies can be differentiated based on their approach and delivery: single- or multi-component approach and individualized or group delivery. Certain therapeutic approaches have been efficacious for reducing blood pressure in hypertensive subjects: transcendental meditation (a single-component, individualized therapy), cognitive behavioral therapy (a multi-

component, individualized therapy) and, more recently, contemplative meditation[12] (a multi-component, group therapy).

Transcendental meditation (TM) is a standardized form of meditation where an individual repeats a mantra to move the mind towards a ~~state of greater~~ higher state of concentration; this in turn leads to a greater sense of relaxation and ~~bliss~~physiological calming[9]. Evidence indicates that single-component interventions like TM are efficacious in some conditions[13-18,18,18] including hypertension[19], with possible long term effects[16]. The blood pressure lowering effect of TM has been further supported by two meta-analyses, each suggesting TM can reduce both systolic and diastolic blood pressure[20,21]. However, other meta-analyses have suggested that the available clinical trials had significant "methodological weaknesses and [were] potentially biased by the affiliation of authors to the TM organization"[9]; thus, one must proceed with caution when evaluating if TM has a cumulative positive effect on lowering blood pressure[9]. Cognitive behavioral therapy (CBT) teaches subjects to be aware of stressors~~,~~ and to re-evaluate negative life events ~~and to decrease sympathetic arousal~~[22]. In a carefully controlled trial, Linden et al demonstrated that CBT decreased blood pressure in unmedicated hypertensive participants[23]. While CBT, a multi-component individualized therapy, has demonstrated efficacy in treating hypertension the cost of administering this one-on-one therapy presents a significant barrier to its widespread use. Contemplative meditation has demonstrated promising results however ~~the~~ limited research on the topic indicates that more work must be done before final conclusions can be drawn[12].

Mindfulness Based Stress Reduction (MBSR), like CBT, is a multi-component therapy that encourages participants to ~~achieve results by changing~~modify their thought pattern~~s, more specifically how to~~through changing their relationship and approach to stressors in their

lives[24]. However, unlike CBT, MBSR is a standardized group therapy which can be delivered to a heterogeneous population. It is now available for stress reduction through some community and hospital alternative medicine programs and in Ontario it is covered in part by the Ontario Health Insurance Plan. While CBT can be viewed as an acute treatment option, MBSR works as both an acute and preventative treatment as it provides participants with ~~a new method of thinking and functioning~~ strategies for working with the challenges and stressors in their lives[25]. MBSR teaches participants to use mindfulness ~~meditation~~ as an approach ~~strategy~~ to adapt to stress, pain and illness. In both clinical and non-clinical populations, MBSR and related mindfulness based therapeutic practices have ~~MBSR has~~ demonstrated benefits for: chronic pain[26-29], anxiety[30-34], depression[30,33-37], fibromyalgia[38-40], binge-eating[41]~~,~~ and psoriasis[42], as well as improved psychological wellbeing, immune function and cortisol levels of~~in~~ cancer subjects[43-54], psychological well-being of cancer patient's partners[55] and glycemic control in diabetic populations[56]. Three meta-analyses[57-59] support the efficacy of MBSR for improving both physical and mental well-being in groups of subjects with mixed medical illness. ~~Through its cognitive restructuring format, MBSR improves participants' resistance to stress.~~ By bringing mindfulness to life stressors~~,~~ MBSR participants may more clearly see the full context of a situation, ~~It changes the participant's cognitive appraisals~~have access to a broader range of emotional responses and therefore ~~, reduces anxiety and enables the participant to~~ cope with ~~future~~ stressful situations more effectively[32].

Preliminary information suggests that participating in an MBSR program also lowers blood pressure[23,43,56] and improves certain components of cardiovascular functioning[60]. Barnes et al initiated one of the earliest studies investigating MBSR and blood pressure; compared to control, those who participated in a two month meditation intervention based on

MBSR techniques demonstrated lower systolic blood pressure as measured by an automated device: -4 mmHg (intervention) compared to +2 mmHg (control)[61]. A follow-up study using ambulatory blood pressure monitoring (ABPM) also found significant differences in blood pressure reduction for the meditation group at specific time periods (e.g. after school)[62]. In an abstract, Van Wielingen reported that breast cancer patients who participated in MBSR had lower automated home blood pressure compared to those on wait list control[63]. Examining the treatment group alone, those with higher blood pressure at baseline demonstrated a greater decrease in systolic blood pressure compared to those with lower systolic blood pressure at baseline[63]. A similar treatment effect was described by Linden in subjects also starting with higher blood pressure levels[64]. Two studies by Carlson et al demonstrated ~~-~~high rates of MBSR class attendance, compliance and home meditation[44,45], with the follow-up study reporting consistent drops in clinic blood pressure persisting up to one year[43]. A randomized controlled trial of an abbreviated 6 week program using MBSR principles for pain tolerance in normotensive university students found improved pain tolerance and lower diastolic blood pressure in both the treatment and control groups[65]. These early studies point towards a blood pressure lowering effect from MBSR. However, more rigorous methodology and larger sample sizes are required to demonstrate whether MBSR can truly lower blood pressure.

Before a large outcome study can evaluate the use of ~~of~~ MBSR for the treatment of hypertension~~, can be conducted,~~ it is necessary to collect data documenting efficacy and treatment effect. The HARMONY study, a randomized controlled pilot trial investigating the use MBSR for unmedicated stage 1 hypertension, will test whether MBSR can significantly lower blood pressure in unmedicated hypertensives. If found effective, the HARMONY study will

provide evidence to support a larger randomized controlled trial by evaluating the feasibility and safety of MBSR as a complementary or alternative treatment for hypertension.

METHODS

Study Design

The HARMONY study is a randomized, prospective, two-armed, wait-list controlled pilot trial. The intervention is a standard 8 week MBSR program. A wait-list controlled trial design was chosen in order to model our methodology after Linden[23]. The main outcome measure is mean awake and 24 hour systolic and diastolic ambulatory blood pressure. The study population consists of unmedicated men and women with stage 1 hypertension. Based on the power analysis the established recruitment goal was one hundred subjects. Screening ~~B~~baseline ambulatory blood pressure monitoring determine~~d~~s hypertensive eligibility. Screening and follow-up visits take place at Sunnybrook Health Sciences Centre, Toronto Ontario. All MBSR therapy ~~was~~ is conducted at the University Health Network's Toronto General Hospital, Toronto Ontario.

Study Participants

Eligible participants ~~were~~ include adults aged 20 to 75 years old ~~who had a~~with mean awake systolic or diastolic ambulatory blood pressure equal to or greater than 135 mmHg or 85 mmHg, or mean 24 hour ambulatory blood pressure equal to or greater than 130 mmHg or 80 mmHg. There must be no antihypertensive use within six months of the screening/baseline ABPM visit. We recognize the possibility that an individual may choose to go off antihypertensive therapy when they should not, and may potentially base this decision on wanting to be in the HARMONY Study. In these events, screening with the BPTru and ABPM should capture those individuals whose blood pressure is too high and who should be on active

Formatted: Line spacing: Double
Formatted: Font: Times New Roman, 12 pt, Not Bold
Formatted: Font: Times New Roman, 12 pt, Not Bold
Formatted: Font: Times New Roman, 12 pt, Not Bold
Formatted: Font: Times New Roman, 12 pt, Not Bold
Formatted: Font: Times New Roman, 12 pt, Not Bold
Formatted: Font: Times New Roman, 12 pt, Not Bold
Formatted: Font: Times New Roman, 12 pt, Not Bold
Formatted: Font: Times New Roman, 12 pt, Not Bold
Formatted: Font: Times New Roman, 12 pt, Not Bold

antihypertensive therapy. In a situation where screening blood pressure is too high, individuals are counselled one-on-one with the primary investigator, Dr Sheldon Tobe, about their blood pressure, antihypertensive therapy and why they could not be in the study. Using this methodology we hope to only recruit those who have moderately elevated blood pressure (Stage 1) and do not require anti-hypertensive therapy at the time of enrollment.

Study participants consist of those who meet the screening criteria, ~~were~~ are willing and able to participate in the MBSR program, ~~could~~ can attend all necessary study visits and complete all safety blood pressure evaluations. Further details regarding inclusion and exclusion criteria can be found in Table 1.

Table 1: Study inclusion and exclusion criteria.

Inclusion criteria:
1. Age 20 to 75 years. 2. Hypertensive as determined ~~on~~ by ABPM at baseline (daytime ≥ 135/85 mmHg or 24-hour ABPM ≥ 130/80 mmHg). 3. Willing and able to participate in the MBSR program. 4. Willing to be followed for safety BP checks during the primary outcome period. 5. Willing to accept a possible waiting period of 12-weeks for MBSR. 6. Written informed consent. 7. Able to participate in mindfulness meditation program following screening ABPM.
Exclusion criteria:

Formatted: Font: Times New Roman, 12 pt, Not Bold
Formatted: Font: Times New Roman, 12 pt, Not Bold
Formatted: Font: Times New Roman, 12 pt, Not Bold
Formatted: Font: Times New Roman, 12 pt, Not Bold
Formatted: Font: Times New Roman, 12 pt, Not Bold
Formatted: Font: Times New Roman, 12 pt, Not Bold
Formatted: Font: Times New Roman, 12 pt, Not Bold
Formatted: Font: Times New Roman, 12 pt
Formatted: Indent: First line: 0.5"

1. Use of antihypertensive within 6 months of the screening ABPM.
2. Screening office BP > 180/100 mmHg and ABPM ≥ 160/100 mmHg.
3. Diabetes.
4. Secondary hypertension.
5. Renal disease (GFR < 60 ml/min or overt nephropathy).
6. History of heart attack.
7. Stroke or TIA or
8. Re-vascularization procedure.
9. Active malignant disease (except non-melanoma skin cancer).
10. Epileptic seizure 6 months before the screening visit.
11. Congestive heart failure.
12. Severe liver disease.
13. Pregnancy or lactation period.
14. Participation in a clinical trail or receipt of investigational compound or treatment in the 3 months prior to the initial screening visit.
15. Planned elective surgery during the study period except for cataract surgery.
16. Inability or unwillingness to perform 3 ABPM over 6 months.

Study Recruitment

The original planned recruitment rate was 25 subjects every 6 months for a total of 100 subjects. Potential participants ~~were~~ have been identified through the clinical practices and referral bases of Dr's Abramson, Myers and Tobe. Additional successful screening strategies ~~included~~ have included public information sessions, advertisements in local news papers and

hospital posters. Screening ~~was~~ is performed using a validated automated blood pressure device, the BpTRU (VSM MedTech Ltd Coquitlam, Canada). ~~Those~~ Individuals with unmedicated office blood pressure ≥ 135/85 mmHg ~~were~~ are invited to the next step of screening using ~~of~~ 24 hour ABPM.

Randomization and Study Blinding

Randomization to one of two study arms ~~was~~ is done by sealed envelope method using the permuted block design, with blocks of 2 and 4 subjects to maintain the adequacy of randomization. A computer program generated a random number sequence which was used to allocate subjects to the treatment or wait-list control group. The randomization schedule and sealed envelopes were prepared by an individual who worked closely with the Centre for Statistical Design and Analysis and was not directly involved in the study. Blinding is not possible for HARMONY study due to the wait-list control design of the study. However, those teaching the MBSR course are not informed which arm subjects are randomized to.

Upon review of the screening~~/baseline~~ ABPM results, consenting subjects who meet study inclusion criteria ~~were~~ are randomized. Screening ABP is then used as the baseline ABP for those enrolled in the study. Subjects are randomized to either 'early' or 'delayed'. Those randomized to 'early' ~~the treatment arm began~~ begin ~~the~~ MBSR ~~program~~ within 4 weeks of their screening~~/baseline visit~~baseline visit and ~~had ABPM repeate~~repeat ABPM ~~d~~ 12 weeks after the baseline/screening visit ~~after starting MBSR~~ (coinciding with completion of the MBSR course). Those randomized to "delayed" ~~the wait-list control arm~~ ~~were~~ are wait-listed for 12 weeks ~~and,~~ repeat ABPM after that wait list period and subsequently ~~began~~ begin MBSR within 4 weeks of that ~~their 12 week post baseline~~ ABPM (Figure 1).

Primary Outcome

The primary outcome measure is mean awake and 24 hour ambulatory blood pressure (ABP). The primary objective of the HARMONY study is to compare mean awake and 24 hour ABP between the treatment and control arms at the 12 week post-baseline primary assessment period (Figure 1)

Secondary Outcomes

Secondary outcomes include evaluating a within-group effect of MBSR on ABP from pre- to post- MBSR intervention. Persistence of effect 12 weeks after completing the therapy will also be investigated (Figure 1). Between and within-group comparisons of the effect of MBSR on nighttime ABP will also be assessed. The proportion of subjects achieving blood pressure targets (24 hour ABP < 130/80, daytime ABP < 135/85 mmHg), those requiring the initiation of medical therapy during the study and adverse events will also be examined. The amount of MBSR practiced outside the classroom will be analyzed (via participant diaries and homework logs) with respect to change in blood pressure to evaluate any dose-response interactions. Associations between the effect of MBSR on ABP and individual participant characteristics will also be explored. This will be achieved by examining covariates and incorporating them into a model with blood pressure. See Table 2 for further details regarding data collected at study visits.

Table 2. Baseline and ongoing data collection. All listed measurements were collected baseline. Measurements 1-5 are repeated at subsequent study visits (before MBSR, following MBSR and at the 12-week study close-out).

1. Ambulatory blood pressure monitoring (ABPM):
▪ Participants wear an ambulatory blood pressure monitor (model 90207, Spacelabs Medical Inc., Redmond, WA).

▪ Blood pressure is recorded every 15 minutes during a typical day and every 30 minutes between 11 pm and 7 am. ▪ Mean values calculated for systolic and diastolic blood pressure
2. Anthropometric measurements:
▪ Body weight and height measured to calculate Body Mass Index. ▪ Waist circumference measured at the top of the iliac crest.
3. Office blood pressure:
▪ Seated office systolic and diastolic blood pressure measured by BpTRU (VSM MedTech Ltd., Vancouver, BC, Canada). ▪ Device takes 6 measurements every 2 minutes. ~~Averages the last~~Last 5 measurements are averaged to determine the average seated blood pressure.
4. Fasting serum samples:
▪ Plasma glucose, HbA1c, total cholesterol, HDL- cholesterol, LDL-cholesterol, triglycerides, creatinine, electrolytes and liver enzyme levels.
5. Urine samples:
▪ Urine creatinine levels and microalbuminuria levels.
6. Electrocardiogram (ECG)
▪ ECG to detect any abnormal heart rhythms and left ventricular hypertrophy.

The following questionnaires were included in the study protocol to account for external confounders: 1) Demographics and Lifestyle Questionnaire, 2) State-Trait Anger Expression Inventory-2[66], 3) Hospital Anxiety and Depression Scale[67], 4) Perceived Stress Scale[68], 5)

Psychosocial Stress Questionnaire[69], 6) Exercise questionnaire, 7) Job Content Questionnaire[70], 8) Five-Facet Mindfulness Questionnaire[71], 9) Clinical Outcome Routine Evaluation Outcome Measure[72], 10) Toronto Mindfulness Scale[73]. All questionnaires are administered at baseline with questionnaires 2, 4, 5, and 6 repeated at each study visit (ie. Pre MBSR, post MBSR, and study close out). The Toronto Mindfulness Scale ~~was~~ is administered after a period of meditation during the 2nd and 7th MBSR class. Planned future analyses include evaluating the relationships between blood pressure, gender and responses from the questionnaires.

Intervention

Mindfulness Based Stress Reduction (MBSR) is a multi-component group therapy that provides systematic training in mindfulness meditation as a self-regulation approach to stress reduction and emotion management. ~~The primary goal of~~ MBSR ~~is to~~ provides ~~participants with formal~~ training in formal meditation ~~techniques~~ approaches ~~that will~~ with the primary goal of cultivating ~~e~~ psychological resilience and resistance to stress. ~~through cognitive restructuring.~~ This is achieved through fostering the quality of "~~mindfulness" which has been defined~~mindfulness", defined as the capacity to intentionally be in the present moment without judgement [24]. MBSR teaches attendees to approach stressful situations "mindfully"; allowing them to identify what is ~~happening~~occurring in their bodies and minds and to step back from thoughts and feelings during stressful situations. This affords participants ~~and~~ the opportunity to make wise choices with respect to managing stressful situations, such as choosing to avoid ~~about how to deal with the situation such as not avoid~~ engaging in anxious worry that may otherwise escalate into a cycle of stress reactivity and contribute to more emotional distress[24,74-76].

The standard MBSR program is delivered by trained therapists to groups of 25 - 30 individuals and consists of 10 sessions: an introductory session, eight weekly sessions of 2.5 hours, and a 6 hour intensive session/silent retreat held between week six and seven of the course on a Saturday or Sunday. The MBSR program incorporates four major therapeutic elements: formal meditation, informal mindfulness practice (such as ~~e.g.~~ bringing mindfulness to daily activities), psycho-educational activities, and self monitoring / reflection exercises. ~~-~~Each session also includes ~~guided imagery, progressive muscle relaxation, breathing exercises and yoga, as well as didactic teaching and~~ group discussion~~-~~. The development of mindfulness depends heavily upon regular and repeated practice; thus participants commit to ~~carry out~~ daily ~~15~~ 45 minute homework ~~assignments. Daily~~ meditation practice~~. is encouraged~~. ~~H; homework~~Homework includes both formal and informal meditation practices, as well as self-observation questions. CDs are included to guide attendees in daily formal meditation practice.

Participants ~~are taught~~learn new ~~MBSR exercises~~mindfulness practices each week, as well as strategies to incorporate ~~MBSR~~mindfulness perspectives and approaches into daily activities. Some examples of ~~learned~~mindfulness practices included ~~in MBSR are~~ the body scan, sitting ~~-~~meditation~~(initially focusing on the breath and then sequentially expanding awareness to include bodily sensation, sound, thoughts and feelings and ultimately bringing awareness to whatever arises in the moment)~~ , mindful yoga, mindful walking ~~meditation~~, mindful eating and loving kindness meditation. Participants are asked to complete a weekly homework log which tracks the number of minutes spent o~~i~~n formal meditation practice and whether ~~they did an~~ informal mindfulness was practiced that day. ~~ing the various learned exercises each day.~~ Subjects are given new homework logs each week when they return for class. Both a~~A~~dherence to MBSR ~~was tracked by participant diary~~ and class attendance is captured via the homework logs.

Homework logs are faxed weekly from Toronto General Hospital to Sunnybrook Health Sciences Centre where they are entered into the electronic database. HARMONY research staff are asked to contact participants if more than two classes are missed without explanation; this also affords study staff and participants an opportunity to discuss causes for poor class attendance. ~~Together, these capture the amount of time participants spent on various learned meditation practices each week.~~ As the MBSR program is standardized ~~and can be offered to both heterogeneous and homogeneous groups~~, subjects ~~were~~ can be accommodated in other MBSR classes throughout the course if necessary for scheduling. If too many classes are missed due to unforeseen personal circumstances (and not due to lack of commitment/interest by the study subject) then attempts are made to accommodate them to another MBSR course if possible

Data Collection

~~All study~~ Study subject~~related~~ information is ~~maintained~~ organized into~~in~~ individual subject~~s~~ charts and~~s well as~~ uploaded electronically into a ~~Microsoft~~Microsoft Access Database file. All data of enrolled participants is collected on denominated data collection forms, with the Contact Information page and homework logs being the only exceptions. Data from potential study participants/screen fail participants are kept in a screening log binder and a screen fail binder respectively. Coding of enrolled study participants is done by study ID, executed in sequential in order (first participant = study ID 001). Data entry is completed by a research assistant; future plans include auditing all study charts and the study database at the end of the trial to ensure data was entered accurately.

All study data is maintained in a secure location only accessible to study related personnel; this includes lab computers which are accessible only through authentication with ID and password. Study data is only shared with family physicians or the Nephrology Research

Formatted: Indent: First line: 0.5"

group at Sunnybrook Health Sciences Center with the participant's consent. All source information collected is retained under the primary investigator (Dr Sheldon Tobe) as custodian. After all data entry/data auditing is completed, paper copies of study data will be stored at Iron Mountain and destroyed after 25 years as per Health Canada guidelines. Electronic study data will be kept in the Microsoft Access Database until data analysis is completed. Maintenance of study data and study confidentiality is done in full conformance with requirements from the Sunnybrook Research Ethics Board, the University Health Network Research Ethics Board and Health Canada.

Safety

Lifestyle therapy is indicated for people who have stage 1 hypertension (140-159/90-99 mmHg) with no underlying risk factors[1]. Linden has previously demonstrated the role and safety of the wait-list control methodology and determined it to be appropriate in studies with stage 1 and 2 hypertensives (140-179/90-109 mmHg)[23,64]. In accordance with the Canadian standard of care for blood pressure management, all participants received standard recommendations of suggested lifestyle modifications for blood pressure management at study entry.

With participant consent, primary care physician(s) are informed of their patient's participation in the study. Physicians are asked to delay the start of their patient's antihypertensive therapy until after they have completed the study. If physicians believe that antihypertensive should be initiated, they are asked to communicate their decision to study staff before doing so. A letter updating their patient's progress, along with laboratory and ABPM results are sent to the primary care physician after each study visit.

Automated office blood pressure safety assessments are included to closely monitor subjects' blood pressure. ~~and t~~The primary investigator is notified if subjects exceed blood pressure safety limits. If any of the following conditions are discovered during study enrollment participants are withdrawn and treated: 1) increases in ambulatory blood pressure of 20/10 mmHg or greater, 2) accelerated hypertension with an office reading of 160/100 mmHg or greater, 3) macrovascular target organ damage, 4) diabetes mellitus or 5) chronic kidney disease (GFR<60 ml/min). Any subject started on antihypertensive therapy during the study remains in the study and the initiation of medical therapy is recorded.

Sample Size Considerations

The main objective of this study is to assess the difference in mean awake and 24 hour systolic and diastolic ambulatory blood pressure 12 weeks post baseline between the treatment and wait-list control arm. The following calculations/analyses are based on Linden's work and the difference in mean systolic blood pressure between treatment groups measured as by ABPM. Linden found a 6.1 mmHg systolic blood pressure drop from baseline to the end of the primary assessment period for participants in the immediate intervention group; ~~whereas~~ the wait-list control group showed a 0.9 mmHg increase in the same time interval[23] This resulted in a 7.0 mmHg difference between the two groups[23], a relatively large treatment effect, due in part to the use of subjects with higher blood pressure.

Unlike Linden who found blood pressure rising in the control group, more recent results from the Double Exposure study ~~in a hypertensive cohort~~ found that blood pressure tend~~s~~ed to fall over time, even in unmedicated hypertensives. This may have been ~~, possibly~~ due in part to an~~to~~ adoption of lifestyle changes[77,78]. Baseline data from the unmedicated hypertensive cohort in the Double Exposure study demonstrated mean awake ABP equal to 137/85 ± 8/5

mmHg. After one year, mean awake ABP had fallen to 133/83 ± 8/7 mmHg. Based on these results, it is reasonable to assume that blood pressure will fall in the HARMONY wait-list control arm.

Very conservative assumptions were made for the HARMONY power analysis. A reduction of 2.0 mmHg for mean systolic ambulatory blood pressure (half the change observed in the Double Exposure study) was assumed for the control group (compared to the rise that Linden found[23]). The variance recorded in Linden's study (9 mmHg) was used for the HARMONY power analysis; ~~a~~ variance higher than that recorded in the Double Exposure cohort (8 mmHg in only 35 subjects). Linden found a blood pressure difference of 7.0 mmHg between the treatment and control group. In our~~the~~ power analysis, the difference between treatment and control groups was reduced from Linden's result to a more conservative value, 6mmHg. This value was chosen for two reasons: 1) ~~as i~~It was closer to findings from Dickinson's meta-analysis[11]and 2) ~~because p~~Participants' overall blood pressure is anticipated to be lower in the HARMONY study (stage 1 hypertensives) compared to Linden's study (stage 1 and stage 2 hypertensives)[23]. Using a two-tailed two-sample t-test, an estimated group standard deviation of 9.0 mmHg and a significance level of 0.05 it was determined that a sample size of 37 subjects in each group would provide sufficient power (81%) to detect a systolic blood pressure difference of 6.0 mmHg between the null hypothesis (both groups start with equal means and have an equal a drop in systolic blood pressure of 8.0 mmHg) and the alternative hypothesis (control group systolic blood pressure will fall by only 2.0 mmHg). To account for potential drop-outs and subjects lost to analysis (25% lost in Linden's study[23]), the number of subjects was increased to 50 subjects per group (Figure 2).

Statistical Analysis

The primary outcome will be examined using an intent-to-treat analysis. An intent-to-treat population is defined as all subjects ~~entered into~~in the study ~~that~~ who completed at least one session of MBSR. The primary outcome measure is mean awake and 24 hour systolic and diastolic ambulatory blood pressure. Ambulatory blood pressure between treatment and control will be compared by two-tailed two-sample t-test at the end of the 12 week primary outcome period. Within subject analysis of the effect of MBSR on ambulatory blood pressure will be performed by a paired t-test. Persistence of effect of MBSR on blood pressure will be assessed using repeated ANOVA measures, comparing group differences between subsequent study visits (baseline, pre MBSR, post MBSR, and study close out). The proportion of subjects achieving blood pressure targets will be analyzed using chi-squared tests. Multiple regression analyses will be employed to assess differences in blood pressure between subjects while adjusting for covariates. Subjects may be started on antihypertensive therapy during the study. If this leads to imbalance between the study arms, a per-protocol analysis may be performed to take this variable into account. All analyses will be carried out using SAS version 9.1 (SAS Institute, Cary North Carolina, USA).

Ethical Considerations

This research project ~~was~~ is approved by the Research Ethics Board at Sunnybrook Research Institute (Toronto, Canada) and the University Health Network Research Ethics Board (Toronto, Canada). Planned data analyses are in full conformance with the principles of the "*Declaration of Helsinki*"[79]. Conduct of the HARMONY study is fully adherent to the principles outlined in the "*Guideline for Good Clinical Practice*" ICH Tripartite Guideline [January 1997][80] and in the 2nd edition of Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans[81].

Dissemination Plans

Data collection will be completed by early spring 2012. Primary and secondary analysis will commence immediately after data monitoring is completed; publications will be prepared for submission in summer ~~of~~ 2012. Study findings are also planned to be presented at the following conferences: October 2012: Hypertension Canada, May 2013: American Society of Hypertension, June 2013: European Society of Hypertension, September 2013: International Society of Hypertension.

Authors' Contributions

ST and BB conceptualized the study and MD, ~~BB,~~ MM, SA, BA, NP and JI assisted with the study design. KB, MH and MD collected data which was overseen by NP. KB and MH cleaned the collected data, preformed interim analyses and interpreted interim results. ST is the guarantor. KB, MD, MH, and ST wrote and revised the article, as well as designed figures. NP, BB, MM, SA, BA and JI critically revised the draft for important intellectual content. All authors approved this final version to be published.

Funding Statement

This work was supported by Heart and Stroke Foundation of Ontario (#NA 6349). The Heart & Stroke Foundation of Ontario played no role in the study design, data collection, analysis and interpretation of data, writing of the article or the decision to submit it for publication.

Competing Interests Statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with

any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

REFERENCES

1 Rabi DM, Daskalopoulou SS, Padwal RS, et al. *The 2011 Canadian Hypertension Education Program Recommendations for the Management of Hypertension: Blood Pressure Measurement, Diagnosis, Assessment of Risk, and Therapy.* Can J Cardiol 2011;**27**:415-433.

2 Chockalingam A, Campbell NR, Fodor JG. *Worldwide epidemic of hypertension.* Can J Cardiol 2006;**22**:553-555.

3 Vasan RS, Larson MG, Leip EP, et al. *Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study.* Lancet 2001;**358**:1682-1686.

4 Julius S, Nesbitt S, Egan B, et al. *Feasibility of treating prehypertension with an angiotensin-receptor blocker.* N Engl J Med 2006;**354**:1685-1697.

5World Health Organization. Preventing chronic diseases: a vital investment. Available at: www.who.int/chp/chronic_disease_report/contents/en/index.html. Accessed 04/27, 2007.

6 Stamler J, Rose G, Stamler R, et al. *INTERSALT study findings. Public health and medical care implications.* Hypertension 1989;**14**:570-577.

7 Appel LJ. *Lifestyle modification as a means to prevent and treat high blood pressure.* Journal of the American Society of Nephrology 2003;**14**:S99-S102.

8 O'Donnell MJ, Xavier D, Liu L, et al. *Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study.* Lancet 2010;**376**:112-123.

9 Canter PH, Ernst E. *Insufficient evidence to conclude whether or not Transcendental Meditation decreases blood pressure: results of a systematic review of randomized clinical trials.* J Hypertens 2004;**22**:2049-2054.

10 Parati G, Steptoe A. *Stress reduction and blood pressure control in hypertension: a role for transcendental meditation?* J Hypertens 2004;**22**:2057-2060.

11 Dickinson HO, Mason JM, Nicolson DJ, et al. *Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials.* J Hypertens 2006;**24**:215-233.

12 Manikonda JP, Stork S, Togel S, et al. *Contemplative meditation reduces ambulatory blood pressure and stress-induced hypertension: a randomized pilot trial.* J Hum Hypertens 2008;**22**:138-140.

13 Wenneberg SR, Schneider RH, Walton KG, et al. *A controlled study of the effects of the Transcendental Meditation program on cardiovascular reactivity and ambulatory blood pressure.* Int J Neurosci 1997;**89**:15-28.

14 Castillo-Richmond A, Schneider RH, Alexander CN, et al. *Effects of stress reduction on carotid atherosclerosis in hypertensive African Americans.* Stroke 2000;**31**:568-573.

15 Schneider RH, Staggers F, Alxander CN, et al. *A randomised controlled trial of stress reduction for hypertension in older African Americans.* Hypertension 1995;**26**:820-827.

16 Schneider RH, Alexander CN, Staggers F, et al. *Long-term effects of stress reduction on mortality in persons > or = 55 years of age with systemic hypertension.* Am J Cardiol 2005;**95**:1060-1064.

17 Paul-Labrador M, Polk D, Dwyer JH, et al. *Effects of a randomized controlled trial of transcendental meditation on components of the metabolic syndrome in subjects with coronary heart disease.* Arch Intern Med 2006;**166**:1218-1224.

18 Schneider RH, Alexander CN, Staggers F, et al. *A randomized controlled trial of stress reduction in African Americans treated for hypertension for over one year.* American Journal of Hypertension 2005;**18**:88-98.

19 Nidich SI, Rainforth MV, Haaga DA, et al. *A randomized controlled trial on effects of the Transcendental Meditation program on blood pressure, psychological distress, and coping in young adults.* American Journal of Hypertension 2009;**22**:1326-1331.

20 Anderson JW, Liu C, Kryscio RJ. *Blood pressure response to transcendental meditation: a meta-analysis.* American Journal of Hypertension 2008;**21**:310-316.

21 Rainforth MV, Schneider RH, Nidich SI, et al. *Stress reduction programs in patients with elevated blood pressure: a systematic review and meta-analysis.* Curr Hypertens Rep 2007;**9**:520-528.

22 Beck AT. *The current state of cognitive therapy: a 40-year retrospective.* Arch Gen Psychiatry 2005;**62**:953-959.

23 Linden W, Lenz JW, Con AH. *Individualized stress management for primary hypertension: a randomized trial.* Arch Intern Med 2001;**161**:1071-1080.

24Kabat-Zinn J. Full catastrophe living: using the wisdom of your body and mind to face stress, pain and illness. New York: Delta 1990:.

25 Praissman S. *Mindfulness-based stress reduction: a literature review and clinician's guide.* J Am Acad Nurse Pract 2008;**20**:212-216.

26 Plews-Ogan M, Owens JE, Goodman M, et al. *A pilot study evaluating mindfulness-based stress reduction and massage for the management of chronic pain.* Journal of General Internal Medicine 2005;**20**:1136-1138.

27 Morone NE, Greco CM, Weiner DK. *Mindfulness meditation for the treatment of chronic low back pain in older adults: a randomized controlled pilot study.* Pain 2008;**134**:310-319.

28 Esmer G, Blum J, Rulf J, et al. *Mindfulness-based stress reduction for failed back surgery syndrome: a randomized controlled trial.* J Am Osteopath Assoc 2010;**110**:646-652.

29 Rosenzweig S, Greeson JM, Reibel DK, et al. *Mindfulness-based stress reduction for chronic pain conditions: variation in treatment outcomes and role of home meditation practice.* J Psychosom Res 2010;**68**:29-36.

30 Shapiro SL, Schwartz GE, Bonner G. *Effects of mindfulness-based stress reduction on medical and premedical students.* J Behav Med 1998;**21**:581-599.

31 Astin JA. *Stress reduction through mindfulness meditation. Effects on psychological symptomatology, sense of control, and spiritual experiences.* Psychotherapy & Psychosomatics 1997;**66**:97-106.

32 Kabat-Zinn J, Massion AO, Kristeller J, et al. *Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders.* Am J Psychiatry 1992;**149**:936-943.

33 Vieten C, Astin J. *Effects of a mindfulness-based intervention during pregnancy on prenatal stress and mood: results of a pilot study.* Archives of Women's Mental Health 2008;**11**:67-74.

34 Vollestad J, Sivertsen B, Nielsen GH. *Mindfulness-based stress reduction for patients with anxiety disorders: evaluation in a randomized controlled trial.* Behaviour Research & Therapy 2011;**49**:281-288.

35 Barnhofer T, Duggan D, Crane C, et al. *Effects of meditation on frontal alpha-asymmetry in previously suicidal individuals.* Neuroreport 2007;**18**:709-712.

36 Kenny MA, Williams JM. *Treatment-resistant depressed patients show a good response to Mindfulness-based Cognitive Therapy.* Behaviour Research & Therapy 2007;**45**:617-625.

37 Kingston J, Chadwick P, Meron D, et al. *A pilot randomized control trial investigating the effect of mindfulness practice on pain tolerance, psychological well-being, and physiological activity.* J Psychosom Res 2007;**62**:297-300.

38 Grossman P, Tiefenthaler-Gilmer U, Raysz A, et al. *Mindfulness training as an intervention for fibromyalgia: evidence of postintervention and 3-year follow-up benefits in well-being.* Psychotherapy & Psychosomatics 2007;**76**:226-233.

39 Sephton SE, Salmon P, Weissbecker I, et al. *Mindfulness meditation alleviates depressive symptoms in women with fibromyalgia: results of a randomized clinical trial.* Arthritis & Rheumatism 2007;**57**:77-85.

40 Schmidt S, Grossman P, Schwarzer B, et al. *Treating fibromyalgia with mindfulness-based stress reduction: results from a 3-armed randomized controlled trial.* Pain 2011;**152**:361-369.

41 Kristeller JL, Hallett CB. *An Exploratory Study of a Meditation-based Intervention for Binge Eating Disorder.* Journal of Health Psychology 1999;**4**:357-363.

42 Kabat-Zinn J, Wheeler E, Light T, et al. *Influence of a mindfulness meditation-based stress reduction intervention on rates of skin clearing in patients with moderate to severe psoriasis undergoing phototherapy (UVB) and photochemotherapy (PUVA).* Psychosom Med 1998;**60**:625-632.

43 Carlson LE, Speca M, Faris P, et al. *One year pre-post intervention follow-up of psychological, immune, endocrine and blood pressure outcomes of mindfulness-based stress reduction (MBSR) in breast and prostate cancer outpatients.* Brain, Behavior, & Immunity 2007;**21**:1038-1049.

44 Carlson LE, Speca M, Patel KD, et al. *Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress and levels of cortisol, dehydroepiandrosterone sulfate (DHEAS) and melatonin in breast and prostate cancer outpatients.* Psychoneuroendocrinology 2004;**29**:448-474.

45 Carlson LE, Speca M, Patel KD, et al. *Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress, and immune parameters in breast and prostate cancer outpatients.* Psychosom Med 2003;**65**:571-581.

46 Henderson VP, Clemow L, Massion AO, et al. *The effects of mindfulness-based stress reduction on psychosocial outcomes and quality of life in early-stage breast cancer patients: a randomized trial.* Breast Cancer Research & Treatment 2012;**131**:99-109.

47 Lengacher CA, Johnson-Mallard V, Barta M, et al. *Feasibility of a mindfulness-based stress reduction program for early-stage breast cancer survivors.* Journal of Holistic Nursing 2011;**29**:107-117.

48 Lengacher CA, Johnson-Mallard V, Post-White J, et al. *Randomized controlled trial of mindfulness-based stress reduction (MBSR) for survivors of breast cancer.* Psychooncology 2009;**18**:1261-1272.

49 Ledesma D, Kumano H. *Mindfulness-based stress reduction and cancer: a meta-analysis.* Psychooncology 2009;**18**:571-579.

50 Matchim Y, Armer JM, Stewart BR. *Mindfulness-based stress reduction among breast cancer survivors: a literature review and discussion.* Oncol Nurs Forum 2011;**38**:E61-71.

51 Matchim Y, Armer JM, Stewart BR. *Effects of mindfulness-based stress reduction (MBSR) on health among breast cancer survivors.* West J Nurs Res 2011;**33**:996-1016.

52 Matousek RH, Dobkin PL. *Weathering storms: a cohort study of how participation in a mindfulness-based stress reduction program benefits women after breast cancer treatment.* Current Oncology 2010;**17**:62-70.

53 Smith JE, Richardson J, Hoffman C, et al. *Mindfulness-Based Stress Reduction as supportive therapy in cancer care: systematic review.* J Adv Nurs 2005;**52**:315-327.

54 Witek-Janusek L, Albuquerque K, Chroniak KR, et al. *Effect of mindfulness based stress reduction on immune function, quality of life and coping in women newly diagnosed with early stage breast cancer.* Brain, Behavior, & Immunity 2008;**22**:969-981.

55 Birnie K, Garland SN, Carlson LE. *Psychological benefits for cancer patients and their partners participating in mindfulness-based stress reduction (MBSR).* Psychooncology 2010;**19**:1004-1009.

56 Rosenzweig S, Reibel DK, Greeson JM, et al. *Mindfulness-based stress reduction is associated with improved glycemic control in type 2 diabetes mellitus: a pilot study.* Alternative Therapies in Health & Medicine 2007;**13**:36-38.

57 Baer RA. *Mindfulness Training as a Clinical Intervention: A Conceptual and Empirical Review.* Clinical Psychology: Science and Practice 2003;**10**:125-143.

58 Grossman P, Niemann L, Schmidt S, et al. *Mindfulness-based stress reduction and health benefits. A meta-analysis.* J Psychosom Res 2004;**57**:35-43.

59 Bohlmeijer E, Prenger R, Taal E, et al. *The effects of mindfulness-based stress reduction therapy on mental health of adults with a chronic medical disease: a meta-analysis.* J Psychosom Res 2010;**68**:539-544.

60 Ditto B, Eclache M, Goldman N. *Short-term autonomic and cardiovascular effects of mindfulness body scan meditation.* Annals of Behavioral Medicine 2006;**32**:227-234.

61 Barnes VA, Treiber FA, Davis H. *Impact of Transcendental Meditation on cardiovascular function at rest and during acute stress in adolescents with high normal blood pressure.* J Psychosom Res 2001;**51**:597-605.

62 Barnes VA, Davis HC, Murzynowski JB, et al. *Impact of meditation on resting and ambulatory blood pressure and heart rate in youth.* Psychosom Med 2004;**66**:909-914.

63 LE Van Wielingen, LE Carlson and TS Campbell. *Mindfulness-based stress reduction (MBSR), blood pressure and psychological functioning in women with cancer.* [abstract]. Psychosom.Med. 2007;69:A43.

64 Linden W, Moseley JV. *The efficacy of behavioral treatments for hypertension.* Applied Psychophysiology & Biofeedback 2006;**31**:51-63.

65 Kingston T, Dooley B, Bates A, et al. *Mindfulness-based cognitive therapy for residual depressive symptoms.* Psychology & Psychotherapy: Theory, Research & Practice 2007;**80**:193-203.

66 Spielberger C, Jacobs G, Russel S, Crane R. Assessment of Anger: The State-Trait Anger Scale. In: Butcher J, Spielberger C, eds. Advances in Personality Assesment. Hillsdale, NJ: Lawrence Erlbaum Associates 1983:112-189.

67 Bjelland I, Dahl AA, Haug TT, et al. *The validity of the Hospital Anxiety and Depression Scale. An updated literature review.* J Psychosom Res 2002;**52**:69-77.

68 Cohen S, Kamarck T, Mermelstein R. *A global measure of perceived stress.* Journal of Health & Social Behavior 1983;**24**:385-396.

69 Rosengren A, Hawken S, Ounpuu S, et al. *Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study.* Lancet 2004;**364**:953-962.

70 Karasek R, Brisson C, Kawakami N, et al. *The Job Content Questionnaire (JCQ): an instrument for internationally comparative assessments of psychosocial job characteristics.* J Occup Health Psychol 1998;**3**:322-355.

71 Baer RA, Smith GT, Lykins E, et al. *Construct validity of the five facet mindfulness questionnaire in meditating and nonmeditating samples.* Assessment 2008;**15**:329-342.

72 Evans C, Connell J, Barkham M, et al. *Towards a standardised brief outcome measure: psychometric properties and utility of the CORE-OM.* British Journal of Psychiatry 2002;**180**:51-60.

73 Lau MA, Bishop SR, Segal ZV, et al. *The Toronto Mindfulness Scale: development and validation.* J Clin Psychol 2006;**62**:1445-1467.

74 Kabat-Zinn J, Lipworth L, Burney R. *The clinical use of mindfulness meditation for the self-regulation of chronic pain.* J Behav Med 1985;**8**:163-190.

75 Bishop SR. *What do we really know about mindfulness-based stress reduction?* Psychosom Med 2002;**64**:71-83.

76 Kabat-Zinn J. *An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results.* Gen Hosp Psychiatry 1982;**4**:33-47.

77 Baker B, Paquette M, Szalai JP, et al. *The influence of marital adjustment on 3-year left ventricular mass and ambulatory blood pressure in mild hypertension.* Arch Intern Med 2000;**160**:3453-3458.

78 Tobe SW, Kiss A, Sainsbury S, et al. *The impact of job strain and marital cohesion on ambulatory blood pressure during 1 year: the double exposure study.* American Journal of Hypertension 2007;**20**:148-153.

79World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. From the 59th World Medical Association Assembly, Seoul. 2008; Available at: http://www.wma.net/en/30publications/10policies/b3/17c.pdf. Accessed 12/29, 2011.

80Health Canada. International Conference on Harmonization (ICH) Guidance E6: Good Clinical Practice: Consolidated Guidelines. 1997; Available at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e6-eng.php. Accessed 12/29, 2011.

81Goverment of Canada: Panel of Research Ethics. 2nd Edition of Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. 2010; Available at: http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/. Accessed 12/29, 2011.