Mindfulness-based Coaching to Reduce Ambulatory Hypertension in Atrial Fibrillation: A Pilot-Feasibility Randomized Controlled Trial

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Abstract

Background: Hypertension (HTN) is widely implicated in the prevention and management of Atrial Fibrillation (AF), given its centrality in AF pathogenesis and prognosis. As impaired autonomic cardiovascular functioning is the basis of both conditions, strategies that improve autonomic balance can reduce HTN-AF burden.

Methods: The objective of this study was to evaluate the effectiveness of a 16-week mindfulness-based risk reduction (MBRR) coaching program compared to a diet-based risk reduction coaching (DBRR) coaching program based on the Dietary Approaches to Stop Hypertension (DASH) guidelines. The primary outcome was 24-hr ambulatory systolic blood pressure (SBP) during waking and sleeping.

Results: In 30 stable AF patients with elevated waking SBP (≥ 135mmHg), results for SBP showed statistically significant main effects of time, indicating overall mean reductions in SBP from baseline to 8-weeks (Waking: -6.68, $p = 0.002$; Sleeping: -5.88, $p = 0.006$), and from baseline to 16-weeks (Waking: -9.68, $p = 0.0001$; Sleeping: -6.46, $p = 0.009$) irrespective of study interventions. Participants in both groups also showed statistically significant improvements from baseline to 8 and 16-weeks in indices of general anxiety, cardiac anxiety, POMS tension, anger, and confusion subscales, along with improvements in mindfulness describing and nonreactivity facets, with no statistically significant between-group differences.

Discussion: Both MBRR and DBRR were effective in lowering SBP during waking and sleeping. Both groups also saw improvements in general and cardiac anxiety, in addition to other mood and mindfulness indices, supporting the use of MBRR and DBRR interventions in AF.

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List of Abbreviations

ACE Angiotensin Converting Enzyme
AF Atrial Fibrillation
ANS Autonomic Nervous System
BP Blood Pressure
BPL Blood Pressure Load
BPV Blood Pressure Variability
BRS Baroreceptor Sensitivity
CAQ The Cardiac Anxiety Questionnaire
CVD Cardiovascular Diseases
DASH Dietary Approach to Stop Hypertension
DBP Diastolic Blood Pressure
DBPL Diastolic Blood Pressure Load
DBPV Diastolic Blood Pressure Variability
DBRR Diet-based Risk Reduction
FFMQ-SF Five Factor Mindfulness Questionnaire - Short Form
HADS Hospital Anxiety and Depression Scale
HFA Heart Focused Anxiety
HRV Heart Rate Variability
HTN Hypertension
LF Low Frequency
LVEF Left Ventricular Ejection Fraction
MBCT Mindfulness-based Cognitive Therapy
MBI Mindfulness-based Interventions
MBRR Mindfulness-based risk reduction
MBSR Mindfulness-based Stress Reduction
MCID Minimal Clinically Important Difference
MSNA Muscle Sympathetic Nerve Activity
PACE Partners in Advanced Cardiac Evaluation
PNS Parasympathetic Nervous System
POMS-SF Profile of Mood States - Short Form
PVAI Pulmonary Vein Antrum Isolation
RAAS Renin–Angiotensin–Aldosterone System
RM-ANOVA Repeated measures analysis of variance
RSDN Renal Sympathetic Denervation
SBP Systolic Blood Pressure
SBPL Systolic Blood Pressure Load
SBPV Systolic Blood Pressure Load
SDNN Standard Deviation of Normal to Normal RR intervals
SNS Sympathetic Nervous System
SRHC Southlake Regional Health Centre
VLF Very Low Frequency

1.0 Introduction

1.1 Atrial Fibrillation and Hypertension: Autonomic Imbalance as a Common Link

Atrial fibrillation (AF) is the most prevalent cardiac rhythm dysfunction, characterized by rapid irregular atrial electrical activity, uncoordinated atrio-ventricular contractions, and an increased likelihood of thrombogenesis.[1] Globally, AF affected an estimated 33 million individuals in 2010,[2] and is projected to reach between 12-16 million individuals by 2050 in the United states,[3] and between 14-18 million individuals by 2060 in the European Union.[4,5] Driven largely by progressive structural, functional, and electrical remodeling in response to hypertension (HTN),[6,7] AF is associated with nearly 2-5 times elevated risk of cardiovascular diseases (CVD), notably coronary artery disease, ischemic stroke, and heart failure, and places those affected at twice the risk of mortality.[8] In effect, given HTN's importance in AF pathophysiology, AF is commonly regarded as a secondary consequence of hypertensive heart disease,[9,10] a diagnostic classification representing HTN-related structural changes in the myocardium and coronary arteries.

Autonomic nervous system (ANS) imbalance, characterized by sympathetic nervous system (SNS) hyperactivity and/or parasympathetic (PNS) hypo-activity, has prominently been implicated in the pathogenesis and progression of both HTN and AF,[11-15] indicating a common pathophysiologic link. Accordingly, reduction of HTN and by extension excess SNS activity are critical steps in prevention and management of HTN and AF. Predominantly medical and pharmacologically-based, HTN and AF management strategies include: (a) catheter-based ablation procedures, specifically renal sympathetic denervation (RSDN) in treatment of resistant HTN and pulmonary vein isolation ablation (PVAI) in treatment of AF,[16-18] and more commonly (b) pharmacological anticoagulation and inhibition of the renin–angiotensin–aldosterone system (RAAS), shown to be effective in lowering the risks of AF development,[19-22] AF recurrence post-

ablation,[19,21] and adverse CVD outcomes (e.g. cardiovascular events, heart failure) in high-risk patients,[23] in addition to lowering blood pressure and vascular damage.[24,25]

1.2. Mindfulness, Autonomic Balance, and CVD Risk Reduction

While HTN and AF management strategies prioritize medical and pharmacological management, behavioural approaches, including mindfulness-based strategies have seen increasing applications in CVD management.[26-28] In addition to mental health benefits,[29] mindfulness, practiced through sitting meditation and mindful awareness of daily life, improves autonomic (SNS-PNS) balance,[30,31] indicating their potential as viable self-regulatory mechanisms and personal resource in countering excess SNS and/or low PNS prevalent in HTN, CVD, and the broader chronic disease context. Indeed, SNS-PNS imbalance, manifested in neural, hormonal, and immune-related aberrations, appears to be the common psycho-physiological mechanism linking psychological phenomena, including chronic stress,[32] maladaptive personality attributes (i.e. neuroticism, negative affectivity, hostility, social inhibition),[33-36] coping styles (i.e. defensive coping),[37] and psychopathology,[38-40] with CVD development and progression. Conversely, greater psychological resilience and resting PNS (vagal) tone are linked to more adaptive stress recovery responses,[41,42] suggesting therapeutic usefulness of psychophysiological PNS-enhancement strategies, including mindfulness meditation, psychotherapy, and relaxation-based interventions, in CVD risk reduction and management.

1.3. Study Objectives

To evaluate the effectiveness of MBRR compared to DBRR in improving mean SBP during waking and sleeping periods. This additionally include evaluation of psychological status, including indices of mood, anxiety, mindfulness, and sleep quality.

1.4 Hypotheses

We hypothesize SBP to improve in both MBRR and DBRR groups during periods of waking. However, we hypothesized the MBRR group to show significantly greater improvement in SBP during sleeping, in light of nocturnal SBP being an indicator of AI, in addition to previous research on the effectiveness of Mindfulness-based Interventions (MBI) in improving SNS-PNS balance. In relation to psychometric outcomes, we hypothesized the MBRR group to show greater improvements in psychological status, including anxiety, heart focused anxiety, and sleep quality.

2.0 Literature Review

2.1 Current Perspectives on Cardiovascular Disease Management

2.1.1 The Increasing Burden of Morbidity

Cardiovascular diseases (CVD), primarily ischemic heart disease, cerebrovascular disease, and hypertensive heart disease, accounted for nearly 18 million global deaths in 2015-2016, representing a 14.5% increase in deaths since 2006 worldwide.[43,44] As the largest source of global morbidity and mortality,[43] CVD mortality trends show marked differences between low-middle income and economically-developed counties, characterized by: (a) progressive increases in CVD mortality in low-middle income countries, indicative of a demographic and epidemiologic transition toward chronic non-infectious diseases,[45,46] and (b) steady declines in absolute and age-standardized CVD mortality across economically-developed countries,[47-51] reflecting greater efforts at risk factor management and medical therapies.[52,53] In fact, recently, cancers have begun to surpass CVD as the leading cause of death in Canada,[54] United Kingdom,[51] 19 states of the United States,[55] and most western European countries,[56] a trend partly explained by improvements in CVD survival.

Despite encouraging trends in CVD mortality reduction in economically-developed nations, the burden of morbidity from CVD is on the rise, considering the increasing prevalence of cardio-metabolic risk factors in younger and socioeconomically-disadvantaged sectors of the population,[57-62] and the growing need for continued medical care in an ageing population often living with multiple chronic conditions. According to various national estimates, multimorbidity, defined as co-occurrence of two or more chronic conditions in the same individual, is prevalent in as many as 30-90% of adults over the aged 45 and above.[63-67] Multimorbidity is especially common among cardio-metabolic risk factors and disorders, with HTN, hyperlipidemia, ischemic heart

disease, and diabetes among the most commonly clustered conditions.[68,69] An increasing reality in current chronic disease management, multimorbidity presents healthcare professionals and patients with significant challenges, giving rise to greater complexity in medical and self-care regimens,[69,70] reduced quality of life,[71] increased healthcare utilization-costs,[72] and mortality.[73,74]

2.1.2 The Emerging Epidemic of Atrial Fibrillation

As a deviation from the normal atrio-ventricular electrical conduction and contraction sequence, AF involves rapid uncoordinated atrial contractions driven by multiple ectopic signal-generating foci and re-entrant circuits,[1,75] leading to a range of cellular, structural, and functional changes within the left atrium that increase the potential for thrombogenesis and thromboembolism.[1,76] Affecting an estimated 33.5 million individuals globally in 2010,[2] AF is independently associated with increased risk of ischemic stroke (pooled relative risk: 2.3), ischemic heart disease (pooled relative risk: 1.6), congestive heart failure (pooled relative risk: 4.9), cardiovascular events (pooled relative risk: 1.9), sudden cardiac death (pooled relative risk: 1.8), and mortality (pooled relative risk: 1.5-2.0).[8] AF-related symptoms (e.g. palpitations, dyspnea, fatigue, and chest pain) are further associated with substantial reductions in quality of life, manifesting as declines in physical and psychological functioning.[77,78] Accordingly, AF management guidelines prioritize: (a) sinus rhythm restoration using pharmacological, electrical cardioversion, and cardiac ablation approaches along with (b) CVDs risk reduction through antihypertensive and anticoagulant medications in reducing the risk of stroke and heart failure.[79,80]

According to global and country-specific evaluations,[2,3,81,82] age-standardized incidence and prevalence rates of AF rates have progressively increased since the 1960s, reflecting the ageing of populations, increasing prevalence cardio-metabolic risk factors, and improving screening and diagnostic abilities.[2,3,5,81] In the coming years, AF prevalence is projected to increase to an

estimated 12-16 million individuals in the United States by 2030-2050,[3] and to 14-18 million individuals in the European Union between 2030-2060.[4,5] AF-related-conditions and hospitalizations are therefore expected to result in substantial economic burden on healthcare systems across the globe,[5,83] underscoring the importance of timely AF diagnosis and treatment in reducing subsequent AF-related complications and economic burden.

2.1.3 The Leading role of Hypertension in CVD

As the leading risk factor behind global morbidity and mortality trends,[84] HTN affects an estimated 30 percent (1.13-1.39 billion individuals) of the global adult population.[85,86] According to current international estimates, global HTN prevalence increased by 5.2 percent increase between 2000-2010,[86] and is ultimately projected to significantly affect 1.56 billion individuals by 2025.[87] Despite this increase in global HTN prevalence, international estimates show important regional variations, demonstrated by reductions in age-standardized prevalence within high income (-2.6% between 2000-2010) versus less economically-developed regions (+7.9% between 2000-2010).[86] An etiologically complex phenomenon,[88] HTN plays a central role in the development of CVDs, including coronary artery disease,[89] cardiac arrhythmias,[7,10] heart failure,[90,91] stroke,[92] and chronic kidney disease.[93]

Chronic elevation of blood pressure (BP) is a key driver of adverse structural, inflammatory, electrical, and functional remodeling within the myocardium,[94] manifesting in left ventricular hypertrophy,[90,95] left atrial enlargement,[96,97] and myocardial fibrosis.[98,99] Similarly, at vasculature, chronically elevated BP induces a range of adverse structural and inflammatory changes within the vascular smooth muscle and endothelium, setting the stage for increased vasoconstriction, atherosclerosis, and systemic vascular resistance.[94,100,101] The resultant hemodynamic and pro-inflammatory stress further predispose to changes in cardiac electrical

activity,[7,10] ultimately disrupting coordinated atrio-ventricular contractions seen in cardiac arrhythmias.

2.1.4 Autonomic Imbalance and Pathogenesis of Cardio-Metabolic Diseases

The ANS, comprised of SNS and PNS branches, plays a central role in regulation of physiological balance across multiple bodily systems, predominantly the cardiovascular,[102,103] digestive,[104] immune,[103,105] metabolic,[106-108] respiratory,[103] and thermoregulatory systems.[109] In regulation of multiple physiologic functions, the ANS remains responsive to multiple physiologic and environmental perturbations, mobilizing the SNS in response to threatening physical and psychological stressors (actual or anticipated), and activating the PNS as a vital counterbalancing influence against excess SNS activation, thereby restoring SNS-PNS balance and stable physiological functioning.[110]

Recent years have seen a growing understanding of the role of autonomic imbalance (AI) in the pathogenesis and progression of cardiovascular,[11,111,112] metabolic,[106-108] inflammatory,[113] and psychiatric disorders.[114] AI, indicated by a hyperactive SNS without a counterbalancing PNS (i.e. Vagal) influence, is prominently involved in the impaired regulation of heart rate,[115] BP,[111,116] cardiac electrical activity,[117] and endothelial function.[118,119] AI is known to precede the development of conventional CVDs risk factors and facilitates sub-clinical left ventricular hypertrophy, renal damage, and subsequent disease progression.[111,112,116]

AI, indicated by an elevated resting heart rate and a relatively slower heart rate recovery post-exertion, has been shown to independently predict all-cause mortality.[115,120] As ANS input is the primary influence in regulation of heart rate, increased heart rates at rest, exertion, and recovery remain important indicators of excess SNS and/or low PNS tone.[115,120,121] Likewise, evaluations heart rate variability (HRV) provide important indications of AI, signified by low SDNN time

intervals (i.e. standard deviation of the normal to normal R-R time intervals) and high values in low frequency (LF) and very low frequency (VLF) bands, commonly associated with cardio-metabolic morbidity and all-cause mortality.[112,122-126]

Excess SNS activity, driven by physical and psychological stressors, is a central mechanism of HTN development and maintenance, observed among at-risk non-hypertensive, pre-hypertensive, and individuals with established HTN.[116,127,128] The ANS regulates BP through a range of neuro-hormonal mechanisms, primarily: (a) the arterial and cardiopulmonary baroreceptors, BP sensing neurons located along the carotid sinus and the aortic arch, and (b) the renin angiotensin-aldosterone system (RAAS), a complex neuro-hormonal network involving the SNS and the hormones renin, angiotensin I, angiotensin-converting enzyme (ACE), angiotensin II, and aldosterone.[129-131]

Arterial baroreceptors, sense both increases and declines in BP, in turn activating the appropriate ANS response (i.e. increased PNS activation and decreased SNS activation in case of elevated BP), thus initiating subsequent changes in heart rate and vascular tone, including reduction in heart rate and vascular resistance to maintain steady BP levels. Reduced arterial baroreceptor sensitivity (BRS), characterized by a diminished PNS (i.e. vagal) compensatory action in response to increased BP, is an important marker of AI, contributing to impaired regulation of BP.[128,130-132] Reduced BRS has been observed among non-hypertensive but obese children,[133,134] adolescents,[133,135]and adults.[136] Reduced BRS has further been associated cardio-metabolic disease progression,[137-139] RSDN treatment response,[140] and increased risk of CVD complications and mortality in HTN,[141] myocardial infarction,[142-145] acute stroke,[146] and heart failure.[147]

The RAAS serves as another BP regulatory mechanism, intricately linking the central nervous system, ANS, and peripheral tissues. A decrease in renal perfusion pressure, sodium chloride concentrations, in addition to increased SNS activity, serve as initial stimuli for the synthesis of the hormone Renin within the kidney's juxtaglomerular cells. Renin, acts as the first step in the synthesis of Angiotensin I, a precursor of Angiotensin II, an important vasoconstrictor and a stimulus for aldosterone secretion, a regulator of sodium and water reabsorption, together increasing BP.[131,148] AI, mediated by dysfunctional baroreceptor and amplified RAAS activity (i.e. increased Angiotensin II cardiac and vascular effects), therefore plays a key role in HTN pathogenesis. AI is liked to AF development through its role in establishing chronic HTN, in turn promoting structural, functional, and electrical remodeling within the cardiovascular system.[7,149] Nocturnal non-dripping in systolic blood pressure (SBP), another indication of AI, has further been liked to AF development, evident by non-dippers having nearly twice elevated risk of AF development compared to dippers after adjustments 24-hr BP and for left ventricular enlargement/ hypertrophy.[150]

More direct evaluations of AI reflected in HRV indices have provided additional evidence on links between SNS-PNS tone and AF development.[14,151] In the first study, using 45-minute ambulatory electrocardiogram measurements in 784 middle aged adults, Perkiömäki et al.,[151] found reduced LF HRV band to be independently associated with incident AF (Hazard ratio: 2.81) after an average 16.5 years of follow-up after adjustment multiple demographic and clinical variables. More recently, Agarwal et al.[14] evaluated HRV using 2-min electrocardiogram recordings in 11,715 middle-aged adults and found independent associations between lower baseline SDNN time intervals, LF HRV, and high frequency (HF) values and increased risk of AF development following 20 years (Hazard ratio: 1.12, 1.16, 1.10 for 1 SD lower SDNN, LF HRV,

and HF HRV respectively). While the LF HRV band has typically been viewed to reflect SNS activity, more recent understandings indicate LF and HF bands to reflect the PNS influence on the heart,[152,153] underscoring the role of AI, specifically low PNS tone, in AF development.

2.2 Ambulatory Blood Pressure Monitoring in HTN Diagnosis and Management

Accurate evaluation of BP is central to the prevention and management of HTN. BP is routinely assessed in clinic and more recently at home using single or multiple measurements in close succession. Nonetheless, the importance of repeated BP measurements over longer periods of time had been recognized as early as the 1960s as clinic-based BP evaluations were found to be poor estimates of BP in non-clinical settings.[154-157] Efforts at continuous out-of-clinic measurement started shortly thereafter with the development of non-invasive ABPM devices.[158] These developments continue to the present day as advances in electronic technology and digital connectivity provide additional opportunities for remote capture, transmission, and monitoring of BP and other clinical indicators.[159]

In contrast to conventional clinic-based BP assessments, 24-hour ABPM conducts multiple BP measurements at regular intervals throughout the 24-hour period during daily activities and sleep. 24-hour ABPM further enables differentiating between episodic (i.e. white coat hypertension) and sustained elevations in BP. Compared to conventional clinic-based assessments, ABPM-derived BP has emerged as a stronger predictor of target organ damage,[160] CVD morbidity, and mortality.[149,161-167] In addition, elevated BP during sleep, characterized by either nocturnal HTN (i.e. $\geq$ 120 mmHg in systolic BP) or nocturnal non-dipping (i.e. < 10% decline in sleep time BP relative to waking values),[168] has emerged as a novel prognostic indicator of cardiovascular risk, exhibiting stronger associations with morbidity and mortality than ABPM values during daytime/ waking periods.[149,161-163,169-171]

While both nocturnal HTN and dipping provide indications of BP dynamics during sleep, in comparing these measures, several recent evaluations indicate nocturnal HTN (an absolute indicator of nocturnal hemodynamic stress) to exhibit stronger associations with indices of sub-clinical cardiac,[169,172-176] vascular,[172,175-177] and renal[169,176,178] damage than nocturnal non-dipping. Similarly, though both nocturnal HTN and non-dipping represent elevated CVD risk, a comparative review on their respective relationships with CVD morbidity and mortality found nocturnal HTN a more robust indicator of CVDs events and all-cause mortality compared to nocturnal non-dipping.[172]

Nocturnal HTN and non-dipping could indeed represent different underlying pathologies or stages of disease severity; in particular nocturnal HTN represents a direct measure of absolute nocturnal hemodynamic stress while nocturnal non-dipping could indicate stronger AI, a characteristic of more advanced disease.[179,180] For instance, in an evaluation of nearly 43,000 treated and untreated HTN patients within the Spanish ABPM registry,[179] de la Sierra et al. found nocturnal systolic non-dipping to be associated with increased age (i.e. $\geq$ 60 years), body mass index (i.e. $\geq$ 30 kg/m^2), diabetes mellitus, CVD, and renal disease after statistical adjustments for 24-hour systolic and diastolic pressures. In a subsequent investigation within the same registery,[180] de la Sierra et al. further demonstrated distinct patterns of association between nocturnal systolic HTN and non-dipping with indices of cardiovascular risk and renal function. In particular, these included independent associations between nocturnal systolic HTN with smoking, diabetes mellitus, microalbuminuria (an early sign of renal dysfunction), and between nocturnal systolic non-dipping and smoking, diabetes mellitus (only among the untreated patients), more severe renal dysfunction and previous CVDs. Nonetheless, the presence of nocturnal systolic HTN and non-dipping together confers the highest degree of CVD risk.[174,176,180]

24-hour ABPM, compared to conventional modes of BP assessment, further facilitates evaluations of additional hemodynamic indicators, including blood pressure load (BPL), defined as the percentage of 24-hour ABPM readings above HTN diagnostic thresholds (e.g. Waking: % readings >135/85; Sleeping: % readings > 120/70 mmHg),[168] and blood pressure variability (BPV), a volatility-type measure of activity, psychological, or pathophysiologically-related variations around mean BP or between successive measurements.[181,182]

Though BPL and BPV remain less frequently explored than BP averages, increased BPL has shown to be significantly associated with the extent of left ventricular hypertrophy,[97,183] endothelial dysfunction,[184] and impaired renal function in non-hypertensives and those with established HTN.[183] Nonetheless, the contribution of BPL to improvements in CVDs risk prediction, beyond 24-hour ABPM averages, remain less established. In the only focal study to date, Li et al.[185] did not find 24-hour systolic or diastolic BPL, when considered along with the respective 24-hour averages in the same model, to markedly improve prediction of 10-year risk of CVD-related morbidity and mortality in nearly 8700 middle-aged adults (with and without HTN). Long term, visit-to-visit BPV has also been shown to be associated with increased CVD, providing still another ABPM-derived indicator of increased CVDs risk.[186]

2.3 The Promise of Risk Reduction in CVDs Prevention and Management

2.3.1 Pharmacological and Lifestyle-based Risk Reduction

Cardiovascular risk reduction efforts, whether pharmacological or lifestyle-based, have played a central role in lowering CVDs risk factors and mortality rates across economically-developed countries.[52] Pharmacological risk reduction, through statins, antihypertensives, and antithrombotics, is the main line of therapy in reducing BP,[187-189] blood lipids,[190,191] endothelial

dysfunction,[192-194] and blood coagulation,[195] thereby lowering the risk of atherogenesis, thrombosis, and future CVDs.[196-202]

Lifestyle modification, alone or in conjunction with conventional medical therapies, represents another viable strategy in primary and secondary prevention of CVDs.[203-205] As predominantly lifestyle-based diseases, smoking, diet, and physical inactivity, and psychological stress represent chief modifiable lifestyle influences that precede the development of subclinical cardio-metabolic and vascular changes, and CVD, and clinical complications.[33,206,207] In quantifying their respective influences, the INTERHEART and INTERSTROKE studies,[207,208] two global evaluations of modifiable risk factors in CVDs, found lifestyle behaviours, notably smoking, dietary choices (i.e. fruit, vegetable and alcohol consumption), physical activity, psychosocial stress, along with conventional lifestyle-influenced risk factors (i.e. elevated ApoB/ApoA1 lipid ratio, abdominal obesity, HTN, diabetes mellitus) together accounted for over 90 percent of the population attributable fraction of myocardial infarction and stroke. In addressing this immense preventive potential, numerous epidemiological and interventional efforts have demonstrated success in quantifying the extent of risk reduction benefits conferred by various lifestyle-based approaches, notably: healthy dietary composition,[209-211] physical activity,[212-214] stress reduction,[215,216] and smoking cessation.[217-219]

2.3.2 Mindfulness-based Interventions and CVD Risk Reduction

Scientific interest on the physical and psychological effects of MBI has seen considerable growth in the past 40 years, in part due to the growing recognition of the role of cognitions, emotions, and behaviours in the pathogenesis, progression, and successful adjustment to physical and psychiatric disorders.[33,220-222] While the specific elements of MBI vary, these generally involve elements of: (a) sitting mindfulness meditation, aimed at promoting present-focused, non-

judgmental, moment to moment awareness of thoughts, emotions, and bodily sensations,[223,224] (b) mindful awareness of movement within the context of low-impact physical activity (i.e. Yoga, Tai Chi),[225] or (c) mindfulness meditation or related skills, as integrated within the structures of standard modern psychotherapies.[226-230]

As a self-regulatory skill, mindfulness encompasses the capacity to intentionally attend to one's present moment experience and non-judgmentally observe thoughts, feelings, sensations, and associated cognitive-emotional appraisals.[224,231] Mindfulness of breath, thoughts, emotions, and sensations, formally practiced during sitting meditation is a central method of developing mindfulness.[224] The practice involves: (a) focused attention on the breath as the primary attentional focus, (b) non-avoidant and non-judgmental observation of cognitions, emotions, and bodily sensations as they occur in the present moment, and (c) re-direction of attention back to breath in instances of mind-wondering and ruminative thinking, ultimately facilitating a more direct and objective perception of one's subjective experience, devoid of past- or future-oriented ruminations.

As a psychological construct, mindfulness is operationally defined to consist of a regulatory element, involving moment-to-moment regulation of attentional focus, and an attitudinal element, expressed by a receptive and non-avoidant stance toward one's experience.[232] From a cognitive-behavioural standpoint, mindful awareness represents a departure from habitual, often automatic, and reactive styles of attending to experience towards a more adaptive perspective that is characterized by: (a) a de-centered, defused, and re-perceived relationship to one's thoughts and emotions,[229-231] (b) a greater awareness of metacognitions and underlying metacognitive beliefs,[232-234] and (c) an enhanced sensory-affective de-coupling in the context of sensory discomfort.[223] Accordingly, development of mindfulness as a key attention, cognitive, and

emotion-regulatory skill is a central goal of mindfulness-based interventions among healthy individuals and those with physical and psychiatric disorders.[224,235]

Multiple literature syntheses of therapeutic MBI, including established Mindfulness-based Stress Reduction (MBSR) and Mindfulness-based Cognitive Therapy (MBCT), have supported the effectiveness of such programs in lowering anxiety and depressive symptoms,[236-239] psychological stress,[239,240] preventing depression relapse,[237,241] in addition to enhancing empathy and self-compassion[242,243] among healthy[239,240] and psychiatric populations.[236-238,241] MBI have further seen applications in management of psychological health, disease-specific symptoms, autonomic imbalance, and related physiological markers in the context of physical illness, notably cancer,[236] CVDs,[27] and chronic pain,[244] indicating their greater integration in chronic disease management.

In particular, MBI have seen greater applications in CVD management, given the recognition of psychological stress, maladaptive coping styles, and the ensuing AI in CVDs development, progression, and effective management.[33,222,245,246] These include evaluations of MBI impacts beyond mental health, towards a greater focus on their psychophysiological and CVD-related impacts, most notably in regulation of ANS, BP, and disease-specific symptoms.[27,28]

2.4 Personal Health Coaching as a Behavioural Self-Management Strategy

Improving patient adherence to medication and lifestyle regimens has been a pressing priority in contemporary chronic disease management. Poor adherence to prescribed medications and healthy lifestyle practices substantially limits the effectiveness of medical or lifestyle-based risk reduction efforts, resulting in increased risks for hospitalizations [247-250] and mortality. [247,248,250-253] A multifactorial process, patient adherence can be improved by an understanding of its patient, healthcare provider, and health system-level antecedents.[254,255] More specifically, lack of

motivation and self-efficacy in fulfilling prescribed regimens on the patient side, shortage of individualized self-management and adherence support in care settings, and healthcare system's establishment on an acute model of care,[254-256] all point to the need for greater efforts to enhance patient adherence in an era where disease management success greatly depends on successful patient self-management.

In attempts to improve on the status quo of medical and behavioural risk reduction, the category of interventions that employ health coaching to enhance chronic disease self-management demonstrate significant potential.[257-259] In contrast to traditional patient education, characterized by information provision and physician-directed medical management,[256] health coaching aims to facilitate greater patient involvement in disease management via establishment of a supportive psycho-educational coaching relationship to: (a) provide personally-relevant disease management information, (b) support collaborative goal setting, problem solving, and self-efficacy, and (c) monitor adherence and address motivational barriers and complexities inherent in adoption of new behaviours.[258,260]

As a psycho-educational approach that incorporates psychological support alongside disease-specific education and skill development, health coaching's theoretical focus is integrative in nature, utilizing specific and non-specific therapeutic factors.[259,261] These include specific theoretical frameworks, such as motivational interviewing, social cognitive theory, and cognitive-behavioural theory, and non-specific factors, notably a focus on empathic understanding, and active (reflective) listening, and therapeutic alliance (client-coach relationship), analogous to a common-factors approach to psychotherapy.

Nonetheless, despite similarities in theoretical bases and therapeutic goals, coaching is often contrasted with psychotherapy, as indicated by an interview study of professional coaches

and therapists.[262] While they identified coaching to have a *collaborative focus* in facilitating/ guiding adoption of concrete disease-management or personal development objectives in non-psychiatric populations, by comparison, psychotherapy was characterized as therapists having an *expert orientation,* resulting in a more *intensive exploration* of patient's psychological and interpersonal functioning (in the context of psychiatric diagnosis) and a more intensive *direction of* the course of treatment.[262]

In summary, within a chronic disease self-management context, coaching aims to enhance patient self-efficacy, intrinsic motivation, and disease self-management skills as they navigate the behaviour change and self-management process, seeking to promote greater adherence to jointly-defined and personally-meaningful self-management goals, akin to a common factors/ non-directive form of psychotherapy.

3.0 Methods

3.1 Design and Eligibility

This study was a 16-week parallel group randomized controlled trial (RCT). Participants were randomly assigned to one of two study groups: Mindfulness-based Risk Reduction (MBRR) coaching or Diet-based Risk Reduction (DBRR) coaching, using a computerized randomization procedure with an equal 1:1 allocation ratio, performed by a person separated from study administration. Study participants were recruited from the Partners in Cardiovascular Electrophysiology (PACE) Clinic of the Southlake Regional Health Centre (SRHC) in Newmarket, Ontario between March 2017 – April 2019.

Patients between the ages of 50-80 years were eligible to participate if diagnosed with AF and found to have an elevated systolic blood pressure of ≥ 135 mmHg during waking period assessed using ABPM. Their willingness to participate was indicated by signing an informed consent (Appendix B). Participants were ineligible if there was a scheduled surgery, CVD-related or otherwise, during the study period. All study participants received usual medical care at the PACE clinic in addition to MBRR and DBRR. Study procedures and materials were reviewed and approved by SRHC Research Ethics Board (SRHC 0031-1617) (Appendix C). Considered a delegated review, separate approval was not required as indicated by the York University Human Participants Review Committee.

3.2 Procedures

Recruitment was undertaken at the SRHC through phone calls, where a PACE Clinic research assistant contacted potentially-eligible patients. The research assistant provided study information and inquired about possible interest in a phone or face-to-face meeting with the Study Coordinator (MP) to learn more about the research. Only upon indication of patient interest and

willingness to engage in study discussion, did the Study Coordinator undertake additional phone contacts with patients. Recruitment also followed direct referrals from physicians at the PACE Clinic or direct contacts from interested patients.

The Study Coordinator explained the study rationale, procedures, required assessments, and the informed consent procedure. After informed consent was obtained, participants received an ABPM assessment to evaluate eligibility. Following ABPM, participants were informed about results, completed psychometric questionnaires, and were allocated to either MBRR or DBRR study groups using the sequentially-numbered opaque envelopes prepared by a person separated from administration of the intervention.

Following consent, participants received the intervention from a health coach trained in mindfulness and behavioural modification strategies to guide adoption of mindfulness practice and principles or cardiovascular exercise and dietary risk reduction behaviours. In light of travel distance and other considerations (i.e. inability to attend clinic visits, driving or parking considerations, or vacations), the coach and patient remained in contact through the combination of in-person meetings, telephone, and e-mail contacts in light of each participant's circumstances. Participants received additional evaluations of ABPM and psychological status at 8-week (post-intervention) and 16-weeks (follow-up). Upon study completion, participants had the opportunity to receive further information and guidance on the alternate study intervention (i.e. the intervention to which they were not initially exposed).

3.3 Intervention Group: Mindfulness-Based Risk Reduction

Participants in the MBRR group were assigned a mindfulness-based coaching protocol that centered around readings and audio recordings by Dr. Paul Ritvo. Program materials were delivered to participants as physical copy or sent electronically. The program gradually introduced

participants to mindfulness as a mind-body practice and its role in cardiovascular disease and the broader chronic context of disease management, and assisted them in establishing 10-20 minutes of daily sitting mindfulness practice at home. The program emphasized the practice of sitting mindfulness meditation, primarily focused on mindfulness of breath and one's daily life experiences. Delivered as a mixed modality intervention utilizing in person, telephone, and online e-mail contacts, the program was also supplemented by weekly guided mindfulness meditation classes by MP at the SRHC cardiovascular rehabilitation clinic.

Weekly readings (Table 1) during the 8-week intervention phase included: *Natural breath and natural mind* (Chapter 1), *Making sense of a sea of error* (Chapter 2), *Alternatives to being wired and tired* (Chapter 3), *Befriending* (Chapter 4), *Changing* (Chapter 5), *Forgiveness* (Chapter 6), *Interpersonal mindfulness* (Chapter 7), and *Independent benevolence* (Chapter 8). For the follow-up period (weeks 9-16), the emphasis was on deepening one's practice. The coach remained in contact with patients at a lower intensity, bi-weekly basis. As no new topics were introduced, the coach-participant interactions centered around supplementary readings related to *mindfulness, flow*, and *acceptance*, and *scientific research on mindfulness*.

Coach-patient interactions supported participants in establishing a regular mindfulness meditation practice, while taking steps towards more mindful living by applying greater awareness during daily tasks and interpersonal interactions. Specifically, the coaching relationship served as a context for personalized discussions of weekly readings, clarifications of participant questions on readings, and for exploring life experiences with integrating mindfulness. To this end, the coach encouraged discussions on experiences of success and on the difficulties encountered in establishing greater mindfulness practice. The coach and participants then jointly explored

multiple solutions to support greater mindfulness practice, awareness, and the understanding of program themes.

Table 1 Major topics and themes outlined within weekly readings

Topics	Major themes
1) Natural Breath, natural mind	- Breath, present-moment awareness, and relaxation - Mindfulness of breath, mind, and unconditional calm - De-catastrophizing and mindful living
2) Making sense of a sea of error	- Mindfulness, catastrophes, avoidance, and distractions - Uncertainty, self-efficacy, and balanced confidence
3) Alternatives to being wired and tired	- Stress, sympathetic hyper-arousal, and chronic illness - Autonomic self-regulation, and balance
4) Befriending	- Avoidance, anxiety, and automatic living - Mindfulness, non-avoidance, and self-compassion
5) Changing	- Mindfulness as an anti-procrastination practice - Rumination, worry, and present moment-awareness - Mindful awareness of thoughts and cognitive distortions
6) Forgiveness	- Mindfulness, the past, and habitual negative thoughts - The fragmented self, holistic self-awareness and understanding
7) Interpersonal mindfulness	- Mental concepts (i.e. schemas) and relationship dynamics - Mindful communication, listening, and authentic connection
8) Independent benevolence	- Cultivating peace, rediscovering resilience, and generosity - Mindful awareness in transcending conflict to freedom, alienation-to-connection, depression to compassion, and negative to positive

3.4 Comparison Group: Diet-based Risk Reduction

The comparison group, DBRR was guided by principles outlined within *Your Guide to a Healthy Heart*,[263] a publicly-available guide published by the National Heart, Lung, and Blood Institute. The guide, intended for a general audience, included explanations of CVD, conventional CVD risk factors, in addition to lifestyle recommendations on reducing one's risk of CVD through physical activity and the Dietary Approach to Stop Hypertension (DASH) eating plan, an evidence-based dietary strategy,[263,264] shown to be effective in reducing blood pressure.[209]

Similar to MBRR, the coach-participant interactions, through in-person, telephone, or e-mail contacts, focused on exploring ways to integrate DASH dietary-lifestyle principles, notably the focus on limited saturated fat intake, increased fruit and vegetable consumption, reduced Sodium and increased Potassium intake. Coaching sessions comprised of reviews of understanding, progress, and provision of social support for participants in lifestyle change. When compared to MBRR, the DBRR focused on learning about specific health-related principles, including the effects of dietary sodium and potassium on blood pressure, identifying specific sources of dietary sodium and potassium, the reading of food labels to better identify sodium and potassium contents in fresh and prepared foods, and moderate physical activity. DBRR did not require participants to adhere to specific physical activity, meal, or weight loss targets.

3.5 Assessments

3.5.1 ABPM Assessment

24-hour ABPM were performed at baseline, 8-weeks (post-intervention), and 16-weeks (follow-up) using SpaceLabs Healthcare ambulatory blood pressure monitor (Model number: 90207). The validity and reliability of these monitors have both been extensively researched in several studies, with demonstrated accuracy in measuring ambulatory blood pressure.[265] 24-hour

ABPM involved continuous blood pressure assessments every 20 minutes during waking and every 60 minutes during sleeping periods. Prior to ABPM, participants self-reported their typical bedtime and wake-up times, saved into the monitor to allow for automatic shifts between waking (i.e. per 20 minute) and sleeping (i.e. per 60 minute) assessment intervals. During ABPM, participants kept a log (Appendix D) of their daily activities, including their subjective ratings of exertion, and their actual bedtime and wake-up times, used to adjust their waking and sleeping periods in cases of divergence from their pre-ABPM self reports. Participants were instructed to continue with their typical activities of daily living, but to refrain from activities not reflective of their usual daily living to allow for more representative blood pressure evaluations.

3.5.1.1 Primary ABPM Outcome

The primary outcome of this study is the change in mean ABPM SBP from baseline to 8- (post-intervention) and 16-weeks (follow-up) during wake and sleep periods.

3.5.1.2 Additional ABPM Outcomes

Additional secondary outcomes included: (a) mean DBP, (b) mean percentage nocturnal dipping in SBP, calculated as [(Waking SBP – Sleeping SBP)/ Waking SBP] stated as a percentage value, (c) mean SBP load (SBPL) and DBP load (DBPL), defined as the percentage of blood pressure measurements above clinical ABPM HTN criteria during waking and sleeping periods,[168] and (d) mean SBP and DBP BPV, defined as the standard deviations of all individual blood pressure assessments separately for SBP and DBP during waking and sleeping periods.

3.5.2 Psychometric Outcomes

3.5.2.1 Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS)[266] is a 14-item self-report questionnaire evaluating anxiety and depression symptoms in medical populations. This

questionnaire provides separate scores for anxiety and depression symptoms without reliance on somatic symptoms common in anxiety, depression, and medical conditions. The measure has demonstrated a high degree of internal consistency (Cronbach's alpha = 0.82-0.83), sensitivity in identifying depressed and anxious individuals, in addition to associations with Beck Depression Inventory and the State-Trait Anxiety Inventory.[267]

3.5.2.2 Cardiac Anxiety Questionnaire

The Cardiac Anxiety Questionnaire (CAQ) is an 18-item index of heart-focused anxiety (HFA), namely anxiety sensitivity specific to cardiovascular patients,[268] defined as the fear of cardiovascular-related symptoms stemming from their perceived harmful effects. The CAQ conceptualizes HFA as a three-dimensional construct that includes heart-related fear, avoidance, and attention subscales. The CAQ involves participants rating the frequency of experiencing HFA on a 5-point (0-4) Likert scale with higher scores indicating greater HFA. Scores are computed as the mean value of all items (total score) and mean values of the respective subscale items, allowing direct comparisons between total and subscale scores. The CAQ has demonstrated high degree of internal consistency (Cronbach's alpha= 0.83), test-retest reliability, and concurrent validity by showing.[268]

3.5.2.3 Profile of Mood States - Short Form

The Profile of Mood States – Short Form (POMS-SF) is a 37-item version of the larger 65-item POMS, providing assessments of six dimensions of mood, including: tension, depression, anger, vigor, fatigue, and confusion.[269] The POMS-SF has demonstrated high internal consistency for all subscales (Cronbach's alpha= 0.76-0.95) in healthy and clinical samples,[270] including convergent and discriminant validity, evidenced by the pattern of correlations with the original POMS and other validated psychological measures.[270,271]

3.5.2.4 Five Facet Mindfulness Questionnaire - Short Form

The Five Facet Mindfulness Questionnaire – Short Form (FFMQ-SF)[272] is a 24- item questionnaire that evaluates mindfulness, conceptualized as five separate facets of observing, describing, acting with awareness, non-judging of inner experience, and nonreactivity to inner experience. FFMQ-SF has shown acceptable psychometric characteristics, including high internal consistency (Cronbach's alpha= 0.73-0.91), as well as convergent and discriminant validity with mood and related constructs, characterizing FFMQ-SF as a valid and reliable index of mindfulness in adults in both short form and long formats.[272-274]

3.5.2.5 Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI)[275] is a comprehensive measure subjective sleep quality over a month preceding assessment. The instrument widely used in epidemiological or clinical contexts. PSQI leads to an overall global sleep quality score, comprised of components evaluating disordered sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, sleep medication use, and daytime dysfunction. The instrument has demonstrated a high degree of internal consistency (Cronbach's alpha= 0.83), test-retest reliability, discriminant validity in distinguishing between sleep-disordered individuals and controls, in addition to convergence with polysomnographic results.

3.6 Sample Size Estimation

In determination of sample size, G*Power estimation indicated a total sample size of 28 would be required to detect a medium level effect size (Cohen F = 0.25) with statistical power set at 0.80 and a significance level of 0.05.[276] In addition, as a reduction of 5 mmHg has been associated with a reduction of 17% in CVD risk,[277] required sample size was estimated using an

alternative approach to detect a 5 mmHg between-group mean difference, and indicated a required sample size of 32 with power set at 0.80 and a significance level of 0.05.[278]

3.7 Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics version 23. These included evaluation of potential differences in demographic and clinical variables at baseline between MBRR and DBRR groups using independent samples t-test (Welsh-corrected) for numeric and chi-square test for independence for categorical variables. To evaluate change from baseline in primary and additional study outcomes on a between-groups and within-group basis, we used linear mixed modeling (LMM) as the main analytic approach. LMM uses a different approach in handling missing data compared to the conventional repeated measures ANOVA (RM-ANOVA). [279,280] While RM-ANOVA performs list-wise deletion of all participants with missing data necessitating imputations, LMM uses data from all participants with available data and is not sensitive to sphericity, a commonly-observed phenomenon in longitudinal data. Alternatively, analyses were also performed using factorial RM-ANOVA with a last observation carried forward (LOCF) approach to missing data. In the presence of sphericity, a MANOVA approach was used in evaluation of data. In both analytic approaches, the statistically significant effects for time, group, and the group × time interactions were followed by Bonferroni adjusted evaluation of pairwise post-hoc comparisons.

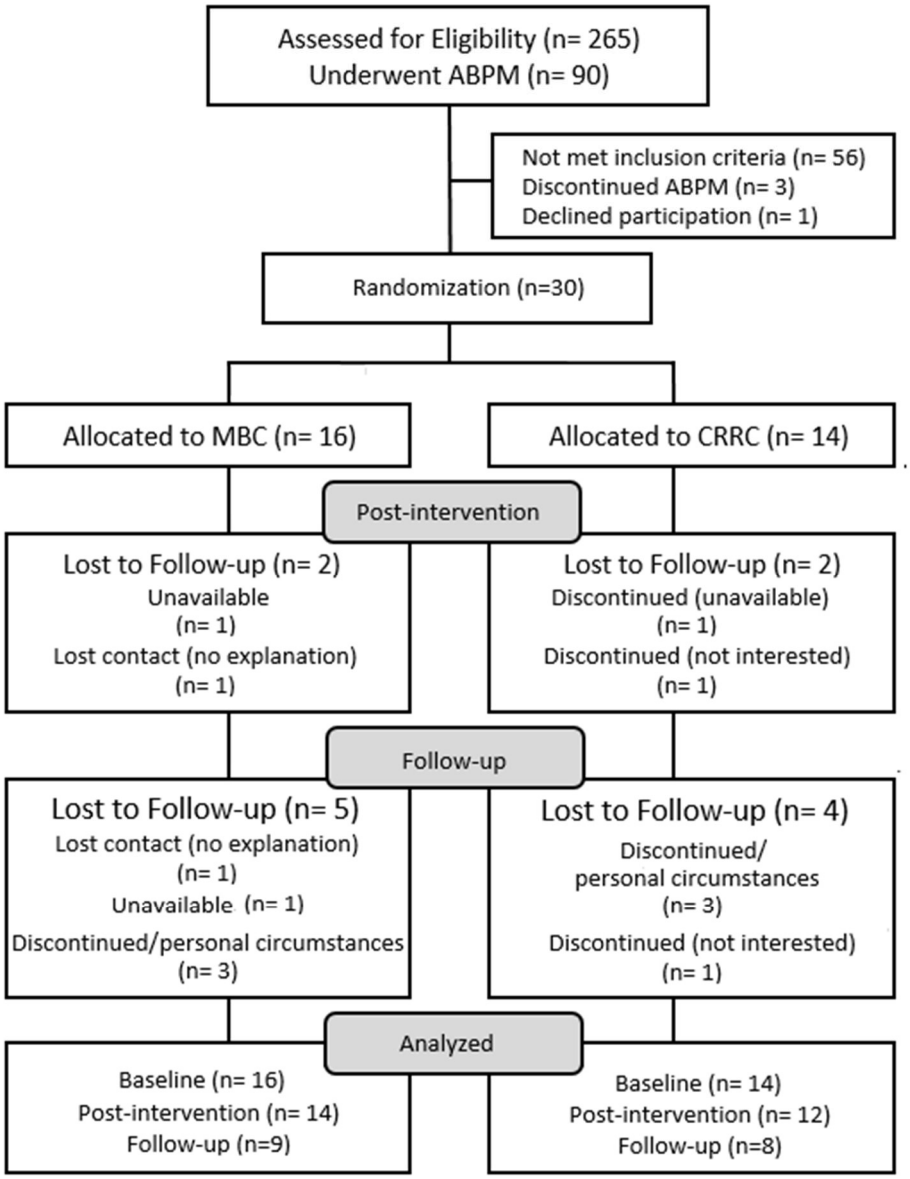
4.0 Results

4.1 Participant Recruitment and Flow

As outlined in the CONSORT flow diagram (Figure 1), 265 individuals were approached for participation, of whom 90 (51.1% female) underwent evaluation of 24-hour ABPM to determine eligibility based on their systolic hypertension levels. Of these 90 individuals, 87 individuals completed the 24-hour ABPM and 3 discontinued 24-hour ABPM assessment. Of the 87 individuals who completed 24-hour ABPM, 31 individuals met study inclusion criteria, of whom 30 indicated interest and were randomized to either MBRR or DBRR.

There was a total of 4 dropouts within MBRR (n = 2) and DBRR (n = 2) at post-intervention (8 weeks) and 9 dropouts within MBRR (n = 5) and DBRR (n = 4) within the 16-week follow up. Altogether, 26 participants completed the 8-week post-intervention assessments and 17 completed the 16-week follow-up. No statistically significant differences were observed on any demographic, behavioural, or clinical characteristics between study participants who completed the study and those who dropped out or were lost to follow up.

Figure 1 Study enrolment flow diagram



4.2 Participant Characteristics

Table 1 presents participants' demographic and clinical characteristics at baseline, including AF symptomology, medical history, and current medications. Participants (56.6 % female) ranged in age between 54-80 years, with a mean age of 69.6 (SD= 7.65) years, and a mean of 4.77 (SD= 5.67) years since AF diagnosis. There were no statistically significant between group

differences observed in age, time since diagnosis, frequency of palpitations, smoking habits, and caffeine use between MBRR versus DBRR. The great majority (90%) of participants had a family history of either AF or other CVD indicated by their parental history of these conditions, with no statistically significant differences observed between MBRR and DBRR groups. In addition, except in 1 participant who qualified as having a mild degree of systolic dysfunction (LVEF= 40-49%), all participants demonstrated normal left ventricular size and function (LVEF= 50-70%), with no statistically significant differences between groups. In relation to AF procedural history, 70% of participants had histories of cardioversions and 43.3% had undergone PVAI ablation, with no statistically significant differences in the frequency of previous cardioversions and ablations between MBRR and DBRR. As outlined in Table 1, there were no statistically significant differences between MBRR and DBRR in the frequency of CVD, Diabetes Mellitus, and Gastrointestinal (e.g. Crohn's disease and Ulcerative Colitis), musculoskeletal (e.g. arthritis and osteoarthritis), or pulmonary diseases. Likewise, there were no statistically significant differences between study groups in prescription of antihypertensive, antiarrhythmic, anticoagulant, and other prescribed medications.

4.3 ABPM Characteristics

Table 1 further presents participants' ABPM characteristics at baseline, including number and percent of successful measurements, SBP dipping, BPV, and BPL separately during waking and sleeping periods. At baseline, MBRR participants wore the BP monitor for an average duration of 23.0 hours (48.9 waking and 9.0 sleeping measurements, 89% success) and DBRR participants wore the BP monitor for an average duration of 23.2 hours (51.0 waking and 8.3 sleeping measurements, 92% success), with no statistically significant differences groups in these parameters at baseline. At post-intervention (8 weeks), except for 1 participant who did not

complete ABPM during sleep, 26 participants completed ABPM for an average duration of 23.6 (43.0 waking and 8.8 sleeping measurements, 90.7% success) hours in MBRR, and for an average duration of 23.9 (45.0 waking and 7.8 sleeping measurements, 93.2% success) in DBRR. Finally, at 16-weeks follow-up, 17 participants completed ABPM for an average duration of 23.5 (43.3 waking and 8.9 sleeping measurements, 92.5% success) hours in MBRR, and for an average duration of 22.6 (43.7 waking and 7.9 sleeping measurements, 93.1% success) in DBRR. There were no statistically significant differences between MBRR and DBRR at either post-intervention (8 weeks) and 16-weeks follow-up in assessment duration, number of BP measurements, and percent of success measurements. In relation to nocturnal SBP dipping status, there were no statistically significant differences between MBRR and DBRR in SBP dipping status, evaluated as either continuous or categorical classification. Likewise, no statistically significant baseline differences were observed in the magnitude of SBPL, DBPL, SBPV, and DBPV during waking and sleeping periods between MBRR and DBRR (see Table 1).

Table 2 Demographic and clinical characteristics of study participants at baseline

Demographic & Clinical Parameters	MBRR (n = 16)	DBRR (n = 14)	P
Age [(mean years (SD)]	70.2 (9.05)	68.9 (5.91)	0.62
Sex [n (% female)]	10 (62.5)	7 (50.0)	0.49
BMI [kg/m^2]	29.7 (5.8)	28.0 (4.9)	0.40
Alcohol consumption [n (%)]	10 (62.5)	8 (57.1)	0.77
Caffeine intake [n (%)]	11 (68.7)	9 (64.3)	0.80
Smoking (former or current) [n (%)]	6 (37.5)	4 (28.6)	0.60
Family history of AF/CVD [n (%)]	14 (87.5)	13 (92.9)	0.63
Years since AF diagnosis [(mean years (SD)]	4.8 (3.8)	4.7 (7.4)	0.96
Palpitations [n (%)]	3 (18.8)	4 (28.6)	0.53
Left Ventricular Ejection Fraction (LVEF)	61.0 (4.6)	58.9 (6.6)	0.18
Previous cardioversion(s) [(mean (SD)]	1.7 (1.8)	1.0 (1.5)	0.28
Previous PVI ablation(s) [n (%)]			
1	6 (37.5)	4 (28.6)	0.72
2-3	1 (6.3)	2 (14.3)	
Comorbidities [n (%)]			
Cerebrovascular disease	0 (0.0)	1 (7.1)	0.28
Coronary artery disease	3 (18.8)	5 (35.7)	0.30
Diabetes mellitus	2 (12.5)	1 (7.1)	0.63
Gastrointestinal disease	2 (12.5)	1 (7.1)	0.63
Musculoskeletal disease	3 (18.8)	5 (35.7)	0.30
Other arrhythmia	5 (31.2)	5 (35.7)	0.80
Sleep apnea	4 (25.0)	3 (21.4)	0.82
Pulmonary disease	3 (18.7)	3 (21.4)	0.86
Current Medications [n (%)]			
Angiotensin II receptor blockers	5 (31.2)	7 (50.0)	0.30
ACE inhibitors	7 (43.7)	4 (28.6)	0.39
Beta blockers	7 (43.7)	5 (35.7)	0.65
Calcium channel blockers	3 (18.8)	4 (28.6)	0.53
Diuretics	4 (25.0)	5 (35.7)	0.53
Antiarrhythmic	13 (81.2)	8 (57.1)	0.15
Anticoagulant/ Antiplatelet inhibitors	16 (100.0)	13 (92.9)	0.28
Lipid lowering medications	9 (56.3)	5 (35.7)	0.26
Psychiatric medication(s)	6 (37.5)	4 (28.6)	0.60
ABPM Parameters			
Duration [hours (SD)]	23.0 (2.4)	23.2 (1.2)	0.85
Number of measurements [(mean (SD)]			
Waking	39.3 (8.5)	42.7 (4.2)	0.17
Sleeping	9.0 (1.9)	8.2 (2.8)	0.37
Successful measurements [% (SD)]	89.0 (13.7)	92.0 (16.6)	0.56
ABPM Average [(mean mmHg (SD)]			
Waking SBP	145.9 (6.9)	145.1 (6.1)	0.72
Waking DBP	75.1 (8.1)	79.2 (8.6)	0.19

	Sleeping SBP	129.5 (14.8)	130.7 (14.6)	0.82
	Sleeping DBP	63.8 (6.9)	67.6 (8.3)	0.18
Nocturnal SBP Dipping [(mean % decline (SD)]		11.1 (10.2)	9.8 (10.0)	0.73
SBP Dipping Status [n (%)][a]				
	Dipper	5 (31.2)	3 (21.4)	0.73
	Non-dipper	8 (50.0)	9 (64.3)	
	Reverse dipper	3 (18.7)	2 (14.3)	
BPL [(% of measurements (SD)][b]				
	Waking SBP	77.4 (17.8)	78.6 (15.6)	0.84
	Sleeping SBP	70.1 (30.9)	75.0 (28.7)	0.65
	Waking DBP	18.4 (17.8)	26.9 (27.7)	0.34
	Sleeping DBP	20.8 (21.8)	38.9 (32.6)	0.10
BPV [(mean (SD)]				
	Waking SBP	12.1 (2.9)	12.2 (3.2)	0.95
	Sleeping SBP	10.8 (3.0)	10.8 (3.7)	0.99
	Waking DBP	8.5 (2.5)	8.1 (2.4)	0.70
	Sleeping DBP	8.0 (2.1)	7.2 (2.6)	0.36

[a] SBP Dipping status categorized as: dipper ≥ 10%, non-dipper <10 %, and reverse dipper <0% drop in nocturnal SBP.

[b] BPL criteria classified according to percent of measurements above 135/85 for waking and 120/70 during sleep.[168]

4.4 ABPM Outcome Evaluation

Tables 3a and 3b outline means and standard deviations for ABPM outcomes according to LMM and RM-ANOVA analytic strategies respectively. These entailed: waking and sleep SBP as the primary outcome, nocturnal dipping as the secondary outcome, and DBP, SBPL, DBPL, SBPV, DBPV as additional outcomes.

4.4.1 Waking and Sleep SBP (LMM)

As seen in Table 3a, under the LMM strategy, waking SBP results showed a statistically significant main effect of time ($F(2, 45.8) = 12.92$, $p = 0.0001$) in addition to non-statistically significant effects for group ($p = 0.77$) and group × time interaction ($p = 0.79$), indicating statistically significant reductions from baseline to 8 (-6.68, $p = 0.002$) and 16-weeks (-9.68, $p = 0.0001$) in mean waking SBP across both study groups.

For sleeping SBP, LMM similarly showed a statistically significant main effect of time ($F(2, 38.2) = 7.43$, $p = 0.002$), reflecting statistically significant reductions in mean sleeping SBP from baseline to 8 (-5.88, $p = 0.006$) and 16 (-6.46, $p = 0.009$) weeks across both study groups.

4.4.2 Waking and Sleep SBP (RM-ANOVA)

ITT analyses for mean SBP, utilizing RM-ANOVA with a LOCF approach to missing data (table 3b), indicated no statistically significant differences between MBRR and DBRR in mean SBP during either waking or sleeping periods at 8-week post-intervention and 16-week follow-up periods.

For Waking SBP, given the significance of Mauchly's test of Sphericity ($p = 0.01$), a MANOVA strategy was adopted in interpreting RM-ANOVA. For waking SBP, results indicated a statistically significant main effect of time ($F(2, 27) = 7.10$, $p = 0.003$, $\eta p2 = 0.34$), but non-significant effects for group ($p = 0.82$) and group × time interaction ($p = 0.77$, $\eta p2 = 0.09$),

reflecting reductions in mean waking SBP from baseline to 8 (-5.71, p = 0.01) and 16 (-6.49, p = 0.002) weeks irrespective of study interventions.

For sleeping SBP, with Mauchly's test of Sphericity not statistically significant (p = 0.19), results showed a statistically significant main effect of time ($F(2, 56) = 6.39$, p = 0.003, $\eta p2 = 0.19$) and non-significant effects for group (p = 0.92) and group × time interaction (p = 0.33), indicating statistically significant reductions from baseline to 8 (-4.44, p = 0.01) and 16 (-4.71, p = 0.03) weeks in mean SBP during sleep irrespective of study interventions.

4.4.3 Nocturnal SBP Dipping (LMM)

LMM showed non-significant results for mean nocturnal SBP dipping, including non-significant effects for time ($F(2, 40.43) = 0.05$, p = 0.95), group (p = 0.51), and group × time interaction (p = 0.17).

4.4.4 Nocturnal SBP Dipping (RM-ANOVA)

No statistically significant differences were observed in mean nocturnal SBP dipping between and within study groups, reflected in non-significant effects for group (p = 0.81), time (p = 0.90), and group × time interaction (p = 0.22).

4.4.5 Additional Outcomes (LMM)

As seen in Table 3a, in relation to DBP, SBPL, DBPL, SBPV, DBPV, LMM analytic strategy, indicated a statistically significant effect of time ($F(2, 45.04) = 13.96$, p = 0.0001) for waking SBPL, reflecting statistically significant reductions from baseline to 8 (-18.8%, p = 0.001) and from baseline to 16 (-26.2%, p = 0.0001) weeks irrespective of group assignment. The LMM analytic strategy, in contrast to RM-ANOVA, additionally indicated a statistically significant effect of time ($F(2, 41.53) = 3.68$, p = 0.03) for Sleeping SBP, showing reductions in sleeping SBP

from baseline to 8 (-11.9%, p = 0.18) and from baseline to 16 (-18.0%, p = 0.04) weeks within both groups.

4.4.6 Additional Outcomes (RM-ANOVA)

In relation to additional study outcomes, namely DBP, SBPL, DBPL, SBPV, DBPV no statistically significant differences were observed either between or within study groups, except for SBPL during both waking and sleeping. Specifically, waking SBPL showed a statistically significant effect of time ($F(2, 56) = 11.60$, $p = 0.0001$, $\eta p2 = 0.29$), but no significant effects for either group ($p = 0.77$) or group × time interaction ($p = 0.70$). Subsequently, post-hoc analyses for indicated overall reductions in both study groups from baseline to 8 (-15.17%, $p = 0.007$) and 16 (-17.9%, $p = 0.001$). For SBPL during sleep, results did not show statistically significant effects for either time ($p = 0.11$), group ($p = 0.91$), or group × time interaction ($p = 0.56$).

Table 3a Mean and standard error for ABPM parameters at study time points under LMM [c]

Outcome	Time point	MBRR	DBRR	Group (*p*)	Time (*p*)	Group × Time (*p*)
Waking SBP	Baseline	145.9 (1.87)	145.1 (2.00)	0.77	0.0001	0.79
	8-weeks	138.4 (1.99)	139.2 (2.15)			
	16-weeks	134.8 (2.45)	136.7 (2.60)			
Waking DBP	Baseline	75.1 (1.99)	79.2 (2.12)	0.07	0.41	0.75
	8-weeks	73.7 (2.07)	78.4 (2.22)			
	16-weeks	72.0 (2.35)	78.4 (2.51)			
Sleeping SBP	Baseline	129.5 (3.67)	130.7 (3.92)	0.67	0.002	0.07
	8-weeks	124.1 (3.81)	124.3 (4.03)			
	16-weeks	127.7 (4.06)	119.6 (4.31)			
Sleeping DBP	Baseline	63.7 (1.94)	67.6 (2.07)	0.18	0.25	0.82
	8-weeks	62.7 (2.04)	67.0 (2.16)			
	16-weeks	62.0 (2.24)	64.7 (2.38)			
SBP Dipping %	Baseline	11.1 (2.21)	10.3 (2.36)	0.51	0.95	0.17
	8-weeks	10.8 (2.36)	11.6 (2.48)			
	16-weeks	8.1 (2.64)	14.0 (2.80)			
Waking SBPL [a]	Baseline	77.4 (5.12)	78.6 (5.48)	0.78	0.001	0.60
	8-weeks	61.1 (5.45)	57.3 (5.88)			
	16-weeks	48.0 (6.66)	55.6 (7.07)			
Waking DBPL	Baseline	18.4 (5.36)	26.8 (5.73)	0.15	0.67	0.80
	8-weeks	16.0 (5.62)	24.7 (6.05)			
	16-weeks	11.7 (6.51)	25.8 (6.92)			

Sleeping SBPL [a]	Baseline	70.1 (8.42)	75.06 (9.00)	0.60	0.03	0.32
	8-weeks	63.6 (9.05)	57.8 (9.5)			
	16-weeks	62.7 (10.24)	46.3 (10.86)			
Sleeping DBPL	Baseline	20.8 (6.92)	38.9 (7.39)	0.21	0.60	0.55
	8-weeks	20.0 (7.49)	30.5 (7.84)			
	16-weeks	28.4 (8.58)	33.3 (9.10)			
Waking SBPV [b]	Baseline	12.1 (0.78)	12.2 (0.83)	0.11	0.48	0.20
	8-weeks	11.9 (0.83)	13.7 (0.89)			
	16-weeks	10.6 (1.00)	13.5 (1.06)			
Waking DBPV	Baseline	8.5 (0.68)	8.1 (0.72)	0.73	0.96	0.34
	8-weeks	7.7 (0.70)	8.7 (0.76)			
	16-weeks	8.1 (0.80)	8.4 (0.85)			
Sleeping SBPV [b]	Baseline	10.7 (0.94)	10.7 (1.01)	0.55	0.74	0.82
	8-weeks	10.9 (1.04)	12.1 (1.09)			
	16-weeks	10.9 (1.25)	11.5 (1.32)			
Sleeping DBPV	Baseline	7.9 (0.66)	7.1 (0.70)	0.93	0.44	0.30
	8-weeks	7.7 (0.72)	7.6 (0.75)			
	16-weeks	7.7 (0.84)	8.9 (0.88)			

[a] based on the percent of ABPM measurements above 135/85 for waking and 120/70 for sleeping.
[b] based on the standard deviation of ABPM measurements.
[c] LMM analysis based on all available participants at baseline (MBRR = 16, DBRR = 14), 8-week post-intervention (MBRR = 14, DBRR = 12), 16-week follow-up (MBRR = 9, DBRR = 8)

Table 3b Mean and standard deviations for ABPM parameters at study time points Under RM-ANOVA

Outcome	Time point	MBRR	DBRR	Group (*p*)	Time (*p*)	Group × Time (*p*)
Waking SBP	Baseline	145.9 (6.87)	145.1 (6.10)	0.82	0.003	0.77
	8-weeks	139.4 (7.38)	140.2 (8.53)			
	16-weeks	138.2 (7.97)	139.7 (9.30)			
Waking DBP	Baseline	75.1 (8.10)	79.2 (8.60)	0.12	0.47	0.69
	8-weeks	73.8 (8.81)	78.1 (6.70)			
	16-weeks	73.1 (9.71)	78.2 (6.55)			
Sleeping SBP	Baseline	129.5 (14.75)	130.7 (14.58)	0.92	0.003	0.33
	8-weeks	125.6 (16.76)	125.7 (15.43)			
	16-weeks	126.9 (16.74)	123.8 (16.97)			
Sleeping DBP	Baseline	63.7 (6.88)	67.6 (8.30)	0.20	0.29	0.89
	8-weeks	63.1 (8.10)	66.9 (7.00)			
	16-weeks	62.7 (9.05)	65.7 (8.29)			
SBP Dipping %	Baseline	11.1 (10.17)	9.8 (10.03)	0.81	0.90	0.22
	8-weeks	10.1 (9.09)	10.5 (7.90)			
	16-weeks	8.4 (9.10)	11.5 (9.65)			
Waking SBPL [a]	Baseline	77.4 (17.77)	78.6 (15.60)	0.78	0.0001	0.70
	8-weeks	63.4 (21.20)	62.3 (26.27)			
	16-weeks	57.3 (24.72)	62.8 (24.61)			
Waking DBPL	Baseline	18.4 (17.81)	26.8 (27.77)	0.27	0.80	0.92
	8-weeks	16.7 (21.77)	23.6 (19.12)			
	16-weeks	16.2 (22.33)	24.8 (22.50)			

Sleeping SBPL [a]	Baseline	70.1 (30.90)	75.0 (28.70)	0.91	0.11	0.56
	8-weeks	67.0 (34.60)	61.8 (40.80)			
	16-weeks	64.3 (39.30)	60.6 (37.70)			
Sleeping DBPL	Baseline	20.8 (21.80)	38.9 (32.60)	0.19	0.64	0.41
	8-weeks	21.5 (22.50)	31.1 (26.60)			
	16-weeks	26.0 (27.70)	33.1 (30.70)			
Waking SBPV [b]	Baseline	12.1 (2.90)	12.2 (3.17)	0.28	0.46	0.45
	8-weeks	12.1 (3.80)	13.5 (2.59)			
	16-weeks	12.2 (2.33)	13.4 (2.09)			
Waking DBPV	Baseline	8.5 (2.55)	8.2 (2.43)	0.97	0.54	0.38
	8-weeks	7.9 (2.80)	8.5 (2.27)			
	16-weeks	8.6 (2.54)	8.5 (2.85)			
Sleeping SBPV [b]	Baseline	10.7 (3.04)	10.8 (3.73)	0.65	0.72	0.71
	8-weeks	10.7 (4.00)	11.9 (4.53)			
	16-weeks	11.2 (3.91)	11.4 (4.11)			
Sleeping DBPV	Baseline	8.0 (2.11)	7.1 (2.60)	0.66	0.16	0.65
	8-weeks	8.4 (3.44)	8.4 (1.70)			
	16-weeks	7.9 (3.60)	7.6 (2.40)			

[a] based on the percent of ABPM measurements above 135/85 for waking and 120/70 for sleeping.[168]
[b] based on the standard deviation of ABPM measurements.

4.5 Psychometric Outcome Evaluation (LMM)

As seen in Table 4a, utilizing the LMM strategy, results for HADS-A indicated a statistically significant main effect of time ($F(2, 41.3) = 4.59$, $p = 0.02$), reflecting non statistically significant reductions from baseline to 8 weeks (-0.90, $p = 0.18$), but statistically significant reductions from baseline to 16 weeks (-1.59, $p = 0.02$). For CAQ, LMM indicated a statistically significant main effects of time for the fear ($F(2, 40.7) = 5.28$, $p = 0.009$) and the HFA ($F(2, 39.9) = 6.67$, $p = 0.003$) subscales. Subsequently, post-hoc analyses indicated statistically significant reductions in CAQ-fear from baseline to 8 (-0.33, $p = 0.01$) but non-significant reductions from baseline to 16 (-0.28, $p = 0.09$) weeks. In CAQ-HFA, however, post-hoc analyses showed non-significant reductions from baseline to 8 weeks (-0.09, $p = 0.10$), but statistically significant reductions from 8 to 16 weeks (-0.33, $p = 0.02$) and from baseline to 16 (-0.42, $p = 0.003$) weeks. Improvements in CAQ-fear and HFA subscales were further reflected in CAQ total score, reflected in statistically significant reductions from baseline to 8 weeks (-0.21, $p = 0.02$) and from baseline to 16 weeks (-0.28, $p = 0.007$).

In relation to POMS and the FFMQ, LMM showed a statistically a significant main effect of time for tension ($F(2, 41.5 = 5.18$, $p = 0.01$), anger ($F(2, 40.9 = 5.02$, $p = 0.01$), and confusion ($F(2, 41.9 = 4.25$, $p = 0.02$) subscales. For POMS tension, the significant main effect of time translated to statistically significant reductions from baseline to 8 weeks (-2.05, $p = 0.04$) and from baseline to 16 weeks (-2.48, $p = 0.02$). For the anger subscale, the significant main effect of time indicated statistically significant reductions from baseline to 8 weeks (-1.98, $p = 0.04$) and from baseline to 16 weeks (-2.53, $p = 0.03$). POMS confusion subscale showed statistically significant reductions from baseline to 8 weeks (-1.49, $p = 0.02$), but non-significantly from baseline to 16 weeks (-1.20, $p = 0.18$).

For the FFMQ, LMM similarly indicated statistically significant main effects for time in the describing ($F(2, 39.8 = 6.31, p = 0.004$) and nonreactivity ($F(2, 41.1 = 5.60, p = 0.007$) subscales. For the describing subscale, this represented statistically significant increases from baseline to 8 weeks (1.57, $p = 0.007$) and from baseline to 16 weeks (1.48, $p = 0.04$). Similarly, nonreactivity showed statistically significant increases from baseline to 8 weeks (1.78, $p = 0.02$) and from baseline to 16 weeks (1.90, $p = 0.03$). The acting with awareness subscale also showed a statistically significant main effect of time ($F(2, 41.4 = 3.64, p = 0.03$), representing only marginally-significant increases from baseline to 8 weeks (1.44, $p = 0.06$). For the global PSQI score, LMM showed no statistically significant main effects for either time, group, or the group × time interaction.

4.6 Psychometric Outcome Evaluation (RM-ANOVA)

Statistically-significant improvements from baseline to subsequent follow-ups were observed in HADS-A in addition to a number of CAQ, POMS, and FFMQ subscales, with no difference between study groups. Specifically, ITT analyses utilizing LOCF for mean HADS-A indicated a statistically significant main effect of time ($F(2, 27) = 5.12$, $p = 0.01$, $\eta_p^2 = 0.27$), but non-significant effects for group ($p = 0.10$) and group × time interaction ($p = 0.63$). These reflected reductions from baseline to 8 (-0.80, $p = 0.28$) and 16 (-1.34, $p = 0.02$) weeks irrespective of study groups. In relation to CAQ, statistically significant reductions were detected in HFA subscale and the CAQ total score. For CAQ-HFA, results indicated a statistically significant main effect of time ($F(2, 27) = 5.84$, $p = 0.008$, $\eta_p^2 = 0.30$), and no significant main effects for group ($p = 0.10$) and the group × time interaction ($p = 0.83$), reflecting non-significant reductions in HFA from baseline to 8 (-0.07, $p = 0.99$), but significant reductions from 8 to 16 weeks (-0.22, $p = 0.009$) and baseline to 16 (-0.30, $p = 0.02$) weeks. Despite no statistically significant effects for the CAQ fear and

avoidance subscales (Table 4b), CAQ total score showed only a statistically significant main effect of time ($F(2, 27) = 5.43$, $p = 0.01$, $\eta_p^2 = 0.29$), reflecting reductions from baseline to 8 (-0.18, $p = 0.04$) and 16 (-0.24, $p = 0.008$) weeks.

Results for the POMS indicated statistically significant improvements on the tension, anger, and confusion subscales. Specifically, the tension subscale showed only a statistically significant main effect of time ($F(2, 27) = 5.72$, $p = 0.008$, $\eta_p^2 = 0.30$), indicating reductions from baseline to 8 (-1.75, $p = 0.07$) and 16 (-2.25, $p = 0.02$) weeks. POMS anger showed a statistically significant main effect of time ($F(2, 27) = 4.19$, $p = 0.03$, $\eta_p^2 = 0.24$), showing reductions from baseline to 8 (-1.70, $p = 0.08$) and 16 (-2.08, $p = 0.02$) weeks. Similarly, POMS confusion indicated only a statistically significant main effect of time ($F(2, 27) = 3.63$, $p = 0.04$, $\eta_p^2 = 0.21$), and showed reductions from baseline to 8 (-1.35, $p = 0.03$) and 16 (-1.34, $p = 0.05$) weeks.

For FFMQ, statistically significant improvements were detected for the effects of time on the describing and nonreactivity subscales. On the describing subscale, results indicated a statistically significant main effect of time ($F(2, 27) = 6.84$, $p = 0.001$, $\eta_p^2 = 0.34$), showing increases from baseline to 8 (1.16, $p = 0.02$) and 16 (1.29, $p = 0.003$) weeks irrespective of study group. For nonreactivity, results similarly indicated statistically significant main effect of time ($F(2, 27) = 4.29$, $p = 0.02$, $\eta_p^2 = 0.24$), reflected in increases from baseline to 8 (1.64, $p = 0.02$) and 16 (1.61, $p = 0.03$) weeks irrespective of study group. For the global PSQI score, there were no statistically significant main effects for either time, group, or the group × time interaction.

Table 4a Mean and standard deviations for psychological parameters and global PSQI at study time points under LMM [a]

Outcome		Baseline	8-weeks	16-weeks	Group (*p*)	Time (*p*)	Group × Time (*p*)
HADS - A							
	MBRR	7.69 (0.90)	6.34 (0.93)	5.56 (1.00)	0.12	0.02	0.51
	DBRR	5.07 (0.96)	4.62 (0.99)	4.02 (1.07)			
HADS - D							
	MBRR	5.81 (0.95)	4.94 (0.97)	4.86 (1.05)	0.25	0.12	0.85
	DBRR	4.14 (1.01)	3.15 (1.04)	3.68 (1.12)			
CAQ - Fear							
	MBRR	1.88 (0.18)	1.52 (0.19)	1.74 (0.21)	0.39	0.009	0.38
	DBRR	1.73 (0.19)	1.44 (0.20)	1.32 (0.22)			
CAQ - Avoidance							
	MBRR	1.58 (0.20)	1.32 (0.20)	1.49 (0.22)	0.54	0.31	0.39
	DBRR	1.37 (0.21)	1.33 (0.22)	1.18 (0.24)			
CAQ - HFA							
	MBRR	1.61 (0.20)	1.57 (0.21)	1.28 (0.22)	0.64	0.003	0.72
	DBRR	1.84 (0.22)	1.70 (0.22)	1.32 (0.24)			
CAQ - Total							
	MBRR	1.72 (0.15)	1.48 (0.16)	1.54 (0.18)	0.63	0.003	0.31
	DBRR	1.66 (0.17)	1.49 (0.17)	1.28 (0.18)			
POMS - Tension							
	MBRR	6.87 (1.14)	5.01 (1.24)	4.83 (1.35)	0.30	0.01	0.89
	DBRR	5.71 (1.21)	3.48 (1.27)	2.80 (1.43)			

POMS - Depression							
	MBRR	5.87 (1.32)	3.87 (1.39)	4.05 (1.52)	0.32	0.06	0.84
	DBRR	3.78 (1.41)	2.59 (1.47)	1.96 (1.61)			
POMS - Anger							
	MBRR	5.81 (1.03)	3.75 (1.11)	2.58 (1.32)	0.42	0.01	0.73
	DBRR	4.21 (1.10)	2.31 (1.16)	2.37 (1.34)			
POMS -Fatigue							
	MBRR	7.56 (1.16)	6.66 (1.23)	6.84 (1.36)	0.81	0.30	0.61
	DBRR	7.43 (1.24)	7.01 (1.29)	5.47 (1.44)			
POMS - Confusion							
	MBRR	3.87 (0.80)	2.16 (0.85)	2.20 (0.95)	0.56	0.02	0.74
	DBRR	2.78 (0.85)	1.53 (0.90)	2.06 (1.01)			
POMS - Vigor							
	MBRR	9.50 (1.39)	10.13 (1.47)	11.43 (1.62)	0.30	0.16	0.72
	DBRR	8.07 (1.49)	7.32 (1.55)	9.72 (1.72)			
FFMQ - Observing							
	MBRR	16.81 (0.80)	16.26 (0.82)	17.04 (0.90)	0.63	0.66	0.49
	DBRR	15.86 (0.86)	16.28 (0.88)	16.35 (0.95)			
FFMQ - Describing							
	MBRR	17.94 (0.85)	19.67 (0.88)	20.36 (0.97)	0.10	0.004	0.24
	DBRR	20.64 (0.91)	22.05 (0.95)	21.17 (1.04)			
FFMQ – Acting with Awareness							
	MBRR	18.44 (0.80)	19.36 (0.84)	18.63 (0.98)	0.76	0.03	0.21
	DBRR	17.57 (0.85)	19.53 (0.90)	20.28 (1.04)			

FFMQ - Nonjudgement							
	MBRR	16.75 (1.10)	17.11 (1.14)	16.56 (1.27)	0.11	0.26	0.54
	DBRR	18.42 (1.18)	20.27 (1.23)	19.15 (1.36)			
FFMQ – Nonreactivity							
	MBRR	14.00 (0.96)	16.58 (0.99)	17.23 (1.12)	0.11	0.007	0.16
	DBRR	17.57 (1.03)	18.55 (1.07)	18.14 (1.20)			
PSQI Global							
	MBRR	8.93 (0.99)	7.26 (1.02)	7.98 (1.07)	0.80	0.15	0.18
	DBRR	7.78 (1.07)	7.76 (1.09)	7.60 (1.16)			

[a] LMM analysis based on all available participants at baseline (MBRR = 16, DBRR = 14), 8-week post-intervention (MBRR = 14, DBRR = 12), 16 week follow-up (MBRR = 9, DBRR = 8)

Table 4b Mean and standard deviations for psychological parameters and global PSQI at study time points under RM-ANOVA

Outcome		Baseline	8-weeks	16-weeks	Group (*p*)	Time (*p*)	Group × Time (*p*)
HADS - A							
	MBRR	7.69 (3.93)	6.44 (3.48)	5.94 (3.38)	0.10	0.01	0.63
	DBRR	5.07 (3.47)	4.71 (3.45)	4.14 (3.08)			
HADS - D							
	MBRR	5.81 (4.02)	5.06 (3.97)	5.01 (3.83)	0.18	0.12	0.96
	DBRR	4.14 (3.46)	3.21 (3.74)	3.28 (2.84)			
CAQ - Fear							
	MBRR	1.88 (0.86)	1.55 (0.80)	1.76 (0.75)	0.48	0.06	0.25
	DBRR	1.73 (0.77)	1.51 (0.58)	1.42 (0.61)			
CAQ - Avoidance							
	MBRR	1.58 (0.97)	1.34 (0.75)	1.43 (0.79)	0.63	0.41	0.07
	DBRR	1.37 (0.78)	1.36 (0.69)	1.24 (0.61)			
CAQ - HFA							
	MBRR	1.61 (1.02)	1.56 (0.85)	1.37 (0.82)	0.55	0.008	0.83
	DBRR	1.84 (0.72)	1.74 (0.71)	1.48 (0.70)			
CAQ - Total							
	MBRR	1.72 (0.79)	1.50 (0.68)	1.51 (0.63)	0.82	0.01	0.09
	DBRR	1.66 (0.57)	1.53 (0.49)	1.39 (0.51)			
POMS - Tension							
	MBRR	6.87 (5.16)	5.37 (4.35)	4.87 (4.92)	0.30	0.008	0.95
	DBRR	5.71 (4.39)	3.71 (3.56)	3.21 (3.26)			

POMS - Depression							
	MBRR	5.87 (6.84)	4.19 (6.07)	4.01 (5.70)	0.33	0.14	0.82
	DBRR	3.78 (4.08)	2.71 (2.76)	2.36 (3.17)			
POMS - Anger							
	MBRR	5.81 (5.02)	4.12 (5.07)	3.43 (4.44)	0.29	0.03	0.71
	DBRR	4.21 (3.84)	2.50 (2.06)	2.42 (2.70)			
POMS -Fatigue							
	MBRR	7.56 (5.38)	6.87 (5.89)	6.94 (4.85)	0.87	0.32	0.82
	DBRR	7.43 (3.46)	6.93 (3.56)	6.28 (3.33)			
POMS - Confusion							
	MBRR	3.87 (4.42)	2.31 (3.70)	2.19 (2.61)	0.47	0.04	0.75
	DBRR	2.78 (2.22)	1.64 (2.00)	1.79 (2.22)			
POMS - Vigor							
	MBRR	9.50 (6.30)	10.06 (6.29)	10.87 (6.22)	0.30	0.15	0.67
	DBRR	8.07 (4.58)	7.43 (4.16)	9.01 (4.71)			
FFMQ - Observing							
	MBRR	16.81 (3.08)	16.37 (2.19)	16.87 (2.19)	0.60	0.61	0.30
	DBRR	15.86 (3.65)	16.28 (3.89)	16.21 (3.87)			
FFMQ - Describing							
	MBRR	18.37 (3.91)	19.62 (3.14)	20.31 (3.10)	0.12	0.001	0.18
	DBRR	20.64 (2.71)	21.71 (3.29)	21.28 (3.22)			
FFMQ – Acting with Awareness							
	MBRR	18.44 (3.77)	19.25 (3.02)	18.50 (2.31)	0.93	0.10	0.16
	DBRR	17.57 (3.47)	19.14 (3.43)	19.71 (3.17)			

FFMQ - Nonjudgement							
	MBRR	16.75 (4.46)	17.18 (4.59)	16.81 (4.40)	0.12	0.23	0.70
	DBRR	18.42 (4.52)	19.86 (3.86)	19.34 (4.21)			
FFMQ – Nonreactivity							
	MBRR	14.00 (3.94)	16.44 (3.14)	16.93 (3.19)	0.09	0.02	0.07
	DBRR	17.57 (3.59)	18.43 (4.38)	17.86 (4.05)			
Global PSQI							
	MBRR	8.93 (4.89)	7.43 (3.81)	7.75 (4.23)	0.85	0.24	0.18
	DBRR	7.78 (3.37)	7.86 (3.30)	7.71 (3.43)			

5.0 Discussion

In this study, there was a comparison of Mindfulness-Based and a Diet-Based Risk Reduction coaching programs (MBRR vs. DBRR), both aimed at improving systolic HTN and psychological outcomes in AF patients. Altogether, results indicate statistically significant within-group reductions in SBP, during waking and sleep from baseline to 8-week post-intervention and from baseline to 16-week follow-up. It is, of course, noteworthy that no between-group differences were found. This is a useful result as for practical purposes, it seems MBRR and DBRR are nearly similar in reducing SBP. The observed reductions were further accompanied by similarly statistically significant within group reductions in Systolic Blood Pressure Load (SBPL) during waking and sleep from baseline to 8-week post-intervention and 16-week follow-up periods.

The absence of statistically significant within-group or between-group differences in waking or sleep DBP is not surprising as DBP of these groups were within normal levels at baseline. This relatively normative condition is linked to an intensive anti-hypertensive medication regimen, firmly standardized at the PACE clinic.

In terms of other improvements, there were statistically significant improvements from baseline to 8-week post-intervention and 16-week follow-up in psychological outcomes in both groups per common improvements in HADS-A, CAQ-HFA, CAQ-Total, FFMQ-SF (describing and non-reactivity subscales) and the POMS anger, tension, and confusion subscales. Once again, no statistically significant between-group differences were found between MBRR vs. DBRR.

Given the absence of between-group differences in waking and sleep SBP, it is not surprising that the RM-ANOVA indicated similar magnitudes of reductions within MBRR and DBRR at 8 weeks (Sleep SBP: -3.9 mmHg in MBRR vs -5.0 mmHg in DBRR). However, at 16-weeks DBRR showed greater declines (-2.6 mmHg in MBRR vs. -6.9 mmHg in DBRR) although

they were not statistically significant. While the study hypotheses in relation to sleeping SBP were initially formulated with assumptions that MBRR only would have a beneficial influence on nocturnal BP and AI, research indicates AI improvements occurred in relation to both mindfulness *and* dietary practices, indicating a more complex physiological mechanism is being affected. The complexity of autonomic imbalance (AI) is suggested by physical activity, notably aerobic exercise, being shown to improve baroreceptor sensitivity,[281-284] a key element of BP regulation and AI. Dietary approaches, particularly caloric restriction and the DASH diet, have also been shown previously to enhance autonomic balance and PNS activity.[285-287] While weight loss is an important mechanism underlying ANS effects,[285,287,288] DASH diet interventions, with or without weight loss, are also associated with increased PNS activity and BP control.[286,288] Accordingly, it would seem exercise, diet, and mindfulness practices all affect BP and autonomic balance in common and divergent ways. For instance, while it is understood that mindfulness practices improve autonomic balance by increasing parasympathetic tone (i.e. increased HF-HRV),[30,31] DASH dietary practices enhance BP and autonomic balance through a range of mechanisms that include: (a) increased Nitric oxide production, bioavailability, and consequent vasodilation, related to DASH diet's greater L-arginine, polyphenol, and anti-oxidant content from nuts, fruit, and vegetables;[289-291] and; (b) increased sodium excretion (natriuresis), related to reduced Sodium and increased Potassium consumption (sodium-potassium ratio).[292,293] In fact, while the exact underpinnings are unclear at present, autonomic and dietary BP-reducing mechanisms do interact, evidenced by the association between increased Sodium intake and reduced parasympathetic tone in hypertensives.[294] Therefore, the current study would benefit from addition of a third study arm, whether it was a wait-list control group or one combining MBRR and DBRR to compare the effectiveness of these interventions against usual care alone or to see whether the convergence of

these modalities and BP-reducing mechanisms would result in greater BP reductions. In previous studies, additive BP improvements have been observed when DASH diets were supplemented *with* weight management and exercise.[286,288]

While between-group declines in sleep-SBP did not reach statistical significance in the current study, the exploration of potential differences between MBRR and DBRR in impacting sleep SBP is a challenge for future studies combining lifestyle interventions, 24-hr ABPM, and evaluations of ANS function. In fact, despite lack of a statistically significant between-group difference in sleep SBP (possibly a reflection of the small sample size), the greater magnitude of sleep SBP reductions in DBRR at 16-week follow-up may point to an interesting possible differential response between MBRR and DBRR that can be fully investigated in a larger future study. As a guiding hypothesis, this potential differential response in sleep SBP reduction may in fact stem from inherent differences between autonomic and non-autonomic BP reducing mechanisms in these interventions. For example, DBRR and associated biochemical effects (i.e. increased Nitric oxide production, bioavailability, and natriuresis) could have produced a more enduring BP reducing response during waking and especially during sleep, while lack of SBP reduction during sleep in MBRR could be attributed to the importance of conscious control in mindfulness and consequent re-focusing of attention that ceases during periods of sleep.

HTN-oriented lifestyle management effectively augments medical (drug-based and surgically-based) efforts. However, historical difficulties with the adoption and maintenance of self-management regimens has substantially limited their effectiveness, leaving patients at increased risks for worsening disease, hospitalizations,[247-250] mortality,[247,248,250,252,253] and increased medical costs.[295] Therefore, patient self-management programs are important to refine and improve patient confidence and skill in self-managing their chronic disease. They impart

important skills while stimulating self-efficacy and patient engagement in the risk reduction process.[256,296] Personal health coaching represents one approach supporting greater patient adherence in self-management regiments and potential clinical improvements.[258,259,297] Nonetheless, despite clinical effectiveness,[258,259] long-term evaluations of costs in personal coaching interventions have been scarce. Still the cost evaluations undertaken of specific interventions in varying healthcare systems support cost effectiveness in Type 2 Diabetes,[298-300] cardiovascular risk reduction,[300] and weight loss.[301]

While medical therapies represent the most frequently applied approaches in AF, *lifestyle interventions* are now considered increasingly relevant in AF management. In one of the first application of MBI to AF, Lakirredy et al.[302] showed 12 weeks of a weekly-attended group-based Yoga class protocol led to statistically significant reductions in the symptomatic and asymptomatic AF symptoms reported, and to statistically significant improvements in non-ABPM measured SBP (-5.3 mmHg). Other improvements involved lowered psychological distress, and increased quality of life (the latter is especially noteworthy as many of the AF patients had recently received catheter ablation). In another evaluation of a group-based weekly Yoga class protocol for AF,[303] Wahlstrom et al. demonstrated within-group improvements in quality of life, in addition to between-group differences in reductions in non-ABPM SBP (-5.0 in Yoga vs.+3.0 in standard care) *and* DBP (-7.0 in Yoga vs. +2 in standard care). Further applications of lifestyle-based approaches in AF include a third study by Malm et al.,[304] where statistically significant improvements in health-related quality of life and sense of coherence (i.e. a construct that relates to locus of control, self efficacy, and meaning) were observed with a 9-week group-based program of mindfulness and cognitive therapy (compared to usual care) at 12 month follow-up. MBI or CBT interventions have also been effective in improving psychological distress amongst patients with Implantable

Cardioverter Defibrillator (ICD) at elevated risk for irregular heart rhythms that set off a corrective shock procedure.[305,306]

Lifestyle-based dietary approaches in AF have been scarcely investigated. Nonetheless, the DASH diet, with its focus on limited saturated fat, increased fruit and vegetable consumption, reduced Sodium, and increased Potassium, has been observed to reduce HTN in CVD patients, generally, with large meta-analytic reviews in multiple CVD populations indicating overall reductions of 5.2-6.7 mmHg in SBP and 2.6-3.5 mmHg in DBP.[209,210] MBI have also been applied in the BP reduction of multiple populations, with overall SBP reductions ranging between 3.8-5.0 mmHg.[307]

While the above studies demonstrate the potential applicability of lifestyle-based approaches, including DASH diet and MBI in AF, they do not represent the difficulties involved in actively applying dietary and mindfulness approaches in AF patients. These difficulties are, particularly relevant to patients who are optimally medicated, as were the subjects in the current trial. Lifestyle-based approaches have the potential to augment medical management with "independent and additive" benefits in risk factor and mortality reductions on top of pharmacotherapy reductions;[308] they can therefore address a treatment gap in HTN control with behaviourally-based strategies that complement and, in some cases, complete HTN control. In the context of the present study, what was addressed was a SBP 'gap' in HTN control. While the DBP of trial subjects was controlled at normal ranges, their SBP remained abnormally high.

The Minimal Clinically Important Difference (MCID) as a concept has been associated with general guidelines on improvements deemed clinically-meaningful and experientially meaningful to the patients, treated. While an exact MCID for SBP for AF has not been determined, average SBP reduction of 5-10 mmHg have been suggested as clinically meaningful in

development/use of antihypertensive medications, and in reducing CVD morbidity and mortality risks.[309-310] Ettehad et al.[310] in their large-scale meta-analysis of BP lowering treatments, deemed SBP reductions of 10 mmHg to be important in CVD risk reduction, noting the reduced risks of coronary heart disease (-17%), stroke (-27%), heart failure (-28%), CVD events (-20%), and mortality (-13%). Ettehad et al. further suggest that BP reductions regardless of baseline BP are useful in CVD risk reduction.

In relation to the mindfulness outcome, despite lack of between-group differences, both groups demonstrated increases in FFMQ-SF describing, nonreactivity, and to some extent the acting with awareness facets. While an increase in mindfulness facets within MBRR was to some extent expected, the increases in FFMQ-SF associated with DBRR represent a challenging but interesting observation. In fact, while the practice of mindfulness meditation in the research literature has predominantly been characterized as the method of developing greater mindfulness, as a psychological construct, mindfulness has been studied from dispositional, cognitive, and emotion regulation perspectives.[234,311] Under these frameworks, mindfulness is conceptualized as a nurtured dispositional, self-regulatory capacity, and a meta-cognitive ability that influences emotion regulation and also chronic disease management.[311,312] In effect, when viewed from a learning perspective, mindfulness has been viewed as a more differentiated state of awareness,[313] characterized by Langer as an *actively-oriented learning* that attends to "novel distinctions" without reliance on habitual self limiting beliefs that hinder learning and adoption of a broader perspective. In this way, personal coaching, namely the conveying of personally-relevant information and problem-solving skills within supportive relationships, could be considered as a mindfulness-facilitating process which enhances non-judgemental and conscious focus on DBRR objectives. For example, while perceptions of discrepancy (i.e. current illness vs. health, current

diet vs. healthier diet) may foster avoidance in some participants (within a traditional information-provision approach), in coaching, participants can see discrepancies in a novel perspective devoid of self-attributed negativity, following current motivational interviewing theory.[314] In this way, DBRR coaching could have facilitated greater conscious awareness of DBRR goals, namely: paying attention to reading nutritional labels while shopping for food, paying attention to dietary sodium and potassium, and other macronutrient content when preparing food at home, or when eating at restaurants, behaviours all emphasized within the DASH eating plan. While evaluation of mindfulness as a learning construct and 'mindfulness-induced learning' was not a focus of the current study, exploration of 'mindfulness-induced learning' in relation to successful chronic disease management and as an adherence-facilitating mechanism remains an interesting topic for future explorations.

This study was limited by the small sample size limiting statistical power in detecting potential between-group differences. This was particularly important when considering attrition at 16-week follow-up, which could have limited the possible detection of a statistically significant between-group difference in sleep SBP at 16-week follow up, necessitating a larger future study. However, as seen within the broader literature, lack of statistically-significant between-group differences in the context of active treatment comparison conditions is not uncommon. For example, in a three-arm parallel-group randomized controlled, van der Zwan et al.[315] evaluated the effectiveness of 5-week physical activity, mindfulness meditation, and heart rate variability biofeedback interventions in lowering stress, anxiety, depression symptoms, and found no statistically-significant between-group differences, suggesting reduction of psychological distress using different intervention methods. Evaluations of other mental health interventions (mindfulness meditation or psychotherapy) against active comparison conditions that include non-

specific therapeutic factors have also demonstrated comparable effectiveness between these therapeutic modalities.[316,317]

Distance considerations were another limitation of the current study, which can be overcome with the use of electronic remote technology. For instance, despite availability of in-person mindfulness group at the cardiac rehabilitation over the course of the study, this opportunity was utilized by only 2 participants, due to travel distance and/or scheduling conflicts. Therefore, we utilized in-person meetings, in addition to phone, and email contacts to deliver the MBRR and DBRR interventions as a mixed-modality remote intervention. However, this flexible use of in-person meetings, telephone calls, and e-mail in accord with patient availabilities and preferences enabled an effective delivery of study interventions. Overall, these included: an average of 6.6 in-person meetings, 5.2 telephone calls, and 7.5 e-mail contacts (4.9 when excluding two frequent email users) in MBRR, and an average of 6.1 in- person meetings, 4.0 telephone calls, and 3.2 e-mail contacts in DBRR.

Distance limitations in sub-urban settings can be overcome through remote care using smartphones, computer-based self-management applications, facilitating remote capture and transmission of clinical variables and personal coaching support.[159,259,318] As a result, greater electronic integration within mainstream healthcare represents an important opportunity and avenue to introduce efficiencies in remote care delivery and cost savings. In the context of the present study, use of patient management applications can facilitate remote transfer of BP, HRV, as well as to provide a more efficient avenue for delivering patient education, motivation support, and coaching feedback to a greater number of study participants. This is can be further complemented with the miniaturized medical devices, facilitating remote capture of clinical information. For example, Lowres et al.[319] used AliveCor portable electrocardiogram device to

monitor AF recurrence post-operation, and found device use (recording 30 second electrocardiograms, four times daily) to improve home detection of AF (symptomatic and non-symptomatic episodes) along with patient knowledge of their condition and sense of empowerment.

In addition, this study did not include a direct evaluation of autonomic function, as the emphasis was on the behavioural adoption of healthy lifestyle practices. In addition, practically speaking, concurrent use of 24-hour ABPM *and* Holter monitoring on multiple occasions would have overburdened participants, limiting their participation in key measurement endpoints. Nonetheless, integration of miniaturized echocardiogram monitors, already seen in smart devices and phones,[319,320] alongside newer less cumbersome 24-hr ABPM devices provides an ideal opportunity to evaluate changes in relation to other ambulatory indicators of activity and cardiovascular function. Finally, in this study, AF was stable with minimal symptoms in patients, as they previously had received medical AF treatments. It would be interesting and worthwhile to evaluate the impact of MBRR or DBRR for AF patients at earlier stages of treatment or in AF patients with treatment resistant recurrences to evaluate how these lifestyle-based interventions might lessen the frequency of AF recurrences.

In addition to the use of ABPM as a more precise way to assess ambulatory HTN, another strength of this study lies in the more exacting evaluation of 'sleeping period'. While, ABPM studies have predominantly relied on pre-defining fixed periods for sleep, the personal activity diary enabled a more exact evaluation of individual sleeping/waking experiences. Patient activity patterns on ABPM assessment days remained within the range of daily living activities, with no difference between study groups, and patient's anti-hypertensive medication regimen remained stable over the course of the intervention.

The similarity of the SBPV and DBPV measures over study time points further indicates similar activity patterns, as BPV is predominantly influenced by variations in physical activity and mood. Similarly, within ABPM literature, there are concerns about the impact of discomfort arising from wearing ABPM devices over long durations that could influence BP assessment. While this has been a possibility, in our experience, this was not an issue, as only 3 out of the 90 individuals assessed did not complete ABPM. Furthermore, as AF diagnosis primarily relies on long duration ambulatory monitoring of the electrocardiogram (1-14 days), participants had greater familiarity with long duration ambulatory clinical assessment.

6.0 Conclusions

In the evaluation of MBRR vs. DBRR in AF patients with elevated 24-hr ABPM SBP HTN, this study found statistically significant within-group reductions in waking and sleep SBP from baseline to 8 and 16-weeks. There were no statistically-significant difference between groups, as both MBRR and DBRR demonstrated significant reductions in SBP. In addition, study participants reported statistically significant improvements from baseline to 8 and 16-weeks in indices of general anxiety, HFA, POMS tension, anger, and confusion subscales, along improvements in FFMQ-SF describing and nonreactivity subscales with no significant statistically-significant between-group differences.

7.0 References

1. Gutierrez C, Blanchard DG. Atrial fibrillation: diagnosis and treatment. *Am Fam Physician.* 2011;83(1):61-68.

2. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation.* 2014;129(8):837-847.

3. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation.* 2006;114(2):119-125.

4. Krijthe BP, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J.* 2013;34(35):2746-2751.

5. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol.* 2014;6:213-220.

6. Dzeshka MS, Shahid F, Shantsila A, Lip GYH. Hypertension and Atrial Fibrillation: An Intimate Association of Epidemiology, Pathophysiology, and Outcomes. *Am J Hypertens.* 2017;30(8):733-755.

7. Verdecchia P, Angeli F, Reboldi G. Hypertension and Atrial Fibrillation: Doubts and Certainties From Basic and Clinical Studies. *Circ Res.* 2018;122(2):352-368.

8. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. *Bmj.* 2016;354:i4482.

9. Alegria-Ezquerra E, Gonzalez-Juanatey JR, Gonzalez-Maqueda I. Hypertensive heart disease: a proposed clinical classification. *Rev Esp Cardiol.* 2006;59(4):398-399.

10. Lip GYH, Coca A, Kahan T, et al. Hypertension and cardiac arrhythmias: a consensus document from the European Heart Rhythm Association (EHRA) and ESC Council on Hypertension, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). *Europace.* 2017;19(6):891-911.

11. Brook RD, Julius S. Autonomic imbalance, hypertension, and cardiovascular risk. *Am J Hypertens.* 2000;13(6 Pt 2):112s-122s.

12. Grassi G, Arenare F, Pieruzzi F, Brambilla G, Mancia G. Sympathetic activation in cardiovascular and renal disease. *J Nephrol.* 2009;22(2):190-195.

13. Jons C, Raatikainen P, Gang UJ, et al. Autonomic dysfunction and new-onset atrial fibrillation in patients with left ventricular systolic dysfunction after acute myocardial infarction: a CARISMA substudy. *J Cardiovasc Electrophysiol.* 2010;21(9):983-990.

14. Agarwal SK, Norby FL, Whitsel EA, et al. Cardiac Autonomic Dysfunction and Incidence of Atrial Fibrillation: Results From 20 Years Follow-Up. *J Am Coll Cardiol.* 2017;69(3):291-299.

15. Carnagarin R, Kiuchi MG, Ho JK, Matthews VB, Schlaich MP. Sympathetic Nervous System Activation and Its Modulation: Role in Atrial Fibrillation. *Front Neurosci.* 2018;12:1058.

16. Linz D, Mahfoud F, Ewen S, et al. Application in Hypertension of Renal Sympathetic Denervation - A Review. *Interv Cardiol.* 2013;8(2):124-126.

17. Haegeli LM, Calkins H. Catheter ablation of atrial fibrillation: an update. *Eur Heart J.* 2014;35(36):2454-2459.

18. Di Biase L, Elayi CS, Fahmy TS, et al. Atrial fibrillation ablation strategies for paroxysmal patients: randomized comparison between different techniques. *Circ Arrhythm Electrophysiol.* 2009;2(2):113-119.

19. Kalus JS, Coleman CI, White CM. The impact of suppressing the renin-angiotensin system on atrial fibrillation. *J Clin Pharmacol.* 2006;46(1):21-28.

20. Anand K, Mooss AN, Hee TT, Mohiuddin SM. Meta-analysis: inhibition of renin-angiotensin system prevents new-onset atrial fibrillation. *Am Heart J.* 2006;152(2):217-222.

21. Schneider MP, Hua TA, Bohm M, Wachtell K, Kjeldsen SE, Schmieder RE. Prevention of atrial fibrillation by Renin-Angiotensin system inhibition a meta-analysis. *J Am Coll Cardiol.* 2010;55(21):2299-2307.

22. Khatib R, Joseph P, Briel M, Yusuf S, Healey J. Blockade of the renin-angiotensin-aldosterone system (RAAS) for primary prevention of non-valvular atrial fibrillation: a systematic review and meta analysis of randomized controlled trials. *Int J Cardiol.* 2013;165(1):17-24.

23. Chaugai S, Sherpa LY, Sepehry AA, Arima H, Wang DW. Effect of RAAS blockers on adverse clinical outcomes in high CVD risk subjects with atrial fibrillation: A meta-analysis and systematic review of randomized controlled trials. *Medicine (Baltimore).* 2016;95(26):e4059.

24. Duprez DA. Role of the renin-angiotensin-aldosterone system in vascular remodeling and inflammation: a clinical review. *J Hypertens.* 2006;24(6):983-991.

25. Messerli FH, Makani H, Benjo A, Romero J, Alviar C, Bangalore S. Antihypertensive efficacy of hydrochlorothiazide as evaluated by ambulatory blood pressure monitoring: a meta-analysis of randomized trials. *J Am Coll Cardiol.* 2011;57(5):590-600.

26. Olex S, Newberg A, Figueredo VM. Meditation: should a cardiologist care? *Int J Cardiol.* 2013;168(3):1805-1810.

27. Abbott RA, Whear R, Rodgers LR, et al. Effectiveness of mindfulness-based stress reduction and mindfulness based cognitive therapy in vascular disease: A systematic review and meta-analysis of randomised controlled trials. *J Psychosom Res.* 2014;76(5):341-351.

28. Viveiros J, Chamberlain B, O'Hare A, Sethares KA. Meditation interventions among heart failure patients: An integrative review. *Eur J Cardiovasc Nurs.* 2019:1474515119863181.

29. Davis DM, Hayes JA. What are the benefits of mindfulness? A practice review of psychotherapy-related research. *Psychotherapy (Chic).* 2011;48(2):198-208.

30. Krygier JR, Heathers JA, Shahrestani S, Abbott M, Gross JJ, Kemp AH. Mindfulness meditation, well-being, and heart rate variability: a preliminary investigation into the impact of intensive Vipassana meditation. *Int J Psychophysiol.* 2013;89(3):305-313.

31. Nijjar PS, Puppala VK, Dickinson O, et al. Modulation of the autonomic nervous system assessed through heart rate variability by a mindfulness based stress reduction program. *Int J Cardiol.* 2014;177(2):557-559.

32. Guan L, Collet JP, Mazowita G, Claydon VE. Autonomic Nervous System and Stress to Predict Secondary Ischemic Events after Transient Ischemic Attack or Minor Stroke: Possible Implications of Heart Rate Variability. *Front Neurol.* 2018;9:90.

33. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation.* 1999;99(16):2192-2217.

34. Bleil ME, Gianaros PJ, Jennings JR, Flory JD, Manuck SB. Trait negative affect: toward an integrated model of understanding psychological risk for impairment in cardiac autonomic function. *Psychosom Med.* 2008;70(3):328-337.

35. Čukić I, Bates TC. The Association between Neuroticism and Heart Rate Variability Is Not Fully Explained by Cardiovascular Disease and Depression. *PLoS One.* 2015;10(5):e0125882.

36. Kupper N, Denollet J. Type D Personality as a Risk Factor in Coronary Heart Disease: a Review of Current Evidence. *Curr Cardiol Rep.* 2018;20(11):104.

37. Malan L, Hamer M, Schlaich MP, et al. Defensive coping facilitates higher blood pressure and early sub-clinical structural vascular disease via alterations in heart rate variability: the SABPA study. *Atherosclerosis.* 2013;227(2):391-397.

38. Pizzi C, Manzoli L, Mancini S, Bedetti G, Fontana F, Costa GM. Autonomic nervous system, inflammation and preclinical carotid atherosclerosis in depressed subjects with coronary risk factors. *Atherosclerosis.* 2010;212(1):292-298.

39. Kemp AH, Quintana DS, Felmingham KL, Matthews S, Jelinek HF. Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: implications for cardiovascular risk. *PLoS One.* 2012;7(2):e30777.

40. Carney RM, Freedland KE. Depression and coronary heart disease. *Nat Rev Cardiol.* 2017;14(3):145-155.

41. Souza GG, Mendonca-de-Souza AC, Barros EM, et al. Resilience and vagal tone predict cardiac recovery from acute social stress. *Stress.* 2007;10(4):368-374.

42. Souza GG, Magalhaes LN, Cruz TA, et al. Resting vagal control and resilience as predictors of cardiovascular allostasis in peacekeepers. *Stress.* 2013;16(4):377-383.

43. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet.* 2017;390(10100):1151-1210.

44. Roth GA, Johnson C, Abajobir A, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J Am Coll Cardiol.* 2017;70(1):1-25.

45. Gaziano TA. Cardiovascular disease in the developing world and its cost-effective management. *Circulation.* 2005;112(23):3547-3553.

46. Bovet P, Paccaud F. Cardiovascular Disease and the Changing Face of Global Public Health: A Focus on Low and Middle Income Countries. *Public Health Reviews.* 2011;33(2):397-415.

47. MMWR Morb Mortal Wkly Rep. Decline in deaths from heart disease and stroke--United States, 1900-1999. *MMWR Morb Mortal Wkly Rep.* 1999;48(30):649-656.

48. Manuel DG, Leung M, Nguyen K, Tanuseputro P, Johansen H. Burden of cardiovascular disease in Canada. *Can J Cardiol.* 2003;19(9):997-1004.

49. Kunst AE, Amiri M, Janssen F. The decline in stroke mortality: exploration of future trends in 7 Western European countries. *Stroke.* 2011;42(8):2126-2130.

50. Nichols M, Townsend N, Scarborough P, Rayner M. Trends in age-specific coronary heart disease mortality in the European Union over three decades: 1980-2009. *Eur Heart J.* 2013;34(39):3017-3027.

51. Bhatnagar P, Wickramasinghe K, Wilkins E, Townsend N. Trends in the epidemiology of cardiovascular disease in the UK. *Heart.* 2016;102(24):1945-1952.

52. Mensah GA, Wei GS, Sorlie PD, et al. Decline in Cardiovascular Mortality: Possible Causes and Implications. *Circ Res.* 2017;120(2):366-380.

53. Jones DS, Greene JA. The contributions of prevention and treatment to the decline in cardiovascular mortality: lessons from a forty-year debate. *Health Aff (Millwood).* 2012;31(10):2250-2258.

54. Lang JJ, Alam S, Cahill LE, et al. Global Burden of Disease Study trends for Canada from 1990 to 2016. *Cmaj.* 2018;190(44):E1296-e1304.

55. Harding MC, Sloan CD, Merrill RM, Harding TM, Thacker BJ, Thacker EL. Transitions From Heart Disease to Cancer as the Leading Cause of Death in US States, 1999-2016. *Prev Chronic Dis.* 2018;15:E158.

56. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J.* 2016;37(42):3232-3245.

57. Sharma S, Malarcher AM, Giles WH, Myers G. Racial, ethnic and socioeconomic disparities in the clustering of cardiovascular disease risk factors. *Ethn Dis.* 2004;14(1):43-48.

58. McCrindle BW, Manlhiot C, Millar K, et al. Population trends toward increasing cardiovascular risk factors in Canadian adolescents. *J Pediatr.* 2010;157(5):837-843.

59. Lee DS, Chiu M, Manuel DG, et al. Trends in risk factors for cardiovascular disease in Canada: temporal, socio-demographic and geographic factors. *Cmaj.* 2009;181(3-4):E55-66.

60. May AL, Kuklina EV, Yoon PW. Prevalence of cardiovascular disease risk factors among US adolescents, 1999-2008. *Pediatrics.* 2012;129(6):1035-1041.

61. Marshall IJ, Wang Y, Crichton S, McKevitt C, Rudd AG, Wolfe CD. The effects of socioeconomic status on stroke risk and outcomes. *Lancet Neurol.* 2015;14(12):1206-1218.

62. Andersson C, Vasan RS. Epidemiology of cardiovascular disease in young individuals. *Nat Rev Cardiol.* 2018;15(4):230-240.

63. Ward BW, Schiller JS. Prevalence of multiple chronic conditions among US adults: estimates from the National Health Interview Survey, 2010. *Prev Chronic Dis.* 2013;10:E65.

64. Roberts KC, Rao DP, Bennett TL, Loukine L, Jayaraman GC. Prevalence and patterns of chronic disease multimorbidity and associated determinants in Canada. *Health Promot Chronic Dis Prev Can.* 2015;35(6):87-94.

65. Bell SP, Saraf AA. Epidemiology of Multimorbidity in Older Adults with Cardiovascular Disease. *Clin Geriatr Med.* 2016;32(2):215-226.

66. Garin N, Koyanagi A, Chatterji S, et al. Global Multimorbidity Patterns: A Cross-Sectional, Population-Based, Multi-Country Study. *J Gerontol A Biol Sci Med Sci.* 2016;71(2):205-214.

67. Sakib MN, Shooshtari S, St John P, Menec V. The prevalence of multimorbidity and associations with lifestyle factors among middle-aged Canadians: an analysis of Canadian Longitudinal Study on Aging data. *BMC Public Health.* 2019;19(1):243.

68. Prados-Torres A, Calderon-Larranaga A, Hancco-Saavedra J, Poblador-Plou B, van den Akker M. Multimorbidity patterns: a systematic review. *J Clin Epidemiol.* 2014;67(3):254-266.

69. Forman DE, Maurer MS, Boyd C, et al. Multimorbidity in Older Adults With Cardiovascular Disease. *J Am Coll Cardiol.* 2018;71(19):2149-2161.

70. Wallace E, Salisbury C, Guthrie B, Lewis C, Fahey T, Smith SM. Managing patients with multimorbidity in primary care. *Bmj.* 2015;350:h176.

71. Makovski TT, Schmitz S, Zeegers MP, Stranges S, van den Akker M. Multimorbidity and quality of life: Systematic literature review and meta-analysis. *Ageing Res Rev.* 2019;53:100903.

72. Lehnert T, Heider D, Leicht H, et al. Review: health care utilization and costs of elderly persons with multiple chronic conditions. *Med Care Res Rev.* 2011;68(4):387-420.

73. Collaboration. ERF, Di Angelantonio E, Kaptoge S, et al. Association of Cardiometabolic Multimorbidity With Mortality. *Jama.* 2015;314(1):52-60.

74. Nunes BP, Flores TR, Mielke GI, Thume E, Facchini LA. Multimorbidity and mortality in older adults: A systematic review and meta-analysis. *Arch Gerontol Geriatr.* 2016;67:130-138.

75. Nattel S, Burstein B, Dobrev D. Atrial remodeling and atrial fibrillation: mechanisms and implications. *Circ Arrhythm Electrophysiol.* 2008;1(1):62-73.

76. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet.* 2009;373(9658):155-166.

77. Thrall G, Lane D, Carroll D, Lip GY. Quality of life in patients with atrial fibrillation: a systematic review. *Am J Med.* 2006;119(5):448.e441-419.

78. McCabe PJ. Psychological distress in patients diagnosed with atrial fibrillation: the state of the science. *J Cardiovasc Nurs.* 2010;25(1):40-51.

79. Andrade JG, Verma A, Mitchell LB, et al. 2018 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. *Can J Cardiol.* 2018;34(11):1371-1392.

80. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2019;74(1):104-132.

81. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet.* 2015;386(9989):154-162.

82. Martinez C, Katholing A, Wallenhorst C, Granziera S, Cohen AT, Freedman SB. Increasing incidence of non-valvular atrial fibrillation in the UK from 2001 to 2013. *Heart.* 2015;101(21):1748-1754.

83. Patel NJ, Deshmukh A, Pant S, et al. Contemporary trends of hospitalization for atrial fibrillation in the United States, 2000 through 2010: implications for healthcare planning. *Circulation.* 2014;129(23):2371-2379.

84. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018;392(10159):1923-1994.

85. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. *Lancet.* 2017;389(10064):37-55.

86. Mills KT, Bundy JD, Kelly TN, et al. Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies From 90 Countries. *Circulation.* 2016;134(6):441-450.

87. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet.* 2005;365(9455):217-223.

88. Carretero OA, Oparil S. Essential hypertension. Part I: definition and etiology. *Circulation.* 2000;101(3):329-335.

89. Escobar E. Hypertension and coronary heart disease. *J Hum Hypertens.* 2002;16 Suppl 1:S61-63.

90. Drazner MH. The progression of hypertensive heart disease. *Circulation.* 2011;123(3):327-334.

91. Messerli FH, Rimoldi SF, Bangalore S. The Transition From Hypertension to Heart Failure: Contemporary Update. *JACC Heart Fail.* 2017;5(8):543-551.

92. Yu JG, Zhou RR, Cai GJ. From hypertension to stroke: mechanisms and potential prevention strategies. *CNS Neurosci Ther.* 2011;17(5):577-584.

93. Ravera M, Re M, Deferrari L, Vettoretti S, Deferrari G. Importance of blood pressure control in chronic kidney disease. *J Am Soc Nephrol.* 2006;17(4 Suppl 2):S98-103.

94. Mayet J, Hughes A. Cardiac and vascular pathophysiology in hypertension. *Heart.* 2003;89(9):1104-1109.

95. Kahan T, Bergfeldt L. Left ventricular hypertrophy in hypertension: its arrhythmogenic potential. *Heart.* 2005;91(2):250-256.

96. Vaziri SM, Larson MG, Lauer MS, Benjamin EJ, Levy D. Influence of blood pressure on left atrial size. The Framingham Heart Study. *Hypertension.* 1995;25(6):1155-1160.

97. Tsioufis C, Stefanadis C, Goumas G, Pitsavos C, Toutouzas P. Relation of ambulatory blood pressure load with left ventricular geometry in untreated patients with mild-to-moderate hypertension. *J Hum Hypertens.* 1999;13(10):677-682.

98. Cuspidi C, Ciulla M, Zanchetti A. Hypertensive myocardial fibrosis. *Nephrol Dial Transplant.* 2006;21(1):20-23.

99. Gonzalez A, Ravassa S, Lopez B, et al. Myocardial Remodeling in Hypertension. *Hypertension.* 2018;72(3):549-558.

100. Bleakley C, Hamilton PK, Pumb R, Harbinson M, McVeigh GE. Endothelial Function in Hypertension: Victim or Culprit? *J Clin Hypertens (Greenwich).* 2015;17(8):651-654.

101. Brown IAM, Diederich L, Good ME, et al. Vascular Smooth Muscle Remodeling in Conductive and Resistance Arteries in Hypertension. *Arterioscler Thromb Vasc Biol.* 2018;38(9):1969-1985.

102. Gordan R, Gwathmey JK, Xie LH. Autonomic and endocrine control of cardiovascular function. *World J Cardiol.* 2015;7(4):204-214.

103. Karemaker JM. An introduction into autonomic nervous function. *Physiol Meas.* 2017;38(5):R89-r118.

104. Browning KN, Travagli RA. Central nervous system control of gastrointestinal motility and secretion and modulation of gastrointestinal functions. *Compr Physiol.* 2014;4(4):1339-1368.

105. Kenney MJ, Ganta CK. Autonomic nervous system and immune system interactions. *Compr Physiol.* 2014;4(3):1177-1200.

106. Carnethon MR, Jacobs DR, Jr., Sidney S, Liu K. Influence of autonomic nervous system dysfunction on the development of type 2 diabetes: the CARDIA study. *Diabetes Care.* 2003;26(11):3035-3041.

107. Moreira MC, Pinto IS, Mourao AA, et al. Does the sympathetic nervous system contribute to the pathophysiology of metabolic syndrome? *Front Physiol.* 2015;6:234.

108. Guarino D, Nannipieri M, Iervasi G, Taddei S, Bruno RM. The Role of the Autonomic Nervous System in the Pathophysiology of Obesity. *Front Physiol.* 2017;8:665.

109. Tansey EA, Johnson CD. Recent advances in thermoregulation. *Adv Physiol Educ.* 2015;39(3):139-148.

110. Stratakis CA, Chrousos GP. Neuroendocrinology and pathophysiology of the stress system. *Ann N Y Acad Sci.* 1995;771:1-18.

111. Grassi G. Sympathetic neural activity in hypertension and related diseases. *Am J Hypertens.* 2010;23(10):1052-1060.

112. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *Int J Cardiol.* 2010;141(2):122-131.

113. Koopman FA, Tang MW, Vermeij J, et al. Autonomic Dysfunction Precedes Development of Rheumatoid Arthritis: A Prospective Cohort Study. *EBioMedicine.* 2016;6:231-237.

114. Alvares GA, Quintana DS, Hickie IB, Guastella AJ. Autonomic nervous system dysfunction in psychiatric disorders and the impact of psychotropic medications: a systematic review and meta-analysis. *J Psychiatry Neurosci.* 2016;41(2):89-104.

115. Fox K, Borer JS, Camm AJ, et al. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol.* 2007;50(9):823-830.

116. Mancia G, Grassi G. The autonomic nervous system and hypertension. *Circ Res.* 2014;114(11):1804-1814.

117. Kapa S, Venkatachalam KL, Asirvatham SJ. The autonomic nervous system in cardiac electrophysiology: an elegant interaction and emerging concepts. *Cardiol Rev.* 2010;18(6):275-284.

118. Bruno RM, Ghiadoni L, Seravalle G, Dell'oro R, Taddei S, Grassi G. Sympathetic regulation of vascular function in health and disease. *Front Physiol.* 2012;3:284.

119. Amiya E, Watanabe M, Komuro I. The Relationship between Vascular Function and the Autonomic Nervous System. *Ann Vasc Dis.* 2014;7(2):109-119.

120. Qiu S, Cai X, Sun Z, et al. Heart Rate Recovery and Risk of Cardiovascular Events and All-Cause Mortality: A Meta-Analysis of Prospective Cohort Studies. *J Am Heart Assoc.* 2017;6(5).

121. White DW, Raven PB. Autonomic neural control of heart rate during dynamic exercise: revisited. *J Physiol.* 2014;592(12):2491-2500.

122. Dekker JM, Schouten EG, Klootwijk P, Pool J, Swenne CA, Kromhout D. Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in middle-aged and elderly men. The Zutphen Study. *Am J Epidemiol.* 1997;145(10):899-908.

123. Nolan J, Batin PD, Andrews R, et al. Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). *Circulation.* 1998;98(15):1510-1516.

124. Buccelletti E, Gilardi E, Scaini E, et al. Heart rate variability and myocardial infarction: systematic literature review and metanalysis. *Eur Rev Med Pharmacol Sci.* 2009;13(4):299-307.

125. Hillebrand S, Gast KB, de Mutsert R, et al. Heart rate variability and first cardiovascular event in populations without known cardiovascular disease: meta-analysis and dose-response meta-regression. *Europace.* 2013;15(5):742-749.

126. Benichou T, Pereira B, Mermillod M, et al. Heart rate variability in type 2 diabetes mellitus: A systematic review and meta-analysis. *PLoS One.* 2018;13(4):e0195166.

127. Esler M. The sympathetic system and hypertension. *Am J Hypertens.* 2000;13(6 Pt 2):99s-105s.

128. Carthy ER. Autonomic dysfunction in essential hypertension: A systematic review. *Ann Med Surg (Lond).* 2014;3(1):2-7.

129. Manrique C, Lastra G, Gardner M, Sowers JR. The renin angiotensin aldosterone system in hypertension: roles of insulin resistance and oxidative stress. *Med Clin North Am.* 2009;93(3):569-582.

130. Kougias P, Weakley SM, Yao Q, Lin PH, Chen C. Arterial baroreceptors in the management of systemic hypertension. *Med Sci Monit.* 2010;16(1):Ra1-8.

131. Thomas GD. Neural control of the circulation. *Adv Physiol Educ.* 2011;35(1):28-32.

132. La Rovere MT, Pinna GD, Raczak G. Baroreflex sensitivity: measurement and clinical implications. *Ann Noninvasive Electrocardiol.* 2008;13(2):191-207.

133. Dangardt F, Volkmann R, Chen Y, Osika W, Marild S, Friberg P. Reduced cardiac vagal activity in obese children and adolescents. *Clin Physiol Funct Imaging.* 2011;31(2):108-113.

134. Latchman PL, Mathur M, Bartels MN, Axtell RS, De Meersman RE. Impaired autonomic function in normotensive obese children. *Clin Auton Res.* 2011;21(5):319-323.

135. Lazarova Z, Tonhajzerova I, Trunkvalterova Z, et al. Baroreflex sensitivity is reduced in obese normotensive children and adolescents. *Can J Physiol Pharmacol.* 2009;87(7):565-571.

136. Skrapari I, Tentolouris N, Perrea D, Bakoyiannis C, Papazafiropoulou A, Katsilambros N. Baroreflex sensitivity in obesity: relationship with cardiac autonomic nervous system activity. *Obesity (Silver Spring).* 2007;15(7):1685-1693.

137. Chesterton LJ, Sigrist MK, Bennett T, Taal MW, McIntyre CW. Reduced baroreflex sensitivity is associated with increased vascular calcification and arterial stiffness. *Nephrol Dial Transplant.* 2005;20(6):1140-1147.

138. Grassi G, Seravalle G, Quarti-Trevano F, et al. Sympathetic and baroreflex cardiovascular control in hypertension-related left ventricular dysfunction. *Hypertension.* 2009;53(2):205-209.

139. Dell'Oro R, Trevano FQ, Gamba P, et al. Sympathetic and baroreflex abnormalities in the uncomplicated prediabetic state. *J Hypertens.* 2018;36(5):1195-1200.

140. Zuern CS, Eick C, Rizas KD, et al. Impaired cardiac baroreflex sensitivity predicts response to renal sympathetic denervation in patients with resistant hypertension. *J Am Coll Cardiol.* 2013;62(22):2124-2130.

141. Ormezzano O, Cracowski JL, Quesada JL, Pierre H, Mallion JM, Baguet JP. EVAluation of the prognostic value of BARoreflex sensitivity in hypertensive patients: the EVABAR study. *J Hypertens.* 2008;26(7):1373-1378.

142. La Rovere MT, Bigger JT, Jr., Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet.* 1998;351(9101):478-484.

143. La Rovere MT, Pinna GD, Hohnloser SH, et al. Baroreflex sensitivity and heart rate variability in the identification of patients at risk for life-threatening arrhythmias: implications for clinical trials. *Circulation.* 2001;103(16):2072-2077.

144. De Ferrari GM, Sanzo A, Bertoletti A, Specchia G, Vanoli E, Schwartz PJ. Baroreflex sensitivity predicts long-term cardiovascular mortality after myocardial infarction even in patients with preserved left ventricular function. *J Am Coll Cardiol.* 2007;50(24):2285-2290.

145. Ranucci M, Porta A, Bari V, Pistuddi V, La Rovere MT. Baroreflex sensitivity and outcomes following coronary surgery. *PLoS One.* 2017;12(4):e0175008.

146. Yperzeele L, van Hooff RJ, Nagels G, De Smedt A, De Keyser J, Brouns R. Heart rate variability and baroreceptor sensitivity in acute stroke: a systematic review. *Int J Stroke.* 2015;10(6):796-800.

147. Mortara A, La Rovere MT, Pinna GD, et al. Arterial baroreflex modulation of heart rate in chronic heart failure: clinical and hemodynamic correlates and prognostic implications. *Circulation.* 1997;96(10):3450-3458.

148. Atlas SA. The renin-angiotensin aldosterone system: pathophysiological role and pharmacologic inhibition. *J Manag Care Pharm.* 2007;13(8 Suppl B):9-20.

149. Verdecchia P, Porcellati C, Schillaci G, et al. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension.* 1994;24(6):793-801.

150. Pierdomenico SD, Lapenna D, Cuccurullo F. Risk of atrial fibrillation in dipper and nondipper sustained hypertensive patients. *Blood Press Monit.* 2008;13(4):193-197.

151. Perkiomaki J, Ukkola O, Kiviniemi A, et al. Heart rate variability findings as a predictor of atrial fibrillation in middle-aged population. *J Cardiovasc Electrophysiol.* 2014;25(7):719-724.

152. Reyes del Paso GA, Langewitz W, Mulder LJ, van Roon A, Duschek S. The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: a review with emphasis on a reanalysis of previous studies. *Psychophysiology.* 2013;50(5):477-487.

153. Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. *Front Public Health.* 2017;5:258.

154. Caldwell JR, Hollinger FW. The unreliability of casual blood pressures as an index to cardiovascular-renal disease. *Postgrad Med.* 1958;24(1):26-29.

155. Kain HK, Hinman AT, Sokolow M. Arterial blood pressure measurements with a portable recorder in hypertensive patients. I. Variability and correlation with "casual" pressures. *Circulation.* 1964;30:882-892.

156. Sokolow M, Werdegar D, Kain HK, Hinman AT. Relationship between level of blood pressure measured casually and by portable recorders and severity of complications in essential hypertension. *Circulation.* 1966;34(2):279-298.

157. Pickering T. Ambulatory blood pressure monitoring: an historical perspective. *Clin Cardiol.* 1992;15(5 Suppl 2):Ii3-5.

158. Hinman AT, Engel BT, Bickford AF. Portable blood pressure recorder. Accuracy and preliminary use in evaluating intradaily variations in pressure. *Am Heart J.* 1962;63:663-668.

159. Parati G, Dolan E, McManus RJ, Omboni S. Home blood pressure telemonitoring in the 21st century. *J Clin Hypertens (Greenwich).* 2018;20(7):1128-1132.

160. Mancia G, Parati G. Ambulatory blood pressure monitoring and organ damage. *Hypertension.* 2000;36(5):894-900.

161. Staessen JA, Thijs L, Fagard R, et al. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *Jama.* 1999;282(6):539-546.

162. Dolan E, Stanton A, Thijs L, et al. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension.* 2005;46(1):156-161.

163. Fagard RH, Celis H, Thijs L, et al. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. *Hypertension.* 2008;51(1):55-61.

164. Hansen TW, Jeppesen J, Rasmussen S, Ibsen H, Torp-Pedersen C. Ambulatory blood pressure monitoring and risk of cardiovascular disease: a population based study. *Am J Hypertens.* 2006;19(3):243-250.

165. Eguchi K, Pickering TG, Hoshide S, et al. Ambulatory blood pressure is a better marker than clinic blood pressure in predicting cardiovascular events in patients with/without type 2 diabetes. *Am J Hypertens.* 2008;21(4):443-450.

166. Niiranen TJ, Maki J, Puukka P, Karanko H, Jula AM. Office, home, and ambulatory blood pressures as predictors of cardiovascular risk. *Hypertension.* 2014;64(2):281-286.

167. Banegas JR, Ruilope LM, de la Sierra A, et al. Relationship between Clinic and Ambulatory Blood-Pressure Measurements and Mortality. *N Engl J Med.* 2018;378(16):1509-1520.

168. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J.* 2018;39(33):3021-3104.

169. O'Flynn AM, Dolan E, Curtin RJ, O'Brien E, Perry IJ, Kearney PM. Night-time blood pressure and target organ damage: a comparative analysis of absolute blood pressure and dipping status. *J Hypertens.* 2015;33(11):2257-2264.

170. Roush GC, Fagard RH, Salles GF, et al. Prognostic impact from clinic, daytime, and night-time systolic blood pressure in nine cohorts of 13,844 patients with hypertension. *J Hypertens.* 2014;32(12):2332-2340; discussion 2340.

171. Salles GF, Reboldi G, Fagard RH, et al. Prognostic Effect of the Nocturnal Blood Pressure Fall in Hypertensive Patients: The Ambulatory Blood Pressure Collaboration in Patients With Hypertension (ABC-H) Meta-Analysis. *Hypertension.* 2016;67(4):693-700.

172. Tsioufis C, Andrikou I, Thomopoulos C, Syrseloudis D, Stergiou G, Stefanadis C. Increased nighttime blood pressure or nondipping profile for prediction of cardiovascular outcomes. *J Hum Hypertens.* 2011;25(5):281-293.

173. Cuspidi C, Sala C, Valerio C, Negri F, Mancia G. Nocturnal hypertension and organ damage in dippers and nondippers. *Am J Hypertens.* 2012;25(8):869-875.

174. Koroboki E, Manios E, Michas F, et al. The impact of nocturnal hypertension and nondipping status on left ventricular mass: a cohort study. *Blood Press Monit.* 2015;20(3):121-126.

175. Androulakis E, Papageorgiou N, Chatzistamatiou E, Kallikazaros I, Stefanadis C, Tousoulis D. Improving the detection of preclinical organ damage in newly diagnosed hypertension: nocturnal hypertension versus non-dipping pattern. *J Hum Hypertens.* 2015;29(11):689-695.

176. Wang C, Deng WJ, Gong WY, et al. Nocturnal Hypertension Correlates Better With Target Organ Damage in Patients With Chronic Kidney Disease than a Nondipping Pattern. *J Clin Hypertens (Greenwich).* 2015;17(10):792-801.

177. Gkaliagkousi E, Anyfanti P, Lazaridis A, et al. Clinical impact of dipping and nocturnal blood pressure patterns in newly diagnosed, never-treated patients with essential hypertension. *J Am Soc Hypertens.* 2018;12(12):850-857.

178. Tsioufis C, Andrikou I, Thomopoulos C, Petras D, Manolis A, Stefanadis C. Comparative prognostic role of nighttime blood pressure and nondipping profile on renal outcomes. *Am J Nephrol.* 2011;33(3):277-288.

179. de la Sierra A, Redon J, Banegas JR, et al. Prevalence and factors associated with circadian blood pressure patterns in hypertensive patients. *Hypertension.* 2009;53(3):466-472.

180. de la Sierra A, Gorostidi M, Banegas JR, Segura J, de la Cruz JJ, Ruilope LM. Nocturnal hypertension or nondipping: which is better associated with the cardiovascular risk profile? *Am J Hypertens.* 2014;27(5):680-687.

181. Rim SJ. Blood pressure variation and cardiovascular risks. *Korean Circ J.* 2008;38:131-134.

182. Parati G, Stergiou GS, Dolan E, Bilo G. Blood pressure variability: clinical relevance and application. *J Clin Hypertens (Greenwich).* 2018;20(7):1133-1137.

183. Wang C, Zhang J, Deng W, et al. Nighttime Systolic Blood-Pressure Load Is Correlated with Target-Organ Damage Independent of Ambulatory Blood-Pressure Level in Patients with Non-Diabetic Chronic Kidney Disease. *PLoS One.* 2015;10(7):e0131546.

184. Ciamei A, Franconi G, Baldoni F, De Nardo D, Sabino D. C054: Endothelial dysfunction in hypertensive patients is correlated with ABPM and blood pressure load. *American Journal of Hypertension.* 2000;13(S2):229A-230A.

185. Li Y, Thijs L, Boggia J, et al. Blood pressure load does not add to ambulatory blood pressure level for cardiovascular risk stratification. *Hypertension.* 2014;63(5):925-933.

186. Stevens SL, Wood S, Koshiaris C, et al. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. *Bmj.* 2016;354:i4098.

187. Wu J, Kraja AT, Oberman A, et al. A summary of the effects of antihypertensive medications on measured blood pressure. *Am J Hypertens.* 2005;18(7):935-942.

188. Baguet JP, Legallicier B, Auquier P, Robitail S. Updated meta-analytical approach to the efficacy of antihypertensive drugs in reducing blood pressure. *Clin Drug Investig.* 2007;27(11):735-753.

189. Paz MA, de-La-Sierra A, Saez M, et al. Treatment efficacy of anti-hypertensive drugs in monotherapy or combination: ATOM systematic review and meta-analysis of randomized clinical trials according to PRISMA statement. *Medicine (Baltimore).* 2016;95(30):e4071.

190. Edwards JE, Moore RA. Statins in hypercholesterolaemia: a dose-specific meta-analysis of lipid changes in randomised, double blind trials. *BMC Fam Pract.* 2003;4:18.

191. Dicembrini I, Giannini S, Ragghianti B, Mannucci E, Monami M. Effects of PCSK9 inhibitors on LDL cholesterol, cardiovascular morbidity and all-cause mortality: a systematic review and meta-analysis of randomized controlled trials. *J Endocrinol Invest.* 2019.

192. Virdis A, Ghiadoni L, Taddei S. Effects of antihypertensive treatment on endothelial function. *Curr Hypertens Rep.* 2011;13(4):276-281.

193. Reriani MK, Dunlay SM, Gupta B, et al. Effects of statins on coronary and peripheral endothelial function in humans: a systematic review and meta-analysis of randomized controlled trials. *Eur J Cardiovasc Prev Rehabil.* 2011;18(5):704-716.

194. Peller M, Ozieranski K, Balsam P, Grabowski M, Filipiak KJ, Opolski G. Influence of beta-blockers on endothelial function: A meta-analysis of randomized controlled trials. *Cardiol J.* 2015;22(6):708-716.

195. Chan NC, Weitz JI. Antithrombotic Agents. *Circ Res.* 2019;124(3):426-436.

196. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *Bmj.* 2002;324(7329):71-86.

197. Turnbull F, Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet.* 2003;362(9395):1527-1535.

198. Cheung BM, Lauder IJ, Lau CP, Kumana CR. Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes. *Br J Clin Pharmacol.* 2004;57(5):640-651.

199. De Caterina R, Scarano M, Marfisi R, et al. Cholesterol-lowering interventions and stroke: insights from a meta-analysis of randomized controlled trials. *J Am Coll Cardiol.* 2010;55(3):198-211.

200. Mukete BN, Cassidy M, Ferdinand KC, Le Jemtel TH. Long-Term Anti-Hypertensive Therapy and Stroke Prevention: A Meta-Analysis. *Am J Cardiovasc Drugs.* 2015;15(4):243-257.

201. Lopez-Lopez JA, Sterne JAC, Thom HHZ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. *Bmj.* 2017;359:j5058.

202. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence. 12. Effects in individuals with high-normal and normal blood pressure: overview and meta-analyses of randomized trials. *J Hypertens.* 2017;35(11):2150-2160.

203. Smith SC, Jr., Benjamin EJ, Bonow RO, et al. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and other Atherosclerotic Vascular Disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation.* 2011;124(22):2458-2473.

204. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical

Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J.* 2016;37(29):2315-2381.

205. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. *Circulation.* 2019:Cir0000000000000678.

206. Mozaffarian D, Wilson PW, Kannel WB. Beyond established and novel risk factors: lifestyle risk factors for cardiovascular disease. *Circulation.* 2008;117(23):3031-3038.

207. O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet.* 2016;388(10046):761-775.

208. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet.* 2004;364(9438):937-952.

209. Saneei P, Salehi-Abargouei A, Esmaillzadeh A, Azadbakht L. Influence of Dietary Approaches to Stop Hypertension (DASH) diet on blood pressure: a systematic review and meta-analysis on randomized controlled trials. *Nutr Metab Cardiovasc Dis.* 2014;24(12):1253-1261.

210. Siervo M, Lara J, Chowdhury S, Ashor A, Oggioni C, Mathers JC. Effects of the Dietary Approach to Stop Hypertension (DASH) diet on cardiovascular risk factors: a systematic review and meta-analysis. *Br J Nutr.* 2015;113(1):1-15.

211. Grosso G, Marventano S, Yang J, et al. A comprehensive meta-analysis on evidence of Mediterranean diet and cardiovascular disease: Are individual components equal? *Crit Rev Food Sci Nutr.* 2017;57(15):3218-3232.

212. Sattelmair J, Pertman J, Ding EL, Kohl HW, 3rd, Haskell W, Lee IM. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. *Circulation.* 2011;124(7):789-795.

213. Li J, Siegrist J. Physical activity and risk of cardiovascular disease--a meta-analysis of prospective cohort studies. *Int J Environ Res Public Health.* 2012;9(2):391-407.

214. Schroeder EC, Franke WD, Sharp RL, Lee DC. Comparative effectiveness of aerobic, resistance, and combined training on cardiovascular disease risk factors: A randomized controlled trial. *PLoS One.* 2019;14(1):e0210292.

215. Linden W, Phillips MJ, Leclerc J. Psychological treatment of cardiac patients: a meta-analysis. *Eur Heart J.* 2007;28(24):2972-2984.

216. Richards SH, Anderson L, Jenkinson CE, et al. Psychological interventions for coronary heart disease: Cochrane systematic review and meta-analysis. *Eur J Prev Cardiol.* 2018;25(3):247-259.

217. Mottillo S, Filion KB, Belisle P, et al. Behavioural interventions for smoking cessation: a meta-analysis of randomized controlled trials. *Eur Heart J.* 2009;30(6):718-730.

218. Mons U, Muezzinler A, Gellert C, et al. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. *Bmj.* 2015;350:h1551.

219. Suissa K, Lariviere J, Eisenberg MJ, et al. Efficacy and Safety of Smoking Cessation Interventions in Patients With Cardiovascular Disease: A Network Meta-Analysis of Randomized Controlled Trials. *Circ Cardiovasc Qual Outcomes.* 2017;10(1).

220. Baum A, Posluszny DM. Health psychology: mapping biobehavioral contributions to health and illness. *Annu Rev Psychol.* 1999;50:137-163.

221. Salovey P, Rothman AJ, Detweiler JB, Steward WT. Emotional states and physical health. *Am Psychol.* 2000;55(1):110-121.

222. de Ridder D, Geenen R, Kuijer R, van Middendorp H. Psychological adjustment to chronic disease. *Lancet.* 2008;372(9634):246-255.

223. 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(1):33-47.

224. Kabat-Zinn J. Mindfulness-Based Interventions in Context: Past, Present, and Future. *Clinical Psychology: Science and Practice.* 2003;10(2):144-156.

225. Clark D, Schumann F, Mostofsky SH. Mindful movement and skilled attention. *Front Hum Neurosci.* 2015;9:297.

226. Teasdale JD, Segal Z, Williams JM. How does cognitive therapy prevent depressive relapse and why should attentional control (mindfulness) training help? *Behav Res Ther.* 1995;33(1):25-39.

227. Teasdale JD, Segal ZV, Williams JM, Ridgeway VA, Soulsby JM, Lau MA. Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. *J Consult Clin Psychol.* 2000;68(4):615-623.

228. Hayes SC. Acceptance and commitment therapy, relational frame theory, and the third wave of behavioral and cognitive therapies *Behav Ther.* 2004;35:639-665.

229. Hayes SC, Luoma JB, Bond FW, Masuda A, Lillis J. Acceptance and commitment therapy: model, processes and outcomes. *Behav Res Ther.* 2006;44(1):1-25.

230. Segal ZV, Williams JMG, Teasdale JD. *Mindfulness-based cognitive therapy for depression (2nd ed.).* New York: Guilford Press; 2013.

231. Shapiro SL, Carlson LE, Astin JA, Freedman B. Mechanisms of mindfulness. *J Clin Psychol.* 2006;62(3):373-386.

232. Bishop SR, Lau M, Shapiro S, et al. Mindfulness: A Proposed Operational Definition. *Clinical Psychology: Science and Practice.* 2004;11(3):230-241.

233. Wells A. GAD, Meta-cognition, and Mindfulness: An Information Processing Analysis. 2006;9(1):95-100.

234. Jankowski T, Holas P. Metacognitive model of mindfulness. *Conscious Cogn.* 2014;28:64-80.

235. Crane RS, Brewer J, Feldman C, et al. What defines mindfulness-based programs? The warp and the weft. *Psychol Med.* 2017;47(6):990-999.

236. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. *J Consult Clin Psychol.* 2010;78(2):169-183.

237. Chiesa A, Serretti A. Mindfulness based cognitive therapy for psychiatric disorders: a systematic review and meta-analysis. *Psychiatry Res.* 2011;187(3):441-453.

238. Strauss C, Cavanagh K, Oliver A, Pettman D. Mindfulness-based interventions for people diagnosed with a current episode of an anxiety or depressive disorder: a meta-analysis of randomised controlled trials. *PLoS One.* 2014;9(4):e96110.

239. Khoury B, Sharma M, Rush SE, Fournier C. Mindfulness-based stress reduction for healthy individuals: A meta-analysis. *J Psychosom Res.* 2015;78(6):519-528.

240. Chiesa A, Serretti A. Mindfulness-based stress reduction for stress management in healthy people: a review and meta-analysis. *J Altern Complement Med.* 2009;15(5):593-600.

241. Kuyken W, Warren FC, Taylor RS, et al. Efficacy of Mindfulness-Based Cognitive Therapy in Prevention of Depressive Relapse: An Individual Patient Data Meta-analysis From Randomized Trials. *JAMA Psychiatry.* 2016;73(6):565-574.

242. Raab K. Mindfulness, self-compassion, and empathy among health care professionals: a review of the literature. *J Health Care Chaplain.* 2014;20(3):95-108.

243. Luberto CM, Shinday N, Song R, et al. A Systematic Review and Meta-analysis of the Effects of Meditation on Empathy, Compassion, and Prosocial Behaviors. *Mindfulness (N Y).* 2018;9(3):708-724.

244. Hilton L, Hempel S, Ewing BA, et al. Mindfulness Meditation for Chronic Pain: Systematic Review and Meta-analysis. *Ann Behav Med.* 2017;51(2):199-213.

245. Pickering TG. Mental stress as a causal factor in the development of hypertension and cardiovascular disease. *Curr Hypertens Rep.* 2001;3(3):249-254.

246. Hering D, Lachowska K, Schlaich M. Role of the Sympathetic Nervous System in Stress-Mediated Cardiovascular Disease. *Curr Hypertens Rep.* 2015;17(10):80.

247. Ho PM, Rumsfeld JS, Masoudi FA, et al. Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. *Arch Intern Med.* 2006;166(17):1836-1841.

248. van der Wal MH, van Veldhuisen DJ, Veeger NJ, Rutten FH, Jaarsma T. Compliance with non-pharmacological recommendations and outcome in heart failure patients. *Eur Heart J.* 2010;31(12):1486-1493.

249. Pittman DG, Chen W, Bowlin SJ, Foody JM. Adherence to statins, subsequent healthcare costs, and cardiovascular hospitalizations. *Am J Cardiol.* 2011;107(11):1662-1666.

250. Fitzgerald AA, Powers JD, Ho PM, et al. Impact of medication nonadherence on hospitalizations and mortality in heart failure. *J Card Fail.* 2011;17(8):664-669.

251. Currie CJ, Peyrot M, Morgan CL, et al. The impact of treatment noncompliance on mortality in people with type 2 diabetes. *Diabetes Care.* 2012;35(6):1279-1284.

252. Herttua K, Martikainen P, Batty GD, Kivimäki M. Poor Adherence to Statin and Antihypertensive Therapies as Risk Factors for Fatal Stroke. *J Am Coll Cardiol.* 2016;67(13):1507-1515.

253. Gathright EC, Dolansky MA, Gunstad J, et al. The impact of medication nonadherence on the relationship between mortality risk and depression in heart failure. *Health Psychol.* 2017;36(9):839-847.

254. Miller NH, Hill M, Kottke T, Ockene IS. The multilevel compliance challenge: recommendations for a call to action. A statement for healthcare professionals. *Circulation.* 1997;95(4):1085-1090.

255. Ockene IS, Hayman LL, Pasternak RC, Schron E, Dunbar-Jacob J. Task force #4--adherence issues and behavior changes: achieving a long-term solution. 33rd Bethesda Conference. *J Am Coll Cardiol.* 2002;40(4):630-640.

256. Bodenheimer T, Lorig K, Holman H, Grumbach K. Patient self-management of chronic disease in primary care. *Jama.* 2002;288(19):2469-2475.

257. Vale MJ, Jelinek MV, Best JD, et al. Coaching patients On Achieving Cardiovascular Health (COACH): a multicenter randomized trial in patients with coronary heart disease. *Arch Intern Med.* 2003;163(22):2775-2783.

258. Olsen JM, Nesbitt BJ. Health coaching to improve healthy lifestyle behaviors: an integrative review. *Am J Health Promot.* 2010;25(1):e1-e12.

259. Pirbaglou M, Katz J, Motamed M, Pludwinski S, Walker K, Ritvo P. Personal Health Coaching as a Type 2 Diabetes Mellitus Self-Management Strategy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Am J Health Promot.* 2018;32(7):1613-1626.

260. Palmer S, Tubbs I, Whybrow A. Health coaching to facilitate the promotion of healthy behaviour and achievement of health-related goals. *International Journal of Health Promotion and Education.* 2003;41(3):91-93.

261. Wolever RQ, Simmons LA, Sforzo GA, et al. A Systematic Review of the Literature on Health and Wellness Coaching: Defining a Key Behavioral intervention in Healthcare. *Glob Adv Health Med.* 2013;2(4):38-57.

262. Hart V, Blattner J, Leipsic S. Coaching versus therapy: A perspective. *Consulting Psychology Journal: Practice and Research.* 2001;53(4):229-237.

263. U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute. Your guide to a healthy heart. https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/your-guide-healthy-heart. Published December 2005. Accessed October 2019.

264. U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute. Your guide to lowering your blood pressure with DASH. https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/your-guide-lowering-your-blood-pressure-dash. Revised April 2006. Accessed October 2019.

265. O'Brien E, Waeber B, Parati G, Staessen J, Myers MG. Blood pressure measuring devices: recommendations of the European Society of Hypertension. *Bmj.* 2001;322(7285):531-536.

266. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67(6):361-370.

267. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res.* 2002;52(2):69-77.

268. Eifert GH, Thompson RN, Zvolensky MJ, et al. The cardiac anxiety questionnaire: development and preliminary validity. *Behav Res Ther.* 2000;38(10):1039-1053.

269. Shacham S. A shortened version of the Profile of Mood States. *J Pers Assess.* 1983;47(3):305-306.

270. Curran SL, Andrykowski MA, Studts JL. Short form of the profile of mood states (POMS-SF): Psychometric information. *Psychological Assessment.* 1995;7(1):80-83.

271. Baker F, Denniston M, Zabora J, Polland A, Dudley WN. A POMS short form for cancer patients: psychometric and structural evaluation. *Psychooncology.* 2002;11(4):273-281.

272. Bohlmeijer E, ten Klooster PM, Fledderus M, Veehof M, Baer R. Psychometric properties of the five facet mindfulness questionnaire in depressed adults and development of a short form. *Assessment.* 2011;18(3):308-320.

273. Baer RA, Smith GT, Lykins E, et al. Construct validity of the five facet mindfulness questionnaire in meditating and nonmeditating samples. *Assessment.* 2008;15(3):329-342.

274. de Bruin EI, Topper M, Muskens JG, Bogels SM, Kamphuis JH. Psychometric properties of the Five Facets Mindfulness Questionnaire (FFMQ) in a meditating and a non-meditating sample. *Assessment.* 2012;19(2):187-197.

275. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989;28(2):193-213.

276. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods.* 2007;39(2):175-191.

277. Hermida RC, Ayala DE, Mojon A, Fernandez JR. Decreasing sleep-time blood pressure determined by ambulatory monitoring reduces cardiovascular risk. *J Am Coll Cardiol.* 2011;58(11):1165-1173.

278. Kane SP. Sample Size Calculator. ClinCalc. https://clincalc.com/stats/samplesize.aspx. Updated July 24, 2019. Accessed August 2019.

279. Chan YH. Biostatistics 301A. Repeated measurement analysis (mixed models). *Singapore Med J.* 2004;45(10):456-461.

280. Gueorguieva R, Krystal JH. Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry. *Arch Gen Psychiatry.* 2004;61(3):310-317.

281. Monahan KD, Dinenno FA, Tanaka H, Clevenger CM, DeSouza CA, Seals DR. Regular aerobic exercise modulates age-associated declines in cardiovagal baroreflex sensitivity in healthy men. *J Physiol.* 2000;529 Pt 1(Pt 1):263-271.

282. Iellamo F, Legramante JM, Massaro M, Raimondi G, Galante A. Effects of a residential exercise training on baroreflex sensitivity and heart rate variability in patients with coronary artery disease: A randomized, controlled study. *Circulation.* 2000;102(21):2588-2592.

283. Laterza MC, de Matos LD, Trombetta IC, et al. Exercise training restores baroreflex sensitivity in never-treated hypertensive patients. *Hypertension.* 2007;49(6):1298-1306.

284. La Rovere MT, Pinna GD. Beneficial effects of physical activity on baroreflex control in the elderly. *Ann Noninvasive Electrocardiol.* 2014;19(4):303-310.

285. Nakano Y, Oshima T, Sasaki S, et al. Calorie restriction reduced blood pressure in obesity hypertensives by improvement of autonomic nerve activity and insulin sensitivity. *J Cardiovasc Pharmacol.* 2001;38 Suppl 1:S69-74.

286. Edwards KM, Wilson KL, Sadja J, Ziegler MG, Mills PJ. Effects on blood pressure and autonomic nervous system function of a 12-week exercise or exercise plus DASH-diet intervention in individuals with elevated blood pressure. *Acta Physiol (Oxf).* 2011;203(3):343-350.

287. Ziegler D, Strom A, Nowotny B, et al. Effect of Low-Energy Diets Differing in Fiber, Red Meat, and Coffee Intake on Cardiac Autonomic Function in Obese Individuals With Type 2 Diabetes. *Diabetes Care.* 2015;38(9):1750-1757.

288. Blumenthal JA, Babyak MA, Hinderliter A, et al. Effects of the DASH diet alone and in combination with exercise and weight loss on blood pressure and cardiovascular biomarkers in men and women with high blood pressure: the ENCORE study. *Arch Intern Med.* 2010;170(2):126-135.

289. Lin PH, Allen JD, Li YJ, et al. Blood pressure-lowering mechanisms of the DASH dietary pattern. *J Nutr Metab.* 2012; 2012: 472396.

290. Brown AA, Hu FB. Dietary modulation of endothelial function: Implications for cardiovascular disease. *Am J Clin Nutr.* 2001; 73(4):673-86.

291. Medina-Remón A, Tresserra-Rimbau A, Pons A, et al. Effects of total dietary polyphenols on plasma nitric oxide and blood pressure in a high cardiovascular risk cohort. The PREDIMED randomized trial. *Nutr Metab Cardiovasc Dis.* 2015; 25(1):60-7.

292. Akita S, Sacks FM, Svetkey LP, et al. Effects of the Dietary Approaches to Stop Hypertension (DASH) diet on the pressure-natriuresis relationship. *Hypertension.* 2003; 42(1):8-13.

293. Gritter M, Rotmans JI, Hoorn EJ. Role of dietary K^+ in natriuresis, blood Pressure reduction, cardiovascular protection, and renoprotection.. *Hypertension.* 2019; 73(1):15-23.

294. González SA, Forcada P, de Cavanagh EM, et al. Sodium intake is associated with parasympathetic tone and metabolic parameters in mild hypertension. *Am J Hypertens.* 2012; 25(5):620-4.

295. Iuga AO, McGuire MJ. Adherence and health care costs. *Risk Manag Healthc Policy.* 2014;7:35-44.

296. Lorig KR, Holman H. Self-management education: history, definition, outcomes, and mechanisms. *Ann Behav Med.* 2003;26(1):1-7.

297. Bennett HD, Coleman EA, Parry C, Bodenheimer T, Chen EH. Health coaching for patients with chronic illness. *Fam Pract Manag.* 2010;17(5):24-29.

298. Varney JE, Liew D, Weiland TJ, Inder WJ, Jelinek GA. The cost-effectiveness of hospital-based telephone coaching for people with type 2 diabetes: a 10 year modelling analysis. *BMC Health Serv Res.* 2016;16(1):521.

299. Odnoletkova I, Ramaekers D, Nobels F, Goderis G, Aertgeerts B, Annemans L. Delivering Diabetes Education through Nurse-Led Telecoaching. Cost-Effectiveness Analysis. *PLoS One.* 2016;11(10):e0163997.

300. Oksman E, Linna M, Horhammer I, Lammintakanen J, Talja M. Cost-effectiveness analysis for a tele-based health coaching program for chronic disease in primary care. *BMC Health Serv Res.* 2017;17(1):138.

301. Hersey JC, Khavjou O, Strange LB, et al. The efficacy and cost-effectiveness of a community weight management intervention: a randomized controlled trial of the health weight management demonstration. *Prev Med.* 2012;54(1):42-49.

302. Lakkireddy D, Atkins D, Pillarisetti J, et al. Effect of yoga on arrhythmia burden, anxiety, depression, and quality of life in paroxysmal atrial fibrillation: the YOGA My Heart Study. *J Am Coll Cardiol.* 2013;61(11):1177-1182.

303. Wahlstrom M, Rydell Karlsson M, Medin J, Frykman V. Effects of yoga in patients with paroxysmal atrial fibrillation - a randomized controlled study. *Eur J Cardiovasc Nurs.* 2017;16(1):57-63.

304. Malm D, Fridlund B, Ekblad H, Karlstrom P, Hag E, Pakpour AH. Effects of brief mindfulness-based cognitive behavioural therapy on health-related quality of life and sense of coherence in atrial fibrillation patients. *Eur J Cardiovasc Nurs.* 2018;17(7):589-597.

305. Irvine J, Firestone J, Ong L, et al. A randomized controlled trial of cognitive behavior therapy tailored to psychological adaptation to an implantable cardioverter defibrillator. *Psychosom Med.* 2011;73(3):226-233.

306. Salmoirago-Blotcher E, Crawford SL, Carmody J, et al. Phone-delivered mindfulness training for patients with implantable cardioverter defibrillators: results of a pilot randomized controlled trial. *Ann Behav Med.* 2013;46(2):243-250.

307. Shi L, Zhang D, Wang L, Zhuang J, Cook R, Chen L. Meditation and blood pressure: a meta-analysis of randomized clinical trials. J Hypertens. 2017;35(4):696-706.

308. Brinks J, Fowler A, Franklin BA, Dulai J. Lifestyle modification in secondary prevention: Beyond pharmacotherapy. *Am J Lifestyle Med.* 2017;11(2):137-152.

309. Ting N, Chen DG, Ho S, Cappelleri J. Phase II clinical development of new drugs. Singapore: Springer Nature; 2017.

310. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet.* 2016;387(10022):957-967.

311. Farb NA, Anderson AK, Segal ZV. The mindful brain and emotion regulation in mood disorders. *Can J Psychiatry.* 2012;57(2):70-77.

312. Loucks EB, Schuman-Olivier Z, Britton WB, et al. Mindfulness and cardiovascular disease risk: State of the evidence, plausible mechanisms, and theoretical framework. *Curr Cardiol Rep.* 2015;17(12):112.

313. Langer EJ. Mindful learning. *Curr Dir Psychol Sci.* 2000;9(6):220-223.

314. Westra HA, Aviram A. Core skills in motivational interviewing. *Psychotherapy (Chic).* 2013;50(3):273-278.

315. van der Zwan JE, de Vente W, Huizink AC, Bögels SM, de Bruin EI. Physical activity, mindfulness meditation, or heart rate variability biofeedback for stress reduction: A randomized controlled trial. *Appl Psychophysiol Biofeedback.* 2015; 40(4):257-68.

316. Rosenkranz MA, Davidson RJ, Maccoon DG, Sheridan JF, Kalin NH, Lutz A. A comparison of mindfulness-based stress reduction and an active control in modulation of neurogenic inflammation. *Brain Behav Immun*. 2013; 27(1):174-84.

317. Davis LL, Whetsell C, Hamner MB, et al. A multisite randomized controlled trial of mindfulness-based stress reduction in the treatment of posttraumatic stress disorder. *Psych Res Clin Pract.* 2019*;* 1:39-48.

318. Wildevuur SE, Simonse LW. Information and communication technology-enabled person-centered care for the "big five" chronic conditions: scoping review. *J Med Internet Res.* 2015;17(3):e77.

319. Lowres N, Mulcahy G, Gallagher R, et al. Self-monitoring for atrial fibrillation recurrence in the discharge period post-cardiac surgery using an iPhone electrocardiogram. *Eur J Cardiothorac Surg*. 2015; 50(1):44-51.

320. Li KHC, White FA, Tipoe T, et al. The current state of mobile phone apps for monitoring heart rate, heart rate variability, and atrial fibrillation: Narrative review. *JMIR Mhealth Uhealth.* 2019;7(2):e11606.

8.0 Appendices

Appendix A Psychological Questionnaires

Hospital Anxiety and Depression Scale (HADS)

Instructions: Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he or she will be able to help you more. This questionnaire is designed to help your doctor know how you feel. Read each item and circle the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

I feel tense or 'wound up':	**A**
Most of the time	3
A lot of the time	2
Time to time, occasionally	1
Not at all	0

I feel as if I am slowed down:	**D**
Nearly all of the time	3
Very often	2
Sometimes	1
Not at all	0

I still enjoy the things I used to enjoy:	**D**
Definitely as much	0
Not quite so much	1
Only a little	2
Not at all	3

I get a sort of frightened feeling like 'butterflies in the stomach':	**A**
Not at all	0
Occasionally	1
Quite often	2
Very often	3

I get a sort of frightened feeling like something awful is about to happen:	**A**
Very definitely and quite badly	3
Yes, but not too badly	2
A little, but it doesn't worry me	1
Not at all	0

I have lost interest in my appearance:	**D**
Definitely	3
I don't take as much care as I should	2
I may not take quite as much care	1
I take just as much care as ever	0

I can laugh and see the funny side of things:	**D**
As much as I always could	0
Not quite so much now	1
Definitely not so much now	2
Not at all	3

I feel restless as if I have to be on the move:	**A**
Very much indeed	3
Quite a lot	2
Not very much	1
Not at all	0

Worrying thoughts go through my mind:	**A**
A great deal of the time	3
A lot of the time	2
From time to time but not too often	1
Only occasionally	0

I look forward with enjoyment to things:	**D**
A much as I ever did	0
Rather less than I used to	1
Definitely less than I used to	3
Hardly at all	2

I feel cheerful:	**D**
Not at all	3
Not often	2
Sometimes	1
Most of the time	0

I get sudden feelings of panic:	**A**
Very often indeed	3
Quite often	2
Not very often	1
Not at all	0

I can sit at ease and feel relaxed:	A
Definitely	0
Usually	1
Not often	2
Not at all	3

I can enjoy a good book or radio or TV programme:	D
Often	0
Sometimes	1
Not often	2
Very seldom	3

Profile of Mood States – Short Form (POMS-SF)

Below is a list of words that describe feelings people have. Please read each one carefully. Then circle ONE answer which best describes ***how you have been feeling during the past 24 hours.***

The numbers refer to these phrases:

0= not at all 1= a little 2= moderately 3= quite a bit 4= extremely

1	Tense	0	1	2	3	4	19	Annoyed	0	1	2	3	4
2	Angry	0	1	2	3	4	20	Discouraged	0	1	2	3	4
3	Worn out	0	1	2	3	4	21	Resentful	0	1	2	3	4
4	Unhappy	0	1	2	3	4	22	Nervous	0	1	2	3	4
5	Lively	0	1	2	3	4	23	Miserable	0	1	2	3	4
6	Confused	0	1	2	3	4	24	Cheerful	0	1	2	3	4
7	Peeved	0	1	2	3	4	25	Bitter	0	1	2	3	4
8	Sad	0	1	2	3	4	26	Exhausted	0	1	2	3	4
9	Active	0	1	2	3	4	27	Anxious	0	1	2	3	4
10	On Edge	0	1	2	3	4	28	Helpless	0	1	2	3	4
11	Grouchy	0	1	2	3	4	29	Weary	0	1	2	3	4
12	Blue	0	1	2	3	4	30	Bewildered	0	1	2	3	4
13	Energetic	0	1	2	3	4	31	Furious	0	1	2	3	4
14	Hopeless	0	1	2	3	4	32	Full of pep	0	1	2	3	4
15	Uneasy	0	1	2	3	4	33	Worthless	0	1	2	3	4
16	Restless	0	1	2	3	4	34	Forgetful	0	1	2	3	4
17	Unable to concentrate	0	1	2	3	4	35	Vigorous	0	1	2	3	4
18	Fatigued	0	1	2	3	4	36	Uncertain about things	0	1	2	3	4
							37	Bushed	0	1	2	3	4

Five Facet Mindfulness Questionnaire - Short Form (FFMQ-SF)

Below is a collection of statements about your everyday experience. Using the scale of 1 to 5 below, please indicate, on the line to the left of each statement, how frequently or infrequently you've had each experience ***in the last month*** (or other agreed-upon time period). Please answer according to what really reflects your experience rather than what you think your experience should be.

1 = never or very rarely true
2 = not often true
3 = sometimes true, sometimes not true
4 = often true
5 = very often or always true

____ 1. I'm good at finding the words to describe my feelings.
____ 2. I can easily put my beliefs, opinions, and expectations into words.
____ 3. I watch my feelings without getting carried away by them.
____ 4. I tell myself that I shouldn't be feeling the way I'm feeling.
____ 5. It's hard for me to find the words to describe what I'm thinking.
____ 6. I pay attention to physical experiences, such as the wind in my hair or the sun on my face.
____ 7. I make judgments about whether my thoughts are good or bad.
____ 8. I find it difficult to stay focused on what's happening in the present moment.
____ 9. When I have distressing thoughts or images, I don't let myself be carried away by them.
____ 10. Generally, I pay attention to sounds, such as clocks ticking, birds chirping, or cars passing.
____ 11. When I feel something in my body, it's hard for me to find the right words to describe it.
____ 12. It seems I am running on automatic without much awareness of what I'm doing.
____ 13. When I have distressing thoughts or images, I feel calm soon after.
____ 14. I tell myself I shouldn't be thinking the way I'm thinking.
____ 15. I notice the smells and aromas of things.
____ 16. Even when I'm feeling terribly upset, I can find a way to put it into words.
____ 17. I rush through activities without being really attentive to them.
____ 18. When I have distressing thoughts or images, I can just notice them without reacting.
____ 19. I think some of my emotions are bad or inappropriate and I shouldn't feel them.
____ 20. I notice visual elements in art or nature, such as colors, shapes, textures, or patterns of light and shadow.
____ 21. When I have distressing thoughts or images, I just notice them and let them go.
____ 22. I do jobs or tasks automatically without being aware of what I'm doing.
____ 23. I find myself doing things without paying attention.
____ 24. I disapprove of myself when I have illogical ideas.

Cardiac Anxiety Questionnaire (CAQ)

Please rate each item by circling the answer (number) that best applies to you:

		Never	Rarely	Sometimes	Often	Always
1.	I pay attention to my heart beat	0	1	2	3	4
2.	I avoid physical exertion	0	1	2	3	4
3.	My racing heart wakes me up at night	0	1	2	3	4
4.	Chest pain/discomfort wakes me up at night	0	1	2	3	4
5.	I take it easy as much as possible	0	1	2	3	4
6.	I check my pulse	0	1	2	3	4
7.	I avoid exercise or other physical work	0	1	2	3	4
8.	I can feel my heart in my chest	0	1	2	3	4
9.	I avoid activities that make my heart beat faster	0	1	2	3	4
10.	If tests come out normal, I still worry about my heart	0	1	2	3	4
11.	I feel safe being around a hospital, physician or other medical facility	0	1	2	3	4
12.	I avoid activities that make me sweat	0	1	2	3	4
13.	I worry that doctors do not believe my symptoms are real	0	1	2	3	4
When I have chest discomfort or when my heart is beating fast:						
14.	I worry that I may have a heart attack	0	1	2	3	4
15.	I have difficulty concentrating on anything else	0	1	2	3	4
16.	I get frightened	0	1	2	3	4
17.	I like to be checked out by a doctor	0	1	2	3	4
18.	I tell my family or friends	0	1	2	3	4

PITTSBURGH SLEEP QUALITY INDEX (PSQI)

INSTRUCTIONS: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, when have you usually gone to bed at night?

   USUAL BED TIME _____

2. During the past month, how long (in minutes) has it usually take you to fall asleep each night?

   NUMBER OF MINUTES _____

3. During the past month, when have you usually gotten up in the morning?

   USUAL GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed.)

   HOURS OF SLEEP PER NIGHT _____

INSTRUCTIONS: For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(a) ...cannot get to sleep within 30 minutes	☐	☐	☐	☐
(b) ...wake up in the middle of the night or early morning	☐	☐	☐	☐
(c) ...have to get up to use the bathroom	☐	☐	☐	☐
(d ...cannot breathe comfortably	☐	☐	☐	☐
(e) ...cough or snore loudly	☐	☐	☐	☐
(f) ...feel too cold	☐	☐	☐	☐
(g) ...feel too hot	☐	☐	☐	☐
(h) ...had bad dreams	☐	☐	☐	☐
(i) ...have pain	☐	☐	☐	☐
(j) Other reason(s), please describe _____ _____				
How often during the past month have you had trouble sleeping because of this?	☐	☐	☐	☐

	Very good	Fairly good	Fairly bad	very bad
6. During the past month, how would you rate your sleep quality overall?	☐	☐	☐	☐

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
7. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?	☐	☐	☐	☐
8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?	☐	☐	☐	☐

	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?	☐	☐	☐	☐

	No bed partner or roommate	Partner/ roommate in other room	Partner in same room, but not same bed	Partner in same bed
10. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?	☐	☐	☐	☐

If you have a roommate or bed partner, ask him/her how often in the past month you have had...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(a) ...loud snoring	☐	☐	☐	☐
(b) ...long pauses between breaths while asleep	☐	☐	☐	☐
(c) ...legs twitching or jerking while you sleep	☐	☐	☐	☐
(d) ...episodes of disorientation or confusion during sleep	☐	☐	☐	☐
(e) Other restlessness while you sleep; please describe	☐	☐	☐	☐

_____

_____

Appendix B Informed Consent Form

SOUTHLAKE
REGIONAL HEALTH CENTRE

PARTICIPANT INFORMATION AND CONSENT FORM

Study Title: Mindfulness-based Coaching to reduce Abnormal Nocturnal Hypertension in Atrial Fibrillation: Protocol for a Randomized Controlled Trial.

Site Principal Investigator: Paul Ritvo PhD (C. Psych)

Sub-Investigator(s): Yaariv Khaykin MD; Meysam Pirbaglou PhD (Cand.)

Study Site(s): **PACE Cardiology Clinic:** 581 Davis Drive, Suite 602, Newmarket, Ontario
Cardiac Rehabilitation Clinic: 465 Davis Dr., Suite 404, Newmarket, Ontario

INTRODUCTION

You are being invited to consider participating in a research study involving participants with Atrial Fibrillation (AF) using Mindfulness-based Coaching to help improve blood pressure, especially high blood pressure at nighttime, known as Abnormal Nocturnal Hypertension. This information and consent form describes the purpose, procedures, benefits, discomforts and risks associated with this study. It also informs you of your rights as a study participant. If you have questions or do not understand any of the words contained in this document, please ask the researcher, study doctor or nurse to explain. Before agreeing to participate, it is important for you to understand the study. Feel free to discuss the information in this document with your friends and family and/or your regular doctor.

WHY IS THIS STUDY BEING DONE?

The health benefits of mindfulness meditation are well documented in medical research. In this study the researchers will evaluate the effectiveness of a mindfulness-based coaching program (personal coaching focused on mindfulness meditation and gentle mindful movements) compared to standard cardiovascular risk reduction education aimed at reducing AF related symptoms such as night time blood pressure.

WHAT IS INVOLVED IN PARTICIPATING IN THE STUDY?

Your participation in this study will entail a time commitment of 4 months (16 weeks). If you agree to participate in this study, you will be asked to complete a set of psychological questionnaires at the beginning, midpoint (2 months), and at study completion (4 months) to help us understand your experience with the mindfulness-based coaching program. You will receive a total of three 24 hour ambulatory blood pressure assessments at baseline, midpoint (2 months), and at study completion.

In addition, as a part of your routine treatment for Atrial Fibrillation at PACE Cardiology Clinic, you will receive 24-hour Holter monitoring assessments using the MARS® ambulatory ECG system at the beginning and at study conclusion (4 months).

Study participants will be randomly assigned to one of two study groups:

1) No change to standard of care where you will receive instructions (in person or by phone call) on how to integrate exercise and dietary changes in your lifestyle to reduce your risk of

future cardiovascular events.

2) The mindfulness-based coaching support group, where you will receive instructions on (a) mindfulness meditation and gentle mindful movement through in-class participation at the Southlake Cardiovascular Rehabilitation Clinic and (b) personal coaching support. Your health coach will further assist you through either face-to-face or telephone-based discussions. You will meet with your health coach at mutually-agreed upon on times for designated time periods. In addition, participant will have the opportunity to participate in 16 weekly mindfulness meditation classes (60-80 minutes in duration each) to practice mindfulness meditation and gentle mindful movement in a group setting at the Cardiac Rehabilitation Clinic.

DATA COLLECTION
As mentioned above, to help assess the effectiveness of the program, researchers will ask for you to complete assessments of:

- 24-hr ambulatory blood pressure monitoring
- 24-hr Holter monitoring
- Psychological Questionnaires (20-30 minutes required for completion): the SF –12 Health Survey; Profile of Mood States (POMS-SF); Perceived Stress Scale (PSS); Hospital Anxiety and Depression Scale (HADS); Cardiac Anxiety Questionnaire; Five Facet Mindfulness Questionnaire - Short Form, and the Pittsburgh Sleep Quality Index (PSQI).

With your permission, we would like to access personal information about you, including information about your general health (height, weight, blood pressure, results from blood tests, medications, physical exam results) related to medical treatments and care you receive to better understand the impact of mindfulness-based coaching in relation to your general health characteristics and medication regimen. This information has already been collected as part of the routine treatment you are receiving at the PACE Cardiology Clinic.

ARE THERE ANY RISKS OR BENEFITS OF THE STUDY?
There are no known personal risks associated with taking part in this research study. The information gained from this study may help the development of better ways to treat atrial fibrillation in the future.

WHAT ABOUT CONFLICT OF INTEREST?
This study is being conducted as a result of collaboration between researchers from Southlake Regional Health Centre and York University. The study and its principal investigator are not receiving funds from external sources.

WHAT ARE THE COSTS?
Mindfulness meditation instruction and assessments of ambulatory Blood pressure are provided by York University researchers (Paul Ritvo and Meysam Pirbaglou) free of charge.

You will not be paid or reimbursed for any expenses (i.e. parking) while taking part in this study.

WHAT ABOUT CONFIDENTIALITY?

Your identity will be kept confidential at all times, except where disclosure is required by law. If you agree to participate in this study, the investigator and his/her study team will look at your personal health information and collect only the information they need for this study. This may include both access of information obtained from records already located at this site or from your other healthcare providers, if necessary. "Personal health information" is health information about you that could identify you because it includes information such as your name, address, telephone number, date of birth, new and existing medical records or the types, dates and results of various tests and procedures. The personal health information collected in this study may include:

- Blood pressure, psychological measurements, and demographic information

You will be identified by a study number and initials only. However, as the information obtained in the 24 hour ambulatory blood pressure assessment may be useful in further planning of medical treatment, a copy of the 24 hour assessment will be provided to Dr. Yaariv Khaykin, Director of the PACE Cardiology Clinic at Southlake Regional Health Centre and your cardiologist. Dr. Khaykin or your treating cardiologist will review the ambulatory recordings and if necessary, will consider this information as a part of your course of treatment. If a treatment change is appropriate, an appointment will be scheduled to review treatment, or he will advise your regular cardiologist or physician to follow up with you. If you want, a copy of your ambulatory recordings will be made available to you.

Access to study information is limited to the study team and no other individual will have access to patient information collected as part of this study. Information collected as a part of this study will be safely secured and kept in strict confidence using secure encrypted USB storage devices, password protected study laptop, and locked cabinets at the study site. We will inform you of any potential unforeseen secondary analyses of study data collected as part of this study.

Representatives of the Southlake Regional Health Centre Research Ethics Board (an independent committee that reviews the ethical aspects of this study to help protect the rights and welfare of study participants) may look at your personal health information in order to monitor the research and verify the accuracy of the study data.

You may withdraw your permission to use your personal health information at any time by letting the investigator know, and the investigator will then no longer collect or share your personal health information in connection with the study. However, if you withdraw your permission, you also withdraw from the study. If you withdraw from the study, researchers will continue to use your study data that was recorded before you withdrew. When the results of the study are published or presented, your name will not be used and no information that could identify you will be released.

What Are Your Rights As A Participant?

Your participation in the study is voluntary. You may withdraw from the study at any time, and you can also choose not to answer any questions that you do not feel comfortable answering. This will not affect your care. Your refusal to participate or your withdrawal from the study will not affect your relationship with the researchers, York University or impact the services you receive from Southlake Regional Health Centre or the PACE clinic. If you decide to withdraw from the study and you wish us to destroy the information and data you provided, we will do so upon your request. If you would like to withdraw from this study, please contact the principal investigator, Dr. Paul Ritvo [redacted].

By signing this form you do not give up any of your legal rights nor release the investigators or involved institutions for compensation, nor does this form relieve the investigators, sponsor or involved institutions of their legal and professional responsibilities.

Whom Do You Call If You Have Questions Or Problems?

If you have questions about the research in general or about your role in the study, please feel free to contact Dr. Paul Ritvo (York University) by telephone at [redacted] by e-mail [redacted] have any questions regarding your rights as a study participant or about ethical issues related to this study, please contact the Chair of the Southlake Regional Health Centre Research Ethics Board, Dr. Pravesh Jugnundan [redacted]

CONSENT

You will be given a copy of this consent form after it has been signed and dated by you and the study staff.

My signature on this consent form means the following:

- The study has been fully explained to me, I have been given the chance to discuss it and all of my questions have been answered to my satisfaction,
- I have read each page of this consent form,
- I am aware of what is required of me as a participant in the study,
- I am aware of the risks to me of participating in the study.
- I allow access, use and disclosure of my personal health information and study data as explained in this consent form, and
- I voluntarily consent to take part in this study.

Name of Participant (Print)	**Signature of Participant**	**Date** (yyyy-Mmm-dd)

Person Obtaining Informed Consent:
My signature below signifies that I have explained the nature and purpose of the study and the risks involved to the study participant, and I have answered all questions to the best of my ability.

Name of Person (print) Obtaining Informed Consent	**Signature of Person Obtaining Informed Consent**	**Date** (yyyy-Mmm-dd)

==========

Complete the following section only if the participant is unable to read or requires an oral translation if Non-English speaking (in the case that written consent was not obtainable in the participant's native language):

- The informed consent form was accurately explained to, and apparently understood by, the participant and
- Informed consent was freely given by the participant

Name of Impartial (print) Witness/Qualified Translator	**Signature of Impartial Witness/ Qualified Translator**	**Date** (yyyy-Mmm-dd)

Appendix C Research Ethics Approvals

SOUTHLAKE
REGIONAL HEALTH CENTRE

SRHC Research Ethics Board
Notification of REB Initial Study Approval (Delegated Review)

DATE: October 26, 2016

TO: Paul Ritvo

SITE ADDRESS: Southlake Regional Health Centre/Pace Cardiology Clinic

STUDY TITLE: Mindfulness-based Coaching to reduce Abnormal Nocturnal Hypertension in Atrial Fibrillation: Protocol for a Randomized Controlled Trial.

SRHC REB #: #0031-1617

REB APPROVAL DATE: 2016-OCT-20 **REB APPROVAL EXPIRY DATE:** 2017-Oct-20

DOCUMENTS REVIEWED/APPROVED:

- REB Application dated 09/09/16
- Research Protocol v1.0 dated 07/18/2016 (including Appendices A-E)
- Recruitment Poster titled "Mindfulness Coaching for Atrial Fibrillation (AF) Research Study" v2016-Oct-20
- Participant Information and Consent Form v2016-Sept-20

The Southlake Regional Health Centre Research Ethics Board (SRHC REB) acknowledges receipt of the above study documents that were reviewed and approved by delegated review by designated REB members who are independent of the investigator(s) conducting this research and have no conflict of interest to declare. A copy of the current REB Membership list is available on the Southlake website at www.southlakeregional.org.

The SRHC Research Ethics Board is organized and operates in accordance with the Tri-Council Policy Statement on Ethical Conduct of Research Involving Humans (TCPS2 2014); Canadian General Standards Board (CGSB) 191.1-2013; Clinical Trials Ontario (CTO) REB Qualification Standards, the International Conference on Harmonisation (ICH) Good Clinical Practice Guidelines (GCP); Part C, Division 5 of the Food and Drug Regulations of Canada; Part 4 of the Natural Health Product Regulations; Medical Devices Regulations, and the provisions within the Ontario Personal Health Information Protection Act (PHIPA) and all other applicable laws and regulations. The SRHC REB is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP).

Please note that SRHC retains the authority to deny the implementation of REB-approved protocols for reasons other than research ethics; such reasons may be administrative, programmatic, or resource-based in nature. Participant recruitment may not commence until a Clinical Trial Agreement (CTA) is signed by all relevant parties (if applicable).

As the local Principal Investigator you are responsible for the ethical conduct of this study at your site including the following REB reporting requirements:

Ongoing Review:
Report to the REB any new information generated throughout the course of the research that could affect the rights, safety and well-being of research participants, including information about any serious or continuing non-compliance. Such information may include:

- Modifications or changes to the previously approved research,

- Reports of unanticipated problems involving risks to participants or others,
- Reports of any serious or continuing non-compliance,
- Reports of any changes significantly affecting the conduct of the research or increasing the risk to research participants,
- Results of any interim analysis or Data and Safety Monitoring Board (DSMB) assessments,
- Deviations to the previously approved research,
- Adverse events that meet the reporting criteria,
- Reports of any privacy breaches,
- Summary reports of any audits and inspections,
- Any other new information that my affect adversely the safety of the research participants or the conduct of the research,

The REB approved protocol, informed consent document, other research participant-specific study materials, and the conduct of the study must not be altered unless a prior ethics approval has been granted, except in those situations where a modification is required to eliminate an immediate hazard to research participants, or the changes are minor logistical or administrative in nature.

Please be advised that the REB must be notified no later than 15 calendar days of the time you are made aware of an unanticipated problem (an unexpected event that is study related and involving greater risk) relating to a patient enrolled through Southlake Regional Health Centre. If it is fatal or life-threatening, you must report the event to the REB within (7) seven calendar days of being made aware.

Continuing Review:
A Study Renewal Form for REB annual re-approval must be submitted in advance of the current REB expiry date (as noted above) and is due by the deadline for the applicable REB meeting (i.e., the expiry date must be on or after the REB meeting date and prior to the date of the subsequent REB meeting), regardless of the type of review requested (full board or delegated).

All research activities must stop if you fail to provide the required continuing review information to the REB or if ethics re-approval is not obtained prior to the expiry date unless the REB finds an over-riding safety concern or ethical issue such that the best interests of the study participants are served by continuing to participate in the research.

If the study is completed within the current approval period and a subsequent re-approval is therefore not required, you must submit a Study Closure Notice Form to the REB.

Additional Information:
SRHC personnel may refer to the hospital website to access a full description of the REB reporting requirements, forms, policies and standard operating procedures (SOPS) relating to research. If you do not have authorized access to SRHC SOPs, or if you have any questions or concerns, please contact me [redacted]
at [redacted]

Sincerely,

Sharon Villani, CRA
REB Administrator, SRHC Research Ethics Board

cc: Dr. P. Jugmundan, SRHC REB Chair.

SOUTHLAKE
REGIONAL HEALTH CENTRE

SRHC Research Ethics Board
Notification of REB Approval (Delegated Review)
Protocol Amendment

DATE: April 11, 2017

TO: Paul Ritvo

RESEARCH SITE: Southlake Regional Health Centre//Pace Cardiology Clinic

STUDY TITLE: Mindfulness-based Coaching to reduce Abnormal Nocturnal Hypertension in Atrial Fibrillation: Protocol for a Randomized Controlled Trial.

SRHC REB #: #0031-1617 **REB APPROVAL DATE:** 2017-APR-07

DOCUMENTS REVIEWED/APPROVED:

- Amended Protocol v2.0 dated 04/07/2017

The Research Ethics Board of Southlake Regional Health Centre acknowledges receipt of the above documents for that were reviewed and approved by delegated review by the REB Chair (or designee) who is independent of the investigator(s) conducting this research and has no conflict of interest to declare. A copy of the current REB Membership list is available on the Southlake website at www.southlakeregional.org.

The SRHC Research Ethics Board is organized and operates in accordance with the Tri-Council Policy Statement on Ethical Conduct of Research Involving Humans (TCPS2 2014); Canadian General Standards Board (CGSB) 191.1-2013; Clinical Trials Ontario (CTO) REB Qualification Standards, the International Conference on Harmonisation (ICH) Good Clinical Practice Guidelines (GCP); Part C, Division 5 of the Food and Drug Regulations of Canada; Part 4 of the Natural Health Product Regulations; Medical Devices Regulations, and the provisions within the Ontario Personal Health Information Protection Act (PHIPA) and all other applicable laws and regulations. The SRHC REB is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP).

SRHC retains the authority to deny the implementation of REB-approved protocols for reasons other than research ethics; such reasons may be administrative, programmatic, or resource-based in nature. Participant recruitment under amended protocols may not commence until a revised Clinical Trial Agreement (CTA) is signed by all relevant parties (if applicable).

As the local Principal Investigator you are responsible for the ethical conduct of this study at your site including the following REB reporting requirements:

Ongoing Review:

Report to the REB any new information generated throughout the course of the research that could affect the rights, safety and well-being of research participants, including information about any serious or continuing non-compliance. Such information may include:

- Modifications or changes to the previously approved research,
- Reports of unanticipated problems involving risks to participants or others,

- Reports of any serious or continuing non-compliance,
- Reports of any changes significantly affecting the conduct of the research or increasing the risk to research participants,
- Results of any interim analysis or Data and Safety Monitoring Board (DSMB) assessments,
- Deviations to the previously approved research,
- Adverse events that meet the reporting criteria,
- Reports of any privacy breaches,
- Summary reports of any audits and inspections,
- Any other new information that my affect adversely the safety of the research participants or the conduct of the research,

The REB approved protocol, informed consent document, other research participant-specific study materials, and the conduct of the study must not be altered unless a prior ethics approval has been granted, except in those situations where a modification is required to eliminate an immediate hazard to research participants, or the changes are minor logistical or administrative in nature.

Please be advised that the REB must be notified no later than 15 calendar days of the time you are made aware of an unanticipated problem (an unexpected event that is study related and involving greater risk) relating to a patient enrolled through Southlake Regional Health Centre. If it is fatal or life-threatening, you must report the event to the REB within (7) seven calendar days of being made aware.

Continuing Review:
Continuing review applications (annual re-approval) must be submitted in advance of the REB approval expiry date and are due by the deadline for the applicable REB meeting (i.e., the expiry date must be on or after the REB meeting date and prior to the date of the subsequent REB meeting), regardless of the type of review requested (full board or delegated).

All research activities must stop if you fail to provide the required continuing review information to the REB or if ethics re-approval is not obtained prior to the expiry date unless the REB finds an over-riding safety concern or ethical issue such that the best interests of the study participants are served by continuing to participate in the research.

If the study is completed within the current approval period and a subsequent re-approval is therefore not required, you must submit a Study Closure Notice Form to the REB.

Further Information:
SRHC researchers may refer to the hospital website to access a full description of the REB reporting requirements, forms, policies and standard operating procedures (SOPS) relating to research. If you have any questions or concerns, or do you not have access to the online SOPs, please contact me [redacted] or via email at [redacted]

Sincerely,

SVill

Sharon Villani, CRA
REB Administrator, SRHC Research Ethics Board

cc: Dr. P. Jugnundan, SRHC REB Chair.

SOUTHLAKE
REGIONAL HEALTH CENTRE

SRHC Research Ethics Board
Notification of REB Study Renewal Approval (Delegated Review)

DATE:	October 10, 2017
TO:	Paul Ritvo
RESEARCH SITE:	Southlake Regional Health Centre/Pace Cardiology Clinic
STUDY TITLE:	Mindfulness-based Coaching to reduce Abnormal Nocturnal Hypertension in Atrial Fibrillation: Protocol for a Randomized Controlled Trial.
SRHC REB # :	#0031-1617
REB RE-APPROVAL DATE:	2017-OCT-04 **REB EXPIRY DATE:** 2018- OCT-04

DOCUMENTS REVIEWED/APPROVED:

- REB Annual Renewal Form

The Research Ethics Board (REB) of Southlake Regional Health Centre acknowledges receipt of the REB Annual Renewal Form that was reviewed and approved by the REB Chair (or designee) by delegated review who is independent of the investigator(s) conducting this research and has no conflict of interest to declare. A copy of the current REB Membership list is available on the Southlake website at www.southlakeregional.org.

The SRHC Research Ethics Board is organized and operates in accordance with the Tri-Council Policy Statement on Ethical Conduct of Research Involving Humans (TCPS2 2014); Canadian General Standards Board (CGSB) 191.1-2013; Clinical Trials Ontario (CTO) REB Qualification Standards, the International Conference on Harmonisation (ICH) Good Clinical Practice Guidelines (GCP); Part C, Division 5 of the Food and Drug Regulations of Canada; Part 4 of the Natural Health Product Regulations; Medical Devices Regulations, and the provisions within the Ontario Personal Health Information Protection Act (PHIPA) and all other applicable laws and regulations. The SRHC REB is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP).

As the local Qualified Investigator you are responsible for the ethical conduct of this study at your site including the following REB reporting requirements:

Ongoing Review: Report to the REB any new information generated throughout the course of the research that could affect the rights, safety and well-being of research participants, including information about any serious or continuing non-compliance. Such information may include:

- Modifications or changes to the previously approved research,
- Reports of unanticipated problems involving risks to participants or others,
- Reports of any serious or continuing non-compliance,

- Reports of any changes significantly affecting the conduct of the research or increasing the risk to research participants,
- Results of any interim analysis or Data and Safety Monitoring Board (DSMB) assessments,
- Deviations to the previously approved research,
- Adverse events that meet the reporting criteria,
- Reports of any privacy breaches,
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Please be advised that the REB must be notified no later than 15 calendar days of the time you are made aware of an unanticipated problem (an unexpected event that is study related and involving greater risk) relating to a patient enrolled through Southlake Regional Health Centre. If it is fatal or life-threatening, you must report the event to the REB within (7) seven calendar days of being made aware.

Continuing Review: A Study Renewal Form for REB annual re-approval must be submitted in advance of the current REB expiry date (as noted above) and is due by the deadline for the applicable REB meeting (i.e., the expiry date must be on or after the REB meeting date and prior to the date of the subsequent REB meeting), regardless of the type of review requested (full board or delegated).

All research activities must stop if you fail to provide the required continuing review information to the REB or if ethics re-approval is not obtained prior to the expiry date unless the REB finds an over-riding safety concern or ethical issue such that the best interests of the study participants are served by continuing to participate in the research.

If the study is completed within the current approval period and a subsequent re-approval is therefore not required, you must submit a Study Closure Notice Form to the REB.

Additional Information: SRHC researchers may refer to the hospital website to access a full description of the REB reporting requirements, forms, policies and standard operating procedures (SOPS) relating to research. If you have any questions or concerns, or do you not have access to the online SOPs, please contact me at [redacted] or via email at [redacted].

Sincerely,

SVL

Sharon Villani, REB Administrator
SRHC Research Ethics Board

cc: Dr. P. Jugnundan, SRHC REB Chair

SOUTHLAKE
REGIONAL HEALTH CENTRE

SRHC Research Ethics Board
Notification of REB Study Renewal Approval (Delegated Review)

DATE: September 5, 2018

TO: Paul Ritvo

RESEARCH SITE: Southlake Regional Health Centre/Pace Cardiology Clinic

STUDY TITLE: Mindfulness-based Coaching to reduce Abnormal Nocturnal Hypertension in Atrial Fibrillation: Protocol for a Randomized Controlled Trial

SRHC REB # : #0031-1617

REB RE-APPROVAL DATE: 2018-SEP-05 **REB EXPIRY DATE:** 2019-SEP-05

DOCUMENTS REVIEWED/APPROVED:

- REB Annual Renewal Form

The Research Ethics Board (REB) of Southlake Regional Health Centre acknowledges receipt of the REB Annual Renewal Form that was reviewed and approved by the REB Chair (or designee) by delegated review who is independent of the investigator(s) conducting this research and has no conflict of interest to declare. A copy of the current REB Membership list is available on the Southlake website at www.southlakeregional.org.

The SRHC Research Ethics Board is organized and operates in accordance with the Tri-Council Policy Statement on Ethical Conduct of Research Involving Humans (TCPS2 2014); Canadian General Standards Board (CGSB) 191.1-2013; Clinical Trials Ontario (CTO) REB Qualification Standards, the International Conference on Harmonisation (ICH) Good Clinical Practice Guidelines (GCP); Part C, Division 5 of the Food and Drug Regulations of Canada; Part 4 of the Natural Health Product Regulations; Medical Devices Regulations, and the provisions within the Ontario Personal Health Information Protection Act (PHIPA) and all other applicable laws and regulations. The SRHC REB is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP).

As the local Qualified Investigator you are responsible for the ethical conduct of this study at your site including the following REB reporting requirements:

Ongoing Review: Report to the REB any new information generated throughout the course of the research that could affect the rights, safety and well-being of research participants, including information about any serious or continuing non-compliance. Such information may include:

- Modifications or changes to the previously approved research,
- Reports of unanticipated problems involving risks to participants or others,
- Reports of any serious or continuing non-compliance,
- Reports of any changes significantly affecting the conduct of the research or increasing the risk to research participants,

- Results of any interim analysis or Data and Safety Monitoring Board (DSMB) assessments,
- Deviations to the previously approved research,
- Adverse events that meet the reporting criteria,
- Reports of any privacy breaches,
- Summary reports of any audits and inspections,
- Any other new information that my affect adversely the safety of the research participants or the conduct of the research,

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Please be advised that the REB must be notified no later than 15 calendar days of the time you are made aware of an unanticipated problem (an unexpected event that is study related and involving greater risk) relating to a patient enrolled through Southlake Regional Health Centre. If it is fatal or life-threatening, you must report the event to the REB within (7) seven calendar days of being made aware.

Continuing Review: A Study Renewal Form for REB annual re-approval must be submitted in advance of the current REB expiry date (as noted above) and is due by the deadline for the applicable REB meeting (i.e., the expiry date must be on or after the REB meeting date and prior to the date of the subsequent REB meeting), regardless of the type of review requested (full board or delegated).

All research activities must stop if you fail to provide the required continuing review information to the REB or if ethics re-approval is not obtained prior to the expiry date unless the REB finds an over-riding safety concern or ethical issue such that the best interests of the study participants are served by continuing to participate in the research.

If the study is completed within the current approval period and a subsequent re-approval is therefore not required, you must submit a Study Closure Notice Form to the REB.

Additional Information: SRHC researchers may refer to the hospital website to access a full description of the REB reporting requirements, forms, policies and standard operating procedures (SOPS) relating to research. If you have any questions or concerns, or do you not have access to the online SOPs, please contact me at [redacted] or via email at [redacted]

Sincerely,

Sharon Villani, REB Administrator
SRHC Research Ethics Board

cc: Dr. P. Jugnundan, SRHC REB Chair

Appendix D Activity Log

Ambulatory Blood Pressure Monitoring Activity Form

Name/ Study ID _____ Study ID _____

Your Activity Record

- The ambulatory blood pressure monitoring device will accurately record your blood pressure throughout the day; however, it does not record what you are doing or how you are feeling when the measurement is being taken.
- It is not necessary that you change your behaviours while you are wearing the device, but rather that you record your activities throughout the day so that we can better understand your individual readings.

What to Record?

- The time of the day you take any medications and the dosage
- The time you go to bed
- The time you wake up
- The time you consume any food or snack
- Any emotional events (moments of stress and joy)
- Exercise or strenuous activity
- Periods of Rest or inactivity

What time did you go to bed? __:__ PM
Comments _____

What time did you wake up? __ :__ AM
Comments _____

Time	Activity	Details (optional)
__:__		
__:__		
__:__		
__:__		
__:__		

If you have any questions or concerns throughout the 24-hour period, please do not hesitate to contact the study coordinator – Meysam Pirbaglou – [redacted]

Time	Activity	Details (optional)
__:__		
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If you have any questions or concerns throughout the 24-hour period, please do not hesitate to contact the study coordinator – Meysam Pirbaglou [redacted]

Time	Activity	Details
__:__		
__:__		
__:__		
__:__		
__:__		
__:__		
__:__		
__:__		
__:__		

What happens during a blood pressure reading?

- Between __:__ AM and __:__PM the monitor will 'beep' to alert you before each reading.

- When this happens, let your arm hang still by your side while the cuff inflates and deflates.It will take about 30 seconds for the machine to record each reading. Moving around during this process may result in faulty reading.

- At night the moniotor will continue to take your blood pressure, but there will be nor warning beep and the frequency of measurements will be hourly.

Important Notes

Please do not remove the cuff or the monitor from the pouch during the 24 hours. The ambulatory monitor and the cuff must also ***not get wet***. Please fill this activity record to the best of your ability. No event is too minor to include. Please use additional paper if you wish to expand on an activity beyond the space provided. This information will aid in the interpretation of your results and will ultimately benefit you.

If you have any questions or concerns throughout the 24-hour period, please do not hesitate to contact the study coordinator – Meysam Pirbaglou [redacted]