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Exploring the cardiovascular disease continuum: Blood pressure and target organ damage

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This thesis is submitted to the National University of Ireland, Cork, for the degree of Doctor of Philosophy (Medicine and Health)

Department of Epidemiology and Public Health

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Contents

List of Tables **5**

List of Figures **7**

Glossary **8**

Declaration **9**

Acknowledgements **10**

Abstract **11**

1. Introduction **13**

1.1. Hypertension 13

1.2. Blood pressure measurement 13

1.3. Nocturnal blood pressure 16

1.4. The prognostic importance of nocturnal blood pressure 17

1.5. The cardiovascular disease continuum 20

1.6. Target organ damage 20

1.6.1. Electrocardiography 21

1.6.2. Microalbuminuria 21

1.6.3. Arterial stiffness 21

1.6.4. Echocardiography 22

1.6.5. Carotid intima media thickness 27

1.7. Nocturnal blood pressure and target organ damage 29

1.8. Research aim and objectives 32

1.9. Theoretical framework 32

1.10. Conceptual framework 33

1.11. Thesis layout 34

1.12. References 35

2. Hypertension prevalence, awareness, treatment and control: Should 24 hour ambulatory blood pressure monitoring be the tool of choice? **50**

2.1. Abstract 51

2.2. Introduction 53

2.3. Methods 54

2.4. Results 56

2.5. Discussion 62

2.6. References 66

3. Night-time blood pressure and target organ damage: A comparative analysis of absolute blood pressure and dipping status. 70

3.1. Abstract 71

3.2. Introduction 72

3.3. Methods 73

3.4. Results 76

3.5. Discussion 86

3.6. References 90

4.1. Isolated nocturnal hypertension and subclinical target organ damage: A systematic review 96

4.1.1. Abstract 97

4.1.2. Introduction 99

4.1.3. Methods 100

4.1.4. Results 101

4.1.5. Discussion 109

4.1.6. References 113

4.2. Isolated nocturnal hypertension and subclinical target organ damage in the Mitchelstown Cohort Study: A short report 116

4.2.1. Introduction 117

4.2.2. Methods 117

4.2.3. Results 118

4.2.4. Discussion 124

4.2.5. References 125

5. Imaging protocols and quality control methods for speckle tracking echocardiography and carotid intima media thickness acquisition and analysis 126

5.1. Abstract 127

5.2. Introduction 129

5.3. Methods 130

5.4. Results 135

5.5. Discussion 140

5.6. References 144

6. The association of night-time systolic blood pressure with ultrasound markers of subclinical cardiac and vascular disease 149
6.1. Abstract 150
6.2. Introduction 152
6.3. Methods 153
6.4. Results 157
6.5. Discussion 165
6.6. References 170
7. Discussion 177
7.1. Summary of findings 177
7.2. Where findings fit in the literature 178
7.3. Implications for research 183
7.4. Implications for practice 185
7.5. Implications for policy 186
7.6. Limitations 187
7.7. Conclusion 188
7.8. References 189
Appendix 1: Research training 198
Modules for credit University College Cork 198
Other relevant training 198
Appendix 2: Research output and dissemination 200
Thesis publications 200
Other original manuscript publications 200
Abstract publications 201
Oral presentations 202
Poster presentations 203
Awards 205
Other collaborative work 206
Appendix 3: Supplemental data for chapter 3 208
Appendix 4: Systematic review search strategy 214
MOOSE checklist for search strategy 214
Updated search February 2016 219

Appendix 5: Participant information leaflet and consent form..... 221

Appendix 6: Short report on the reproducibility of nocturnal blood pressure profiles..... 223

Appendix 7: Portable document format (PDF) of publications 227

List of Tables

Table 1.1. Thresholds for hypertension by office and out-of-office blood pressure measurements

Table 2.1. Baseline characteristics of Mitchelstown Cohort and 931 participants with study, clinic and ambulatory blood pressure measurements

Table 2.2. Hypertension prevalence, awareness, treatment and control rates by different measurement techniques and thresholds

Table 2.3. Impact of ABPM on blood pressure classification

Table 3.1. Baseline characteristics of 1046 participants by target organ damage documented by ECG LVH and microalbuminuria

Table 3.2. Blood pressure levels of 1046 participants by target organ damage documented by ECG LVH and microalbuminuria

Table 3.3. Logistic regression results for association of absolute ambulatory blood pressure and target organ damage documented by ECG LVH and microalbuminuria

Table 3.4. Logistic regression results for association of dipping status and target organ damage documented by ECG LVH and microalbuminuria

Table 4.1.1. Quality assessment of studies included in systematic review

Table 4.1.2. Design of studies included in systematic review

Table 4.1.3. Results of studies included in systematic review

Table 4.2.1. Baseline characteristics of 685 untreated participants by blood pressure status

Table 4.2.2. Blood pressure levels of 685 untreated participants

Table 4.2.3. Target organ damage by blood pressure status

Table 5.1. Phantom ultrasound scan results

Table 5.2. CIMT results of 10 healthy controls included in reproducibility analysis

Table 5.3. Global longitudinal strain results of 10 patients included in reproducibility analysis

Table 6.1. Baseline characteristics of Mitchelstown Cohort and participants who underwent ABPM, echocardiogram and carotid ultrasound

Table 6.2. Echocardiogram and carotid ultrasound characteristics

Table 6.3. Univariable linear and logistic regression results for association of night-time blood pressure and ultrasound markers of cardiac and vascular damage

Table 6.4. Sex and age adjusted linear and logistic regression results for association of night-time blood pressure and ultrasound markers of cardiac and vascular damage

Table 6.5. Multivariable adjusted linear and logistic regression results for association of night-time blood pressure and ultrasound markers of cardiac and vascular damage

List of Figures

Figure 1.1. Stages of diastolic dysfunction

Figure 1.2. Myocardial strain dimensions

Figure 1.3. Carotid intima-media thickness tracing at distal 10mm of common carotid artery

Figure 1.4. The cardiovascular disease continuum

Figure 1.5. Conceptual framework

Figure 1.6. Thesis layout

Figure 2.1. Prevalence, awareness, treatment and control rates of hypertension by different measurement thresholds

Figure 3.1. Night-time blood pressure status by dipping status

Figure 3.2. Mean blood pressures by dipping status and target organ damage

Figure 4.1. Flow chart of systematic review search

Figure 5.1. Tracking of acoustic speckles from frame to frame

Figure 5.2. The Meijer Arc

Figure 5.3. Measurement of CIMT at distal 1 cm of common carotid artery

Figure 5.4. Bullseye plot of global longitudinal strain averaged from apical 4-, 2- and 3-chamber views

Figure 5.5. General purpose urethane ultrasound phantom

Figure 5.6. Scatter plot of CIMT measured by investigator 1

Figure 5.7. Scatter plot of CIMT measured by investigators 1 and 2

Figure 5.8. Scatter plot of GLS measured by investigator 1

Figure 5.9. Scatter plot of GLS measured by investigators 1 and 2

Figure 5.10. Bland Altman plot for CIMT intra-observer reproducibility

Figure 5.11. Bland Altman plot for CIMT inter-observer reproducibility

Figure 5.12. Bland Altman plot for GLS intra-observer reproducibility

Figure 5.13. Bland Altman plot for GLS inter-observer reproducibilit

Glossary

2D Two-dimensional

3D Three-dimensional

A Peak late diastolic filling velocity

ABPM Ambulatory blood pressure monitoring

ACR Albumin:creatinine ratio

ANOVA Analysis of variance

AR Atrial reversal

ARdur Atrial reversal duration

BMI Body mass index

BP Blood pressure

BSA Body surface area

CCA Common carotid artery

CI Confidence interval

CIMT Carotid intima media thickness

Coef Coefficient

D Peak diastolic pulmonary vein flow velocity

DBP Diastolic blood pressure

E Peak early diastolic filling velocity

e' Peak early diastolic myocardial velocity

ECG Electrocardiogram

eGFR Estimated glomerular filtration rate

GLS Global longitudinal strain

GLSR Global longitudinal strain rate

GP General practitioner

HbA1C Glycosylated haemoglobin

HBPM Home blood pressure monitoring

ICC Intra-class correlation coefficient

IDACO International Database of Ambulatory Blood Pressure in relation to Cardiovascular Outcomes

IMT Intima media thickness

INH Isolated nocturnal hypertension

IVRT Isovolumetric relaxation time

JNC Joint national committee

LA Left atrium

LDL Low density lipoprotein

LV Left ventricle

LVH Left ventricular hypertrophy

LVMI Left ventricular mass index

NICE National Institute for Health and Care Excellence

OR Odds ratio

S Peak systolic pulmonary vein flow velocity

SBP Systolic blood pressure

SD Standard deviation

TDI Tissue doppler imaging

UACR Urinary albumin:creatinine ratio

UK United Kingdom

Declaration

I declare that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism.

_____

Anne Marie O'Flynn

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Abstract

Introduction

The objectives of this thesis are to: (1) examine how ambulatory blood pressure monitoring (ABPM) refines office blood pressure (BP) measurement; (2) determine if absolute ambulatory BP or dipping status is better associated with target organ damage (TOD); (3) explore the association of isolated nocturnal hypertension (INH) with TOD; and (4) investigate the association of night-time BP with ultrasound markers of cardiovascular damage.

Methods

Data from the first screen of the Mitchelstown Cohort Study was analysed to examine how ABPM refines office BP measurement and investigate if absolute ambulatory BP or dipping status are better associated with left ventricular hypertrophy (LVH) documented by electrocardiogram (ECG) Cornell Product Voltage and microalbuminuria documented by an albumin:creatinine ratio (ACR) ≥ 1.1 mg/mmol. A systematic review of the literature was carried out to explore the association of INH and TOD. In addition analysis of the baseline data from the Mitchelstown Cohort Study examined the association of INH with ECG LVH and microalbuminuria. After 3.9 years of follow-up, a sample of the Mitchelstown Cohort who underwent ABPM in the initial wave of data collection were invited to have an echocardiogram for speckle tracking analysis and carotid ultrasound to further investigate the association of night-time systolic BP with subclinical cardiovascular disease.

Results

Chapter 2 demonstrates that at an individual level ABPM reclassifies approximately a quarter of patients with prevalence rates of white coat and masked hypertension of 11% and 13% respectively in untreated individuals. Chapter 3 finds night-time systolic BP to be better associated with ECG LVH and microalbuminuria than daytime systolic BP and dipping level. In multi-variable models each 10 mmHg rise in night-time systolic BP increased the odds of TOD - odds ratio (OR) LVH 1.4 (95%

CI 1.1 -1.8) and OR ACR ≥ 1.1 mg/mmol 1.5 (95% CI 1.2 – 1.8). Chapter 4 finds the evidence for the association of INH with TOD to be inconclusive. Chapter 6 demonstrates night-time systolic BP to be significantly associated with global longitudinal strain (GLS) (beta coefficient 0.85 for every 10 mmHg rise, 95% CI 0.3 – 1.4) and carotid plaques (OR 1.9 for every 10 mmHg rise, 95% CI 1.1 – 3.2) in univariable models. The findings persist for GLS in sex and age adjusted analysis but are attenuated in fully adjusted models.

Discussion

Hypertension cannot be effectively managed at the individual level without using ABPM. Using ABPM to examine the full twenty four hour BP profile is the way forward in guiding hypertension treatment decisions. The absolute night-time systolic BP seems to be better associated with TOD than the daytime systolic BP and dipping level and may be a better therapeutic target in future studies. However the results of large prospective studies are necessary before chronotherapy can be adopted into guidelines and routine clinical practice.

1. Introduction

1.1. Hypertension

“The great importance of arterial hypertension or the conditions associated with it, as a widespread and apparently increasing cause of disability and death, is a self-evident incentive to investigation. At the same time it must be recognized that our knowledge of the subject is in a very confused state, as respects its phases of etiology, mechanism and treatment”. (1) This quotation from the Journal of the American Medical Association in 1920 demonstrates the challenges that hypertension posed to physicians at the time. Even today in the era of evidence based medicine many of these same challenges still exist.

Hypertension can be defined as the level of blood pressure at which investigation and treatment do more benefit than harm. (2) Most guidelines use a systolic threshold of 140 mmHg and a diastolic threshold of 90 mmHg as this level. (3-5) However blood pressure is a continuous risk factor (6) and one half of the disability adjusted life-years (DALYs) burden attributable to blood pressure occur below the 140/90 mmHg threshold. (7)

In 1961 the Framingham investigators reported on the association of hypertension and other risk factors with the development of coronary heart disease. (8) Today hypertension is one of the leading risk factors for cardiovascular mortality. In 2009 the World Health Organisation estimated that raised blood pressure caused 51% of stroke deaths and 45% of coronary heart disease deaths worldwide. (9) Globally reducing hypertension prevalence would account for the greatest risk reduction in cardiovascular mortality by 2025. (10) However, control rates remain low nationally and internationally. (11, 12)

1.2. Blood pressure measurement

Traditionally blood pressure is measured in the clinical setting by a trained professional and a diagnosis of hypertension is made based on this office blood pressure. Guidelines recommend measurements should be made using standardised methods with the patient in a seated position for 3 to 5 minutes

before beginning. At least 2 measurements should be made 1 to 2 minutes apart with additional measurements if the first two are very different. In addition a diagnosis of hypertension should be made based on at least 2 visits with at least 2 measurements per visit. (4)

Out of office measurement allows blood pressure to be measured away from the clinical setting. This can be achieved either through home blood pressure monitoring (HBPM) or ambulatory blood pressure monitoring (ABPM). For HBPM the patient should carry out their own blood pressure measurements over 7 days. A validated upper arm device with an appropriate cuff size should be used. Two morning and 2 evening readings should be taken 1-2 minutes apart with the patient sitting in a quiet room with their back and arm supported after 5 minutes of rest. With the exception of the first day all of the values should be averaged. (13)

ABPM measures blood pressure at 15 to 30 minute intervals over a 24 or 48 hour period and so provides information on blood pressure during activity and sleep. Rather than a single measurement ABPM more accurately reflects true blood pressure as it gives a blood pressure profile over a prolonged period. ABPM was first introduced in the 1960s. (14-16) The prognostic relevance of ambulatory blood pressure began to be recognised in the 1980s. (17) Subsequent studies demonstrated ambulatory blood pressure to be better than office blood pressure at predicting cardiovascular mortality. (18-20) The use of ABPM has gained steady momentum in recent years. It allows identification of white coat and masked hypertension. White coat hypertension is the condition in which blood pressure is elevated in the office and normal when measured out of the office. Masked hypertension is the situation whereby blood pressure is normal in the office but elevated when measured out of the office. The early morning surge can be examined. The presence of nocturnal hypertension and information on nocturnal dipping can also be gleaned. In addition episodes of hypotension may be identified. Thresholds for hypertension based on HBPM and ABPM are lower than the office blood pressure threshold. Table 1.1.

A systematic review and meta-analysis on the relative effectiveness of office blood pressure measurements and HBPM compared to ABPM concluded that treatment decisions based on office or HBPM alone might result in over-diagnosis of hypertension. (21) A subsequent modelling study examining cost-effectiveness found that ABPM would reduce misdiagnosis and save costs from better targeted treatment if used to confirm the diagnosis of hypertension in primary care. (22) In 2011, the National Institute for Health and Care Excellence in the United Kingdom (UK) recommended the use of ABPM if the office blood pressure is 140/90 or higher to confirm the diagnosis of hypertension. (3) Recently the United States Preventive Services Task Force made a similar recommendation. (23) The 2013 European Society of Hypertension/European Society of Cardiology guidelines for arterial hypertension state that office blood pressure remains the ''gold standard' but out-of-office blood pressure measurement should be considered in cases of suspected white coat or masked hypertension, in cases of considerable office blood pressure variability, to detect hypotensive episodes or resistant hypertension and to assess nocturnal blood pressure. (4)

There are a number of methodological considerations for ABPM. An independently validated device and appropriately sized cuff should be used. (24) The device is usually worn on the non-dominant arm. The patient should be instructed to engage in normal activity and to stop moving and talking and keep the arm straight at the level of the heart when the cuff inflates. (4) Inaccuracies can arise in those with atrial fibrillation as automated devices can lead to overestimates of the diastolic blood pressure in these patients. (25) A software programme that processes the raw data and produces a standardised report appropriate for the intended clinical or research use is also necessary.

Table 1.1. Thresholds for hypertension by office and out-of-office blood pressure measurements

Blood Pressure	Systolic (mmHg)	Diastolic (mmHg)
Office	140	90
Home	135	85
24 hour	130	80
Daytime	135	85
Night-time	120	70

1.3. Nocturnal blood pressure

ABPM allows measurement of blood pressure throughout the 24 hour period. Blood pressure has a circadian or diurnal rhythm that varies over a 24 hour period which was described in the 1970s. (26) There are generally 2 peaks of blood pressure during the day, one shortly after we awaken and the second in the late afternoon or early evening. (27) Blood pressure generally falls at night and reaches its lowest point from 3am to 6am or 1 to 3 hours before we awaken. (28)

Defining the night-time blood pressure window can be done using fixed clock intervals or patient diaries. Research using actigraphy to document sleep/activity cycles has shown that either approach is reasonable. (29) For fixed clock intervals large or narrow intervals can be chosen. For large fixed clock intervals no interval is used between day and night. For narrow fixed clock intervals periods between day and night are excluded as they are subject to inter patient variations in activity and retiring time. (30) For example the period from 1 am to 6 am is used as the night-time window as this is the time that most people will be asleep or at least cease activity and the period from 9 am to 9 pm is taken as the daytime window. (24) Patients may also provide diaries of the time they go to bed and get up at and these times can be used to define day and night.

The prognostic importance of the circadian blood pressure profile was recognised in 1988 when the concept of dippers and non-dippers was introduced after non-dipping hypertensive patients were found to have a higher risk of stroke compared to dippers. (31) Dipping is defined as a 10-20% fall in night-time blood pressure relative to daytime blood pressure while non-dipping is defined as less than 10% fall in night-time blood pressure. In addition extreme dippers are defined as those with a night-time drop of greater than 20% and reverse dippers as those with a night-time blood pressure that rises relative to daytime blood pressure. (32)

Nocturnal hypertension is defined as elevated night-time blood pressure ≥120/70 mmHg. It has been found to be more reproducible than dipping status and therefore some have advocated its use to assess the effect of antihypertensive therapy at night. (33) One study found a higher prevalence of cardiovascular risk

factors and target organ damage in those with both non-dipping and nocturnal hypertension compared to those with either profile alone or a normal profile. (34)

Isolated nocturnal hypertension was described in 2007 and is defined as elevated night-time blood pressure in the presence of normal daytime blood pressure i.e. night-time blood pressure of ≥120/70 mmHg with daytime blood pressure of <135/85 mmHg. (35) Those with isolated nocturnal hypertension have been found to have a higher risk of mortality and cardiovascular events compared to normotensive individuals. (36) Those with sustained day-night hypertension had the greatest risk but those with isolated daytime and nocturnal hypertension had overall similar rates of events.

1.4. The prognostic importance of nocturnal blood pressure

Following the initial description of dipping and non-dipping in 1988 further data on clinical events associated with dipping status followed. In 1997 Ohkubo et al found higher mortality in reverse dippers and non-dippers in a rural Japanese community sample. Findings persisted even after adjustment for absolute blood pressure levels. Kario et al found stroke rates to be higher in extreme dippers and reverse dippers in an older hypertensive sample in 2001. Total mortality and cardiovascular mortality was higher in reverse dippers. However this was attenuated after adjusting for the 24 hour blood pressure level. (37) Clement et al found contradictory findings in 2003 regarding dipping status, while absolute ambulatory blood pressures were independent risk factors for new cardiovascular events the night-day blood pressure ratio was not found to be an independent risk factor in 1963 treated hypertensive patients followed up for 5 years. (18)

Subsequent studies began to focus on the superiority of absolute ambulatory blood pressure levels over office blood pressure levels as well as dipping status. In 2004 Nakano and colleagues found that ambulatory blood pressure levels rather than dipping status better predicted fatal and non-fatal vascular events in a longitudinal analysis of type 2 diabetic subjects, in particular night-time systolic blood pressure was found to be an independent predictor of nonfatal vascular events in an adjusted cox proportional hazards model. (38) In 2005 the Dublin Outcome Study

demonstrated ambulatory blood pressure to be superior to office blood pressure for the prediction of cardiovascular mortality and significantly night-time blood pressure was better than daytime blood pressure as a predictor of outcomes in 5292 untreated hypertensive patients. (19) Hansen et al found similar results in a population study in Denmark in 2006 examining cardiovascular mortality, ischaemic heart disease and stroke. They also found a blunted fall in night-time blood pressure to be a risk factor in those with daytime ambulatory hypertension but not in those with daytime ambulatory normotension. (39) In 2007 Ben-Dov et al specifically focused on sleep blood pressure and all-cause mortality in an ABPM service database. (40) They found sleep blood pressure to have independent and greater predictive power than awake blood pressure. Dipping status also significantly predicted mortality in adjusted models with reverse dippers having the highest risk followed by non-dippers. In addition, compared to dipper normotensives, dipper awake hypertensives, non-dipper awake normotensives and nondipper awake hypertensives were found to have increasing risk in that order.

Boggia et al carried out an analysis of the International Database of Ambulatory Blood Pressure in relation to Cardiovascular Outcomes (IDACO) database consisting of population studies from Denmark, Belgium, Sweden, Japan, China and Uruguay. They found systolic and diastolic night-time blood pressures to be a significant predictor of total, cardiovascular and non-cardiovascular fatal and non-fatal events although significance was lost for coronary events in fully adjusted models. On the other hand while night-to-day ratios were predictive of fatal events they were not consistent predictors of combined fatal and non-fatal events. (41) Brotman et al focused on dipping and non-dipping in 2008 and found higher mortality rate with blunted nocturnal blood pressure decline in patients referred for ABPM although this effect was attenuated when comorbid conditions were also considered. (42) Muxfelt et al found non-dipping to be an independent risk factor for cardiovascular mortality in patients with resistant hypertension attending an outpatient hospital clinic. (43) Fagard et al carried out a meta-analysis on 3468 patients from 4 prospective studies in Europe in 2008 and found daytime ambulatory blood pressure did not add to the prognostic power of night-time ambulatory blood

pressure. (44) Hansen et al carried out a comprehensive meta-analysis in 2011 and confirmed the prognostic importance of night-time over daytime blood pressure. (45) They included studies of hypertensive patients and population studies with mortality or composite cardiovascular endpoints and examined absolute blood pressure and dipping status. The results of 2 further systematic reviews concluded the absolute night-time blood pressure to be better than dipping status in predicting cardiovascular and renal outcomes. (46, 47) Of note these reviews included studies of intermediate and clinical endpoints. A very recent meta-analysis including 10 cohorts with 17312 hypertensive patients examined the prognostic importance of dipping status analysed as a continuous and categorical variable. (48) The authors found the continuous systolic night-to-day ratio to be an independent predictor of clinical outcomes when adjusted for twenty four hour blood pressure. However the hazard ratios per 1 standard deviation rise were lower than those for the twenty four hour blood pressure level.

Night-time blood pressure appears to be of particular prognostic importance in both hypertensive and population cohorts. (45) The mechanisms behind this are not clear, nor is it clear that normalising night-time blood pressure improves prognosis. However there have been some promising intervention studies involving chronotherapy, the administration of anti-hypertensive medications in the evening to reduce night-time blood pressure. In the MAPEC (Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares, ie, Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events) study patients were randomised to take all of their anti-hypertensive medications on wakening in the morning or at least 1 of them at bedtime. After a median follow-up period of 5.6 years the decrease in nocturnal blood pressure was associated with a reduced risk of total cardiovascular events even when it was included in the same model as the decrease in daytime blood pressure. Similarly patients with chronic kidney disease who ingested at least one anti-hypertensive medication at night had lower hazard ratio of total cardiovascular events than those taking all of their medications in the morning. (49, 50)

The evidence is clear that night-time blood pressure is of greater prognostic importance than daytime blood pressure. However there is some conflicting data on which nocturnal blood pressure profile is most important. Also there have been relatively few interventional studies aimed at normalising abnormal nocturnal blood pressure profiles and while these have been promising reverse causality remains a possibility. Abnormal nocturnal blood pressure may be a marker rather than a cause of cardiovascular events.

1.5. The cardiovascular disease continuum

Despite improvements in outcomes in some higher and middle income countries cardiovascular disease remains a leading cause of death worldwide. (51) Cardiovascular disease develops as a continuum with risk factors leading to tissue damage which results in organ damage which eventually results in clinical events. (52-54) Asymptomatic organ damage is therefore an intermediate stage on this continuum. The mechanisms involved are numerous, overlap and may not occur in sequence. They include oxidative stress, endothelial dysfunction, inflammation and tissue remodelling. (53) Hypertension leads to damage throughout the cardiovascular system. Imaging and laboratory techniques have allowed us to document intermediate stages of damage in various organs. (4) This information on organ damage can be used to guide prevention strategies. (55) These intermediate stages of organ damage are considered surrogate markers. Surrogate markers are measurements that predict clinical events and ideally should be on the causal pathway. (56) Information on surrogate markers can be gathered in a shorter timeframe and at less expense than clinical outcomes making their use appealing but they are not without controversy. Measurement error or unmeasured confounding affecting the association between the outcome and the surrogate always need to be considered. (57)

1.6. Target organ damage

Target organ damage refers to damage of the vascular system or of organs supplied by the vascular system such as the heart, kidneys, brain or eyes. A number of different techniques that document organ damage will be considered in this thesis.

Some, such as the electrocardiogram and microalbuminuria, are considered routine in the evaluation of patients with hypertension. Others such as pulse wave velocity, echocardiography and carotid ultrasound are recommended based on history, physical examination and routine investigations. (4) All provide important prognostic information.

1.6.1. Electrocardiography

Sokolow and Lyon first proposed electrocardiogram (ECG) voltage criteria for left ventricular hypertrophy (LVH) in 1949. (58) In 1970 analysis from the Framingham Study highlighted the association of ECG LVH with coronary artery disease and death. (59) ECG LVH is now a recognised independent predictor of prognosis. (59, 60) There are many criteria for ECG LVH. (61) Generally sensitivity is low with good specificity but this varies according to the criterion selected. Adding QRS duration to QRS voltage does improve sensitivity but this is still generally less than 50%. (62) New imaging modalities including echocardiography and magnetic resonance imaging allow for more accurate assessment of LVH. However an ECG can cheaply be carried out in most clinical settings and therefore has retained a role in the assessment of those with hypertension. (4)

1.6.2. Microalbuminuria

The detection of albumin in the urine is associated with increased cardiovascular risk. (63) It is accepted as a surrogate marker for renal endpoints. (64) Albuminuria reflects damage to the glomerular filtration barrier and may reflect generalised damage throughout the vascular tree. (65) Endothelial dysfunction may be the pathophysiology behind this. (66) Albumin excretion can be measured by 24 hour collection, urine dipstick or a spot urine sample for albumin:creatinine ratio. Albuminuria is a continuous risk factor and while thresholds of normality are used in clinical practice cardiovascular mortality increases at levels considered within these normal ranges. (63, 67)

1.6.3. Arterial stiffness

Arterial stiffness is the resistance of a vessel to deformation and is one of the earliest detectable abnormalities of the vasculature. (68) Pulse wave velocity is

considered the gold standard measurement of arterial stiffness. (69) It is determined by measuring the transit time of a pulse wave between 2 sites along the vascular tree. The stiffer the vessel the faster the pulse wave is transmitted. (68)

Applanation tonometry is another technique which allows non-invasive derivation of the central blood pressure waveform. This is usually employed at the radial artery. The central waveform is made up of a forward propagating wave and a reflected wave from branching points more distally in the vascular tree. Analysis of the waveform derived from applanation tonometry allows quantification of the augmentation of the central blood pressure by reflected waves i.e. the amount of pressure added to the systolic pressure by reflected waves or the augmented pressure. The ratio of the augmentation pressure to central pulse pressure is known as the augmentation index. (70) Stiffer vessels reflect waves faster and result in a higher augmentation index.

The ambulatory arterial stiffness index (AASI) is a surrogate measurement of arterial stiffness derived from ABPM. It is derived by subtracting the regression slope of diastolic and systolic blood pressure from 1 (1 minus the slope of diastolic on systolic pressure). (71)

A meta-analysis of 17 longitudinal studies found increased arterial stiffness measured by pulse wave velocity to be associated with increased risk of cardiovascular and all-cause mortality. (72) Similarly a meta-analysis found the augmentation index to be associated with cardiovascular events and all-cause mortality. Central systolic blood pressure and central pulse pressure were associated with total cardiovascular events in the same study. (73) Dolan et al found the AASI to be associated with cardiovascular mortality and stroke mortality in hypertensive patients in the Dublin Outcome Study. (74)

1.6.4. Echocardiography

Hypertensive heart disease is characterized by cardiac hypertrophy in response to increased cardiac afterload. This results in systolic and diastolic dysfunction as well as other structural abnormalities. These structural abnormalities progress to

manifest clinically as arrhythmias and symptomatic heart failure. (75) Two-dimensional (2D) echocardiography can demonstrate many of the effects of hypertension on cardiac function and structure.

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is an increase in left ventricular (LV) mass. It is recognised as an independent predictor of morbidity and mortality. (76-78) In addition regression of LVH has been shown to be associated with a reduced incidence of cardiovascular disease. (79) The prevalence of LVH in hypertensive patients ranges from 36-41%. (77) Methods to measure LV mass using echocardiography include Devereux's Formula (76) and the Area Length Method. (77) LV mass should be indexed to allow comparisons between people of different body size and most large population studies have done this to body surface area. (80)

Diastolic dysfunction

Hypertension may lead to diastolic dysfunction which can occur in the presence or absence of LVH. Diastolic dysfunction leads to elevated LV filling pressures. (81) There is no single measure of diastolic dysfunction. The different techniques need to be considered together to make an overall integrated assessment. Diastolic dysfunction is classified into stages using the various echocardiographic parameters:

Stage I - Impaired relaxation

Stage II - Pseudo-normalisation

Stage III - Restrictive which can be reversible or fixed

Pulsed-wave doppler assessment of transmitral flow with the sample volume at the mitral valve tips forms the basis of assessment. From this, peak early diastolic filling velocity (E) and peak late diastolic filling velocity (A), can be obtained as well as E:A ratio. Other important information available from this technique is the E wave deceleration time. (82) E wave deceleration time reflects LV compliance. It increases in early diastolic dysfunction. However, as diastolic dysfunction progresses filling pressures rise and there is a decrease in the deceleration time.

Isovolumetric relaxation time (IVRT) is the time from closure of the aortic valve to opening of the mitral valve. It is measured from a modified apical 4 chamber view which includes the outflow tract and aortic valve. A pulsed-wave doppler signal that simultaneously demonstrates aortic outflow and mitral inflow should be obtained. IVRT is the time interval between the two signals. It is prolonged in early diastolic dysfunction but like the E wave deceleration time becomes shorter as disease progresses.

The myocardium moves as the ventricle fills in diastole and this can be recorded by tissue doppler imaging (TDI). The myocardial diastolic motion pattern is similar to that of mitral inflow but lower in velocity and in the opposite direction. TDI is carried out with the sample volume at the ventricular basal wall at or within 1 cm of the mitral valve leaflet insertion point. Signals are recorded from lateral and septal walls. This allows assessment of peak early diastolic myocardial velocity (e') and peak late diastolic myocardial velocity (a'). The E/e' ratio can then also be calculated which allows an estimation of left atrial (LA) filling pressure to be made. (83)

Pulsed-wave doppler interrogation of pulmonary venous flow allows assessment of LA filling. This should be looked at in conjunction with the other parameters of diastolic function. Peak systolic pulmonary vein flow velocity (S), peak diastolic pulmonary vein flow velocity (D), peak pulmonary vein atrial reversal (AR) velocity and AR duration (ARdur) can be obtained.

The assessment of diastolic dysfunction involves an integrated approach taking into consideration each of the individual parameters. Figure 1.1. The volume status of the patient needs to be considered as it influences findings. Heart rate and rhythm also have an impact. It is normal to see some degree of diastolic dysfunction in older patients so age is also important. A valsalva manoeuvre should be used in order to distinguish the different stages.

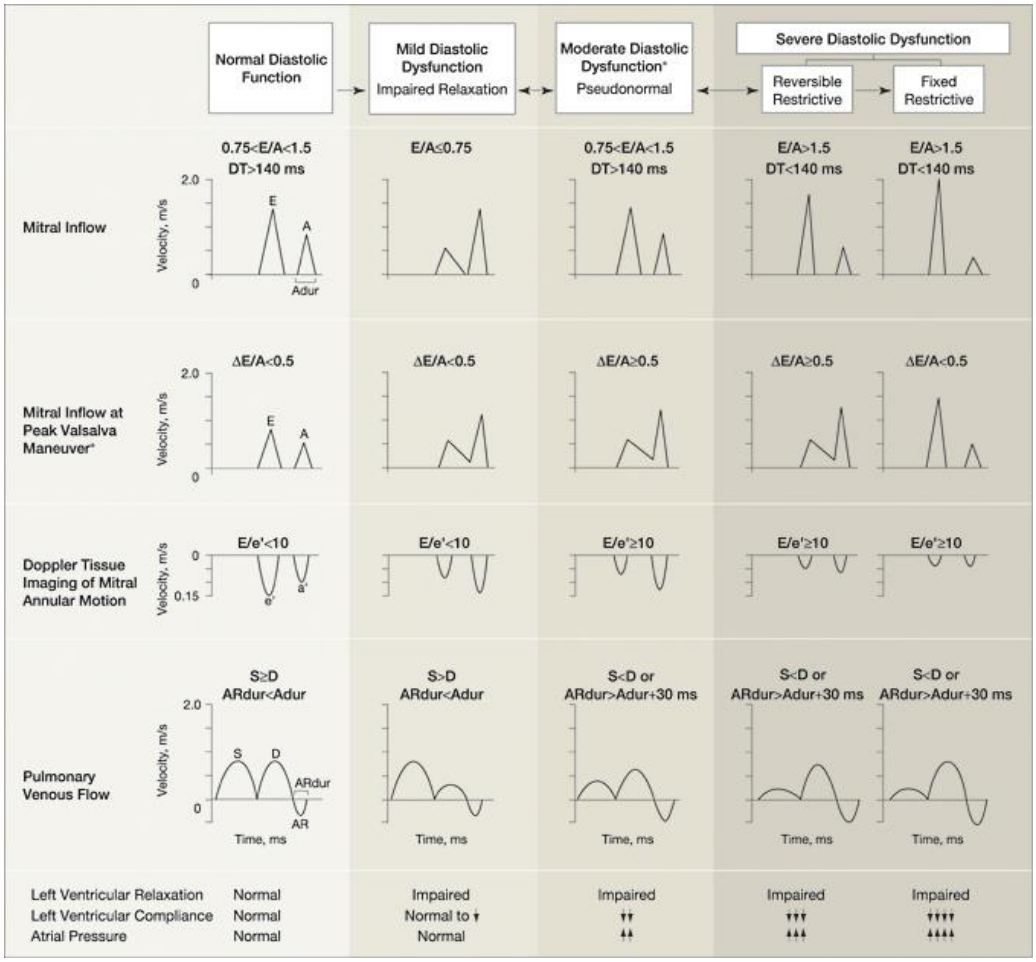


Figure 1.1. Stages of diastolic dysfunction. Redfield MM, Jacobsen SJ, Burnett, Jr JC, Mahoney DW, Bailey KR, et al. JAMA 2003. Reproduced with permission. (84)

Left atrial size

As LV pressure rises so too will LA pressure to maintain diastolic filling of the LV. This increases LA wall tension and leads to chamber dilatation. LA size can therefore be considered a chronic reflection of filling pressures. LA size can be measured by diameter from the parasternal long axis view or alternatively by area or volume from apical views. However, indexed LA volume has been demonstrated to be a more sensitive marker of future cardiovascular events than LA diameter or area. (85) LA volume has also been shown to be a marker for diastolic dysfunction severity. (86) LA enlargement was correlated to blood pressure in the Framingham Heart study. (87) LA volume has been shown to be increased even in those with mild hypertension. (88) LA size is also of clinical relevance with respect to atrial fibrillation and stroke risk.

Myocardial strain

Strain is a measure of myocardial deformation, or contraction and relaxation, usually expressed as a percentage with negative values representing myocardial shortening. Myocardial contraction occurs in three dimensions longitudinal, radial and circumferential (Figure 1.2). (89) Longitudinal strain is measured from apical views while radial and circumferential strain is measured from short axis views of the LV.

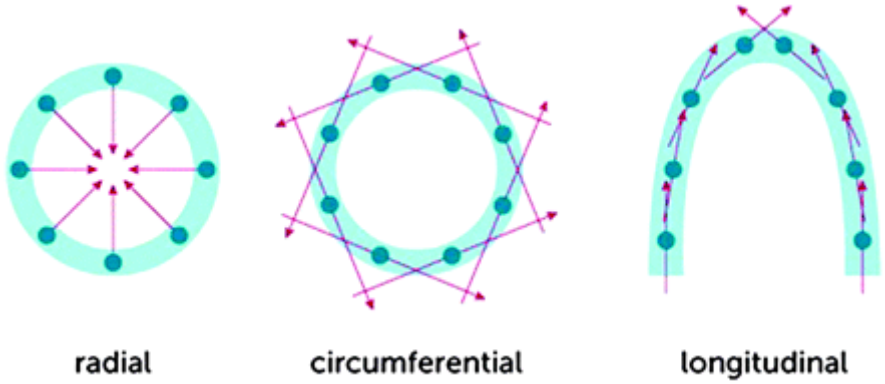


Figure 1.2. Myocardial strain dimensions. Blessberger H, Binder T. Non-invasive imaging: Two dimensional speckle tracking echocardiography: basic principles. Heart 2010. Reproduced with permission. (89)

TDI was initially used to assess strain. (90) However TDI is angle dependent. Speckle tracking echocardiography is a means of assessing myocardial function which is largely angle independent and can be done offline after image acquisition. The myocardium scatters the sound waves which generate speckles specific for an area of myocardium. Blocks of speckles or kernels can be tracked from frame to frame using specialised software and provide information on myocardial displacement. Parameters of myocardial function such as strain and strain rate can be derived. (91) Global longitudinal strain (GLS) is a measure of the myocardial systolic deformation over the longitudinal axis. (90) GLS seems to be more reproducible than radial or circumferential strain. (92)

Speckle tracking echocardiography allows the detection of subtle myocardial dysfunction and may be an appropriate tool to assess subclinical cardiac dysfunction. Abnormal GLS is associated with cardiovascular risk factors such as

type II diabetes mellitus (93) and hypertension. (94) Reduced GLS is associated with abnormal left ventricular geometry in hypertensive patients. (95) Anti-hypertensive therapy has been shown to be associated with improvements in strain. (96) Cumulative blood pressure exposure over 25 years in the CARDIA (Coronary Risk Development in Young Adults) study was associated with subclinical systolic and diastolic dysfunction assessed by speckle tracking echocardiography in middle age. (97)

Few researchers have addressed the association of night-time blood pressure with left ventricular GLS. Seo et al demonstrated reduced strain measured by TDI in non-dippers compared to dippers in 2006. (98) More recently Kalaycioglu et al used speckle tracking echocardiography to demonstrate a significant reduction in GLS in non-dippers compared to dippers in treated hypertensive diabetic patients. They also found night-time systolic blood pressure to be independently associated with GLS and global longitudinal strain rate (GLSR). (99) Tadic et al similarly demonstrated GLS to be significantly lower in non-dippers compared to dippers in untreated hypertensive patients. (100)

Data is also emerging on the prognostic importance of strain. In 2009 Stanton et al found GLS to be a better predictor of mortality than ejection fraction or wall motion score in subjects undergoing clinically indicated echocardiography. (101) Russo et al found impaired GLS in a community sample with normal ejection fraction in 16.1% of a community based sample of middle aged adults. Abnormal GLS was a significant independent predictor of a combined endpoint of ischaemic stroke, myocardial infarction and vascular death. (102) GLS has been found to predict mortality in end stage renal disease in African-American patients on dialysis in a small study. (103)

1.6.5. Carotid intima media thickness

Arteries are composed of 3 layers. The outer layer or the adventitia is made up of connective tissue, the middle layer or media is composed of smooth muscle fibres and elastic tissue and the inner intima is made up of a thin layer of endothelium overlying an elastic membrane.

The arterial tree consists of elastic arteries, muscular arteries and arterioles. Elastic arteries are the conducting vessels and serve as a pressure reservoir. They contain a large amount of collagen and elastin in the media. Muscular arteries are distributing vessels. They contain a large amount of smooth muscle in the media and can dilate or constrict. Arterioles are the smallest arteries and are composed almost entirely of smooth muscle cells. (104)

The carotid artery is an elastic artery. The thickness of the intima and media layer of the carotid artery wall or carotid intima media thickness (CIMT) can be measured by B mode ultrasound. This is usually visible as a double line which is traced over a length of 1 cm and average thickness can be calculated by automated software. Figure 1.3.

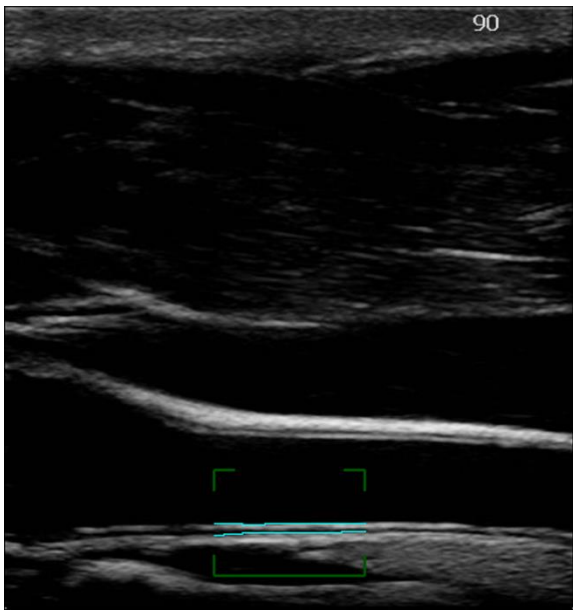


Figure 1.3. Carotid intima-media thickness tracing at distal 1 cm of common carotid artery

Carotid Intima- Media Thickness (CIMT) is recognised to be associated with cardiovascular risk factors and is associated with the incidence of myocardial infarction and stroke. (105, 106) There is evidence for the validity of CIMT as a suitable surrogate measure of atherosclerotic disease. (107, 108) In addition CIMT has been shown to have an additional role beyond traditional risk factors in risk-stratifying patients. (109-111) However there is conflicting data with an earlier

meta-analysis corroborating CIMT as a strong predictor of cardiovascular events (112) and a more recent one concluding that while adding common carotid IMT to traditional tools does improve risk prediction the overall impact is small and is unlikely to be clinically important. (113) The presence of plaques is important as they improve predictive performance (111, 114, 115), and a meta-analysis has confirmed that plaques perform better than CIMT in predicting future coronary events. (116) Anti-hypertensive therapy slows the rate of progression of CIMT. (117, 118) Similarly statin therapy has been shown to reduce the progression of maximum CIMT. (119)

There are difficulties when trying to interpret previous work on CIMT. Different studies have focused on different segments of the carotid system and used different reference points to differentiate these segments. (120) The distal segment of the common carotid segment is easier to image than the internal carotid artery. (121) Some studies have examined maximum CIMT (105) while others have taken mean measurements. (111) Some investigators have included the presence of plaques in their analysis while others have not. Plaques are more likely to form in the bifurcation segment where there is turbulent flow while CIMT is more likely to increase in areas of laminar flow such as the distal common carotid segment. CIMT increases as we age. This occurs even in the absence of atherosclerosis. Therefore increased CIMT does not necessarily mean atherosclerosis. (122) CIMT is most strongly associated with hypertension and plaque area is most strongly associated with smoking and cholesterol while plaque volume is most strongly associated with diabetes. CIMT may reflect hypertrophy of the vessel wall while plaques represent more advanced atherosclerosis. (123)

1.7. Nocturnal blood pressure and target organ damage

Many studies have evaluated the association of non-dipping with target organ damage and found positive associations. (124-129) Fewer studies have assessed the association of the absolute night-time blood pressure with subclinical target organ damage relative to dipping status. In 2007 Perez-Loret et al proposed the definition of nocturnal hypertension by a cut-off of 120/70 mmHg was better than dipping

status as a predictor of LVH documented by echocardiography in a cross-sectional study of consecutively referred out-patients. (130) In another cross-sectional study Leitao et al assessed the association of albumin excretion, LV mass and retinopathy with ambulatory blood pressure patterns in diabetic outpatients. They found systolic blood pressure means rather than dipping status to be better associated with albumin excretion and LV mass. Absolute night-time blood pressures were important as independent predictors of diabetic retinopathy in adjusted models as was diastolic non-dipping but not systolic non-dipping. (131) Cuspidi and colleagues have examined target organ damage in those with persistent nocturnal hypertension and persistent non-dipping in further cross-sectional analyses. They concluded that both patterns can occur independently of each other and that target organ damage is more prevalent in those with nocturnal hypertension despite more than 50% being dippers (132) while they found no significant difference in target organ damage documented by echocardiography, carotid ultrasound and urinary albumin excretion between dippers and non-dippers. (133) In addition in a longitudinal analysis of the PAMELA (Pressioni Arteriose Monitorate E Loro Associazioni) population study absolute night-time blood pressure level rather than non-dipping was a better predictor of new LVH on echocardiography after 10 years of follow-up. (134) Wang et al found Chinese patients with nocturnal hypertension and chronic kidney disease had lower estimated glomerular filtration rate (eGFR), higher left ventricular mass index (LVMI) and higher CIMT compared to those with nocturnal normotension while dippers and non-dippers had similar levels of eGFR, LVMI and CIMT at comparable levels of night-time blood pressure in a further cross-sectional analysis. (135) Yi et al found nocturnal systolic blood pressure levels >127 mmHg rather than non-dipping predicted LVH in adjusted analyses although the effect size was small. (136) Koroboki et al found nocturnal hypertension rather than dipping status to be an independent risk factor for higher LVMI. (137) Recently Androulakis et al found increased arterial stiffness, CIMT and LV mass in those with nocturnal hypertension compared to normotension while non-dipping was found to be associated with differences in arterial stiffness and creatinine clearance. (138)

De La Sierra et al have examined differences in cardiovascular risk profile in those with nocturnal hypertension and non-dipping and found having both profiles was associated with the highest prevalence of risk factors and previous events. Those with neither were at lowest risk while those with either pattern were intermediate risk. They suggest that non-dipping may be a more advanced marker of vascular damage. (34)

The literature suggests that ABPM provides more accurate measurement of blood pressure and that night-time blood pressure has greater prognostic importance than daytime blood pressure. Abnormal nocturnal blood pressure profiles also seem to be associated with greater subclinical target organ damage, but there is some conflicting data about which nocturnal profile is most important. This is important to elucidate so the most appropriate target of future therapeutic trials can be established.

1.8. Research aim and objectives

The overall aim of this thesis is to investigate how using ABPM refines blood pressure measurement and to further explore the association of nocturnal blood pressure and target organ damage.

In particular the objectives are:

1. To examine how using ABPM refines office blood pressure measurement at an individual and population level (Chapter 2)
2. To determine if absolute ambulatory blood pressure or dipping status is better associated with target organ damage (Chapter 3)
3. To explore the association of isolated nocturnal hypertension and target organ damage (Chapter 4)
4. To investigate the association of night-time blood pressure with ultrasound markers of cardiac and vascular damage (Chapter 5 and 6)

1.9. Theoretical framework

Evidence supports the cardiovascular disease continuum with risk factors resulting in organ damage, which eventually leads to clinical events. (52-54) This thesis explores the association of blood pressure with target organ damage and so the cardiovascular disease continuum is the main theory behind this work. Figure 1.4.

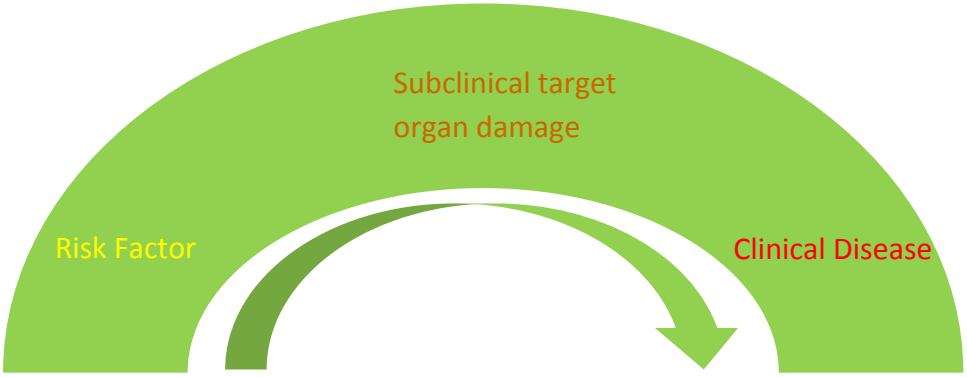


Figure 1.4. The cardiovascular disease continuum

1.10. Conceptual framework

As already discussed ambulatory blood pressure, and nocturnal blood pressure in particular, have greater prognostic significance than office blood pressure. It is not well understood why nocturnal blood pressure should have greater prognostic significance. Exploring the association of nocturnal blood pressure with target organ damage may explain where nocturnal blood pressure sits on the cardiovascular disease continuum and why it has greater prognostic significance. This is the central concept behind this thesis. The questions that will be investigated are outlined in figures 1.5 and 1.6.

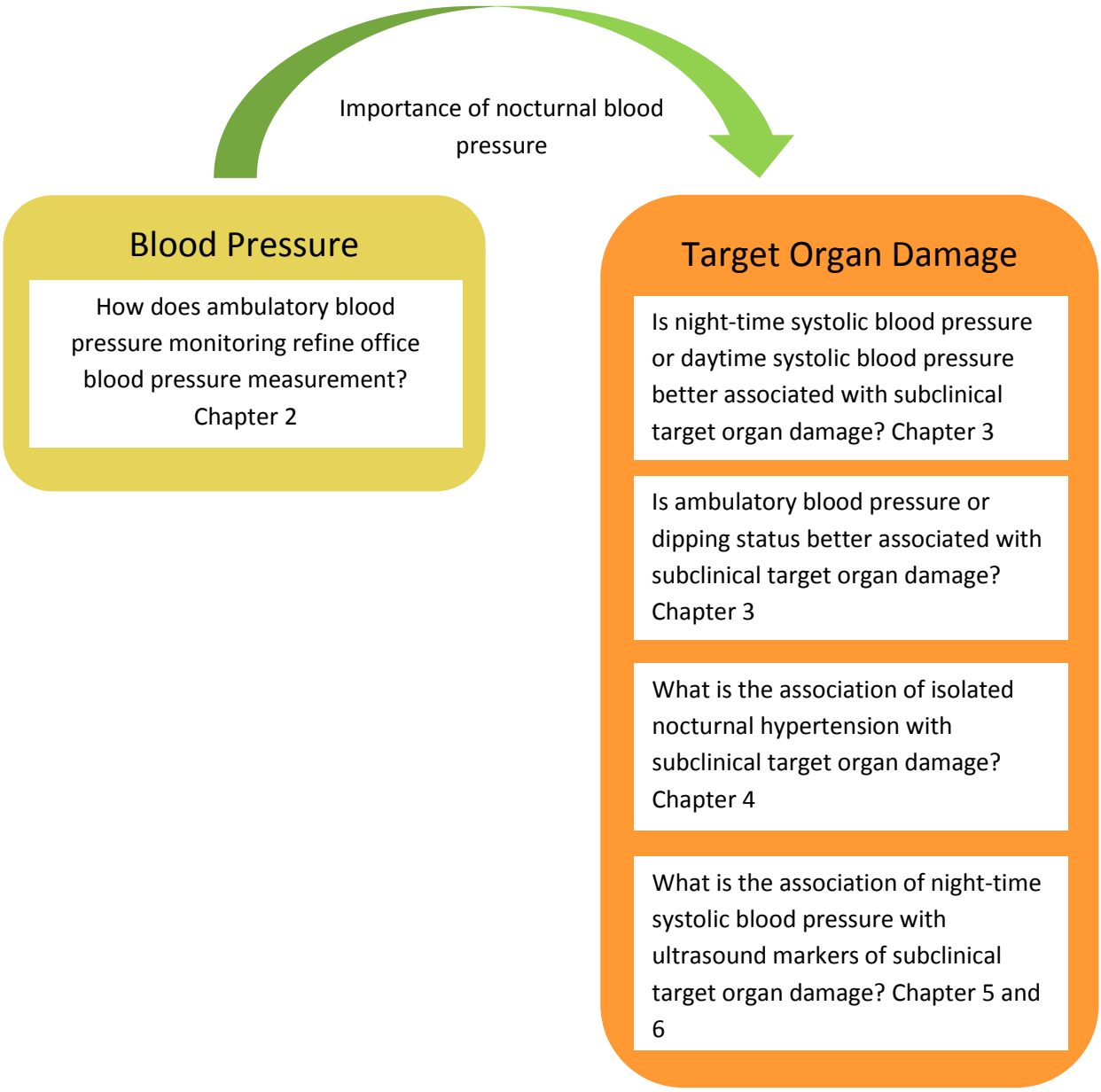


Figure 1.5. Conceptual Framework

1.11. Thesis layout

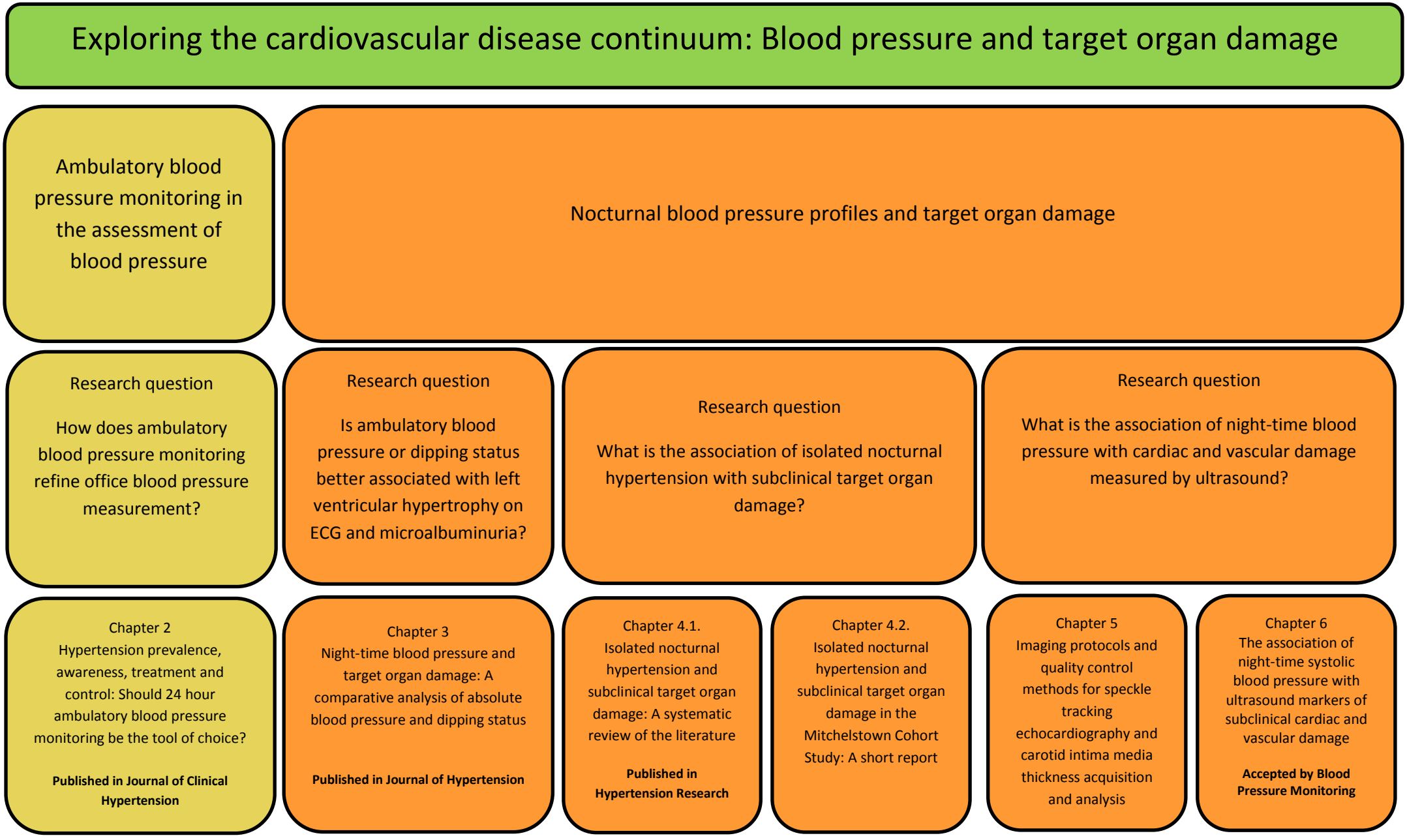


Figure 1.6. Thesis layout

1.12. References

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2. Hypertension prevalence, awareness, treatment and control: Should 24 hour ambulatory blood pressure monitoring be the tool of choice?

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2.1. Abstract

Introduction

Accurate measurement of blood pressure (BP) is essential for diagnosis and management of hypertension. The aim of this paper is to examine the prevalence, awareness, treatment and control rates of hypertension in a community based sample and to examine the impact of using 24 hour ambulatory blood pressure monitoring (ABPM) on these rates. We also aim to examine the sensitivity and specificity of office BP measurements and to describe the prevalence of white coat and masked hypertension.

Methods

The Mitchelstown Cohort Study was established to examine cardiovascular health in a middle-aged Irish community sample. The most recent BP recorded by the participant's GP in the electronic health record was documented as office BP. All participants were invited to have their BP measured during the study visit and the average of the second and third BP readings was defined as the study BP. All participants were invited to undergo 24 hour ABPM. Hypertension was defined using accepted thresholds or by current anti-hypertensive medication use. Participants were defined as aware of their hypertension if they self-reported a doctor diagnosis of hypertension, and as treated if they self-reported anti-hypertensive medication use. Control of hypertension was defined as a measured BP below the normal threshold and was calculated for prevalent and treated cases.

Results

Of 2047 participants, 1207 (response rate 59%), under-went 24 hour ABPM. Nine hundred and thirty one (45%) study participants underwent 24 hour ABPM, had a previous office and study BP available. The mean office BP was 134/79 mmHg and mean study BP was 134/83 mmHg. Based on the study BP, the prevalence of hypertension was 60% with an awareness rate of 59% and 60% were treated. Of the prevalent cases 27% were controlled while 46% of those on treatment were controlled. By ABPM the mean daytime BP was 131/77 mmHg and mean night-time

BP was 112/63 mmHg. Using the daytime ABPM threshold the prevalence of hypertension was 61%. The awareness rate was 59% and 59% were treated. Of the prevalent cases 32% were controlled while 54% of treated cases were controlled. In treated individuals 21% of those with elevated study blood pressure had normal blood pressure based on the daytime ABPM threshold while 14% of those with normal study blood pressure were found to have uncontrolled hypertension by ABPM. In untreated individuals the prevalence of white coat hypertension was 11% and masked hypertension was 13% based on the daytime ABPM threshold.

Discussion

Awareness, treatment and control rates of hypertension remain suboptimal. The routine use of ABPM in the diagnosis and management of hypertension in primary care will facilitate more appropriate treatment initiation and titration.

2.2. Introduction

Hypertension is a leading risk factor for cardiovascular mortality. In 2009 the World Health Organisation estimated that raised blood pressure caused 51% of stroke deaths and 45% of coronary heart disease deaths worldwide. (1) However, many people with hypertension are undiagnosed and of those who are diagnosed many are poorly controlled. (2)

Accurate measurement of blood pressure is essential for the diagnosis and management of hypertension. Traditionally measurements are carried out in a clinical setting and a diagnosis of hypertension is made based on this office reading. Ambulatory blood pressure monitoring (ABPM) provides information over a 24 or 48 hour period and in particular gives important information on night-time blood pressure. Ambulatory blood pressure has been shown to be superior for the prediction of clinical events. (3, 4)

A systematic review and meta-analysis on the relative effectiveness of clinic blood pressure measurements and home blood pressure monitoring (HBPM) compared to ABPM concluded that using clinic or HBPM alone might result in over-diagnosis of hypertension. (5) A subsequent UK study on the cost-effectiveness of options for the diagnosis of hypertension in primary care reported that ABPM would reduce misdiagnosis and save costs. It was suggested that in the UK the increased costs related to ABPM would be counterbalanced by cost savings from better targeted therapy. (6) The National Institute for Health and Care Excellence (NICE) in 2011 recommended that if the office blood pressure is 140/90 mmHg or higher, ABPM should be offered to confirm the diagnosis of hypertension. (7) The European Society of Hypertension (ESH) guidelines in 2013 state that office blood pressure remains the 'gold standard' for screening, diagnosis and management of hypertension. (8) They recommend HBPM or ABPM be carried out in certain clinically indicated situations including suspected white coat hypertension, drug resistance and hypotensive symptoms. Assessment of night-time blood pressure is also a specific indication for ABPM.

Generally studies examining hypertension prevalence have used office or home blood pressure readings measured using standardised techniques. (9) A recent study highlights the prevalence of masked uncontrolled hypertension among those on treatment for hypertension. (10) While many studies have investigated masked hypertension and white coat hypertension diagnosed by ABPM, (11-13) few population studies have compared the effect of different methods of measurement on prevalence rates of hypertension. (14)

The aim of this paper is to examine the prevalence, awareness, treatment and control rates of hypertension in a community based sample and to examine the impact of using ABPM on these rates. We also aim to examine the sensitivity and specificity of office blood pressure measurements and the prevalence of white coat and masked hypertension in the sample.

2.3. Methods

Details of the Mitchelstown Cohort have previously been described. (15) In summary, patients were recruited from a single large primary care centre, the Livinghealth Clinic in Mitchelstown, a town located in the south of Ireland. The practice serves a population catchment area of approximately 20,000. Those registered with the clinic in the 50-69 year old age bracket were assigned a random number. Participants were invited based on this random number in batches of 150 until the target sample size of 2000 was achieved.

Participants self-reported a history of doctor diagnosed hypertension and anti-hypertensive medication use by questionnaire.

After the participant had been in a relaxed seated position for at least 5 minutes three blood pressure readings were taken on the right arm, 1 minute apart, using the OMRON Model M7 digital automatic blood pressure monitor. (16) The average of the second and third blood pressure reading was defined as the study blood pressure.

Participants were offered 24 hour ABPM at the time of their study visit. ABPM measurements were performed using the MEDITECH ABPM-05 and data was stored using the dabl ABPM system. (17)

Consent was obtained to access the electronic patient record and if available the most recent blood pressure recorded by the participant's general practitioner (GP) was documented as the office blood pressure.

Participants whose electronic patient record included codes for elevated blood pressure, uncomplicated hypertension and complicated hypertension (International Classification of Primary Care, Second edition (ICPC 2) codes K85, K86, K87) were defined as having coded hypertension.

Hypertension was defined using the blood pressure thresholds for the different measurement techniques or by current antihypertensive medication use. Study and office thresholds were systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg. For ABPM the daytime and night-time windows were defined by diary records. ABPM data was excluded if there were < 14 daytime readings and/or < 7 night-time readings. (18) The daytime thresholds were a systolic blood pressure ≥ 135 mmHg and/or a diastolic blood pressure ≥ 85 mmHg. Night-time thresholds were a systolic blood pressure ≥ 120 mmHg and/or a diastolic blood pressure ≥ 70 mmHg. Twenty four hour thresholds were a systolic blood pressure ≥ 130 mmHg and/or a diastolic blood pressure ≥ 80 mmHg. Daytime and/or night-time hypertension was defined by combining the daytime hypertension threshold with the night-time hypertension threshold.

Participants were classified as being aware of their hypertension if they answered "yes" to the question "Have you ever been told by a doctor that you have, or have had, high blood pressure?" Participants were classified as treated if they answered "yes" to the question "Has your doctor given you a prescription for blood pressure tablets?"

Control of hypertension was defined by a blood pressure value of < 140/90 mmHg for the study and office blood pressure measurements. For ABPM readings

controlled hypertension was defined by blood pressure values < 135/85 mmHg for daytime, < 120/70 mmHg for night-time and < 130/80 mmHg for twenty four hour blood pressure.

Statistical Analysis:

Statistical analysis was carried out using Stata 12. Baseline characteristics are presented as absolute numbers with corresponding percentages for categorical variables and as means with standard deviations for continuous variables. Prevalence, awareness, treatment and control rates of hypertension were calculated and compared using the different measurement techniques and thresholds. Control rates were calculated for both prevalent cases and treated cases. The sensitivity and specificity of the study and office blood pressure measurements were calculated using the ABPM daytime threshold as the gold standard.

Ethical Approval:

Ethical approval for the study was obtained from the Clinical Research Ethics Committee of the Cork Teaching Hospitals. All participants provided written informed consent. The study was carried out in accordance with the Declaration of Helsinki.

2.4. Results

Of 3051 invitees, 2047 (67%) participants were recruited to the study. Of these 2042 (99.8%) had their blood pressure measured for the study, 1723 (84.2%) had a previous blood pressure documented by their GP and 1207 (59.0%) underwent 24 hour ABPM. We excluded 128 from the ABPM analysis because of incomplete data. Nine hundred and thirty one (45%) study participants had satisfactory data for 24 hour ABPM, study and previous office blood pressures. The baseline characteristics of the full sample and those with all 3 measures are shown in Table 2.1. Those in the subsample were more likely to report a doctor diagnosis of hypertension and to report use of anti-hypertension medications, 36% versus 29% in the overall group for both. The groups were similar in other measured characteristics.

The mean office blood pressure was 134/79 mmHg and the mean study blood pressure was 134/83 mmHg. The mean daytime blood pressure was 131/77 mmHg and mean night-time blood pressure was 112/63 mmHg. The prevalence of hypertension ranged from 50-64% depending on the measurement method and threshold used, Table 2.2 and Figure 2.1. For ABPM the chosen threshold impacted on rates with the twenty four hour threshold resulting in lower prevalence rates and higher awareness, treatment and control rates compared to the other thresholds. Of those who were hypertensive by the office blood pressure, 31% (161/521) were coded as hypertensive in the electronic health record, and of these individuals 80% (120/150) were aware and 81% (128/159) were treated while 49% (63/128) were controlled based on the office blood pressure. (Data not shown, note some missing data for awareness and treatment questions).

Table 2.3 compares ABPM to the study blood pressure. A quarter to a third of individuals included in the study had their blood pressure status changed based on the daytime ABPM threshold. In treated individuals 21% (70/329) with elevated study blood pressure had normal blood pressure based on the daytime ABPM threshold. On the other hand 14% (45/329) were found to have uncontrolled hypertension by ABPM despite normal study blood pressure. In untreated individuals the prevalence of white coat hypertension was 11% (61/577) and masked hypertension was 13% (74/577). Variations are seen depending on the chosen threshold and treatment status, for example, untreated individuals had a higher rate of white coat hypertension (21%, 124/577), and a lower rate of masked hypertension (5%, 28/577), when the twenty four hour threshold was chosen.

Using daytime blood pressure measured by ambulatory blood pressure monitoring as the gold standard the sensitivity and specificity of the study blood pressure was 70% (95% CI 66% – 75%) and 76% (95% CI 72% – 79%) respectively, versus 56% (95% CI 51% – 61%) and 74% (95% CI 70 – 77%) for office blood pressure.

Table 2.1. Baseline characteristics		
	Total sample n =2047	Subsample with all 3 measures n=931
	n (%)/mean (+/-SD)	n (%)/mean (+/-SD)
Age	60 (+/-6)	60 (+/-5)
Male	1008 (49)	435 (47)
Smoking status		
Non-smoker	1002 (51)	470 (52)
Former smoker	671 (34)	283 (32)
Current smoker	292 (15)	146 (16)
Medical History		
Hypertension	567 (29)	329 (36)
Myocardial Infarction	49 (2)	24 (2.6)
Stroke	22 (1)	11 (1.2)
Heart failure	8 (0.4)	5 (0.6)
Diabetes	174 (9)	82 (9)
Anti-hypertensive medication	584 (29)	329 (36)
Cholesterol lowering medication	711 (36)	352 (38)
BMI	29 (+/-5)	29 (+/-5)
Waist circumference	97 (+/-13)	97 (+/-13)
LDL	3.2 (+/-0.9)	3.2 (+/-0.9)
Creatinine	71 (+/-16)	71 (+/-15)
ACR	0.7 (+/-2.1)	0.7 (+/-1.9)
eGFR	90 (+/-13)	89 (+/-13)
Office systolic	132 (+/-13)	134 (+/-15)
Office diastolic	78 (+/-9)	79 (+/-9)
Study systolic	130 (+/-17)	134 (+/-15)
Study diastolic	80 (+/-10)	83 (+/-10)
Daytime systolic		131 (+/-13)
Daytime diastolic		77 (+/-9)
Night-time systolic		112 (+/-14)
Night-time diastolic		63 (+/-8)
Twenty four systolic		124 (+/-13)
Twenty four diastolic		72 (+/-8)

Table 2.2. Hypertension prevalence, awareness, treatment and control

	Prevalence	Awareness	Treatment	Control Prevalent Cases	Control Treated Cases
		Total n=931			
	n/N (%)	n/N (%)	n/N (%)	n/N(%)	n/N (%)
Study Hypertension	557/931 (60)	314/528 (59)	329/549 (60)	151/557 (27)	151/329 (46)
Office Hypertension	521/931 (56)	313/492 (64)	329/512 (64)	161/521 (31)	161/329 (49)
Daytime Hypertension	568/931 (61)	316/535 (59)	329/553 (59)	179/568 (32)	179/329 (54)
Night-time Hypertension	479/931 (51)	311/450 (69)	329/469 (70)	205/479 (43)	205/329 (62)
Twenty four hour Hypertension	462/931 (50)	309/435 (71)	329/452 (73)	225/462 (49)	225/329 (68)
Daytime and/or night-time Hypertension	593/931 (64)	317/559 (57)	329/577 (57)	151/593 (25)	151/329 (46)

Due to missing data N in columns 2 and 3 do not represent n in column 1

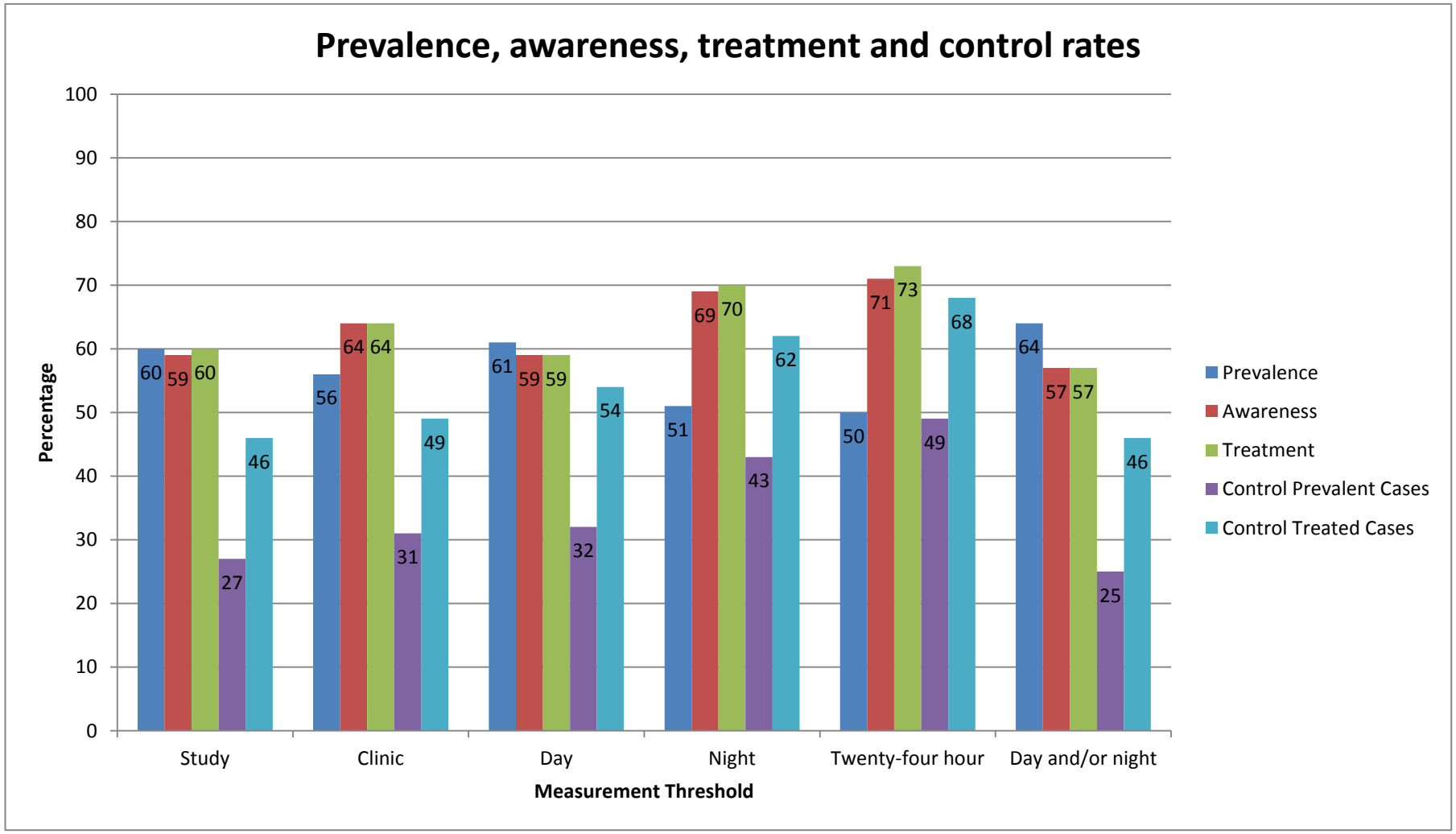


Figure 2.1. Prevalence, awareness, treatment and control rates of hypertension by different measurement thresholds

Table 2.3. Impact of ABPM on blood pressure classification

Total n=931 Treated n = 577 Untreated n = 329	Hypertensive by study BP and ABPM	Normotensive by study BP and ABPM	Study hypertension and ABPM normotension	Study normotension and ABPM hypertension
	n/N(%)	n/N(%)	n/N(%)	n/N(%)
Daytime threshold				
All	273/931 (29)	400/931 (43)	133/931 (14.5)	125/931 (13.5)
Treated	108/329 (33)	106/329 (32)	70/329 (21)	45/329 (14)
Untreated	156/577 (27)	286/577 (49)	61/577 (11)	74/577 (13)
Twenty four hour threshold				
All	181/931 (19)	469/931 (50)	225/931 (24)	56/931 (6)
Treated	81/329 (25)	128/329 (39)	97/329 (29)	23/329 (7)
Untreated	93/577 (16)	332/577 (58)	124/577 (21)	28/577 (5)
Night-time threshold				
All	194/931 (21)	444/931 (48)	212/931 (23)	81/931 (9)
Treated	91/329 (28)	118/329 (36)	87/329 (26)	33/329 (10)
Untreated	97/577 (17)	316/577 (55)	120/577 (21)	44/577 (8)
Combined day and night thresholds				
All	300/931 (32)	383/931 (41)	106/931 (11)	142/931 (15)
Treated	126/329 (38)	99/329 (30)	52/329 (16)	52/329 (16)
Untreated	164/577 (28)	279/577 (48)	53/577 (9)	81/577 (14)

Information on antihypertensive medication was missing for 25 subjects

2.5. Discussion

Our study demonstrates a high prevalence of hypertension ranging from 50-64% depending on the measurement method and blood pressure threshold chosen. The awareness rate varied from 57-71%, while 57-73% were treated. Control rates ranged from 25-49% in prevalent cases and 46-68% in those on treatment. These figures are similar to recent data from a nationally representative sample of community dwelling older Irish adults. Prevalence rate was 63.7%, awareness was 54.5%, 58.9% were on anti-hypertensive medication and 51.6% of those on treatment were controlled. (19) While these figures are suboptimal they do compare favourably internationally. A cross-sectional analysis from the PURE study demonstrated an awareness rate of 46.5% with 40.6% receiving treatment and 32.5% of those on treatment controlled across high, middle and low income countries. The rates for high income countries alone were 49%, 46.7% and 40.7%. (20) A study carried out in Spain demonstrated achieved blood pressure targets in 46.3% of those in the PRESCAP 2010 cross-sectional study. (21) Other work from the same study highlights therapeutic inertia where health care providers often do not initiate or intensify therapy appropriately during visits. This has improved from 2002 to 2010 but remains an issue. Treatment was modified in just 41.4% of those with uncontrolled blood pressure in 2010 improved from 18.3% in 2002. (22)

The prognostic importance of 24 hour ambulatory blood pressure is well known. (3, 4) It is important to examine the day and night blood pressure windows as the night-time blood pressure is recognised to be of greater prognostic significance. (23) Our findings confirm the clinical utility of ABPM in the management of those with hypertension. A large proportion of apparently normotensive participants were hypertensive by ABPM and vice versa. Gijon-Conde et al. recently demonstrated that a half of older apparently uncontrolled hypertensives were normotensive by ABPM. (24) Similarly in our study 21% of those on treatment with apparently uncontrolled hypertension by the study blood pressure were normotensive based on the daytime ABPM threshold. Banegas et al found a high rate of masked suboptimal blood pressure control in individuals with apparently well-controlled office blood pressure. (25) Masked uncontrolled hypertension was

also prevalent in our study at 14%. Therefore ABPM allows appropriate management of treatment. In untreated individuals white coat hypertension prevalence was 11% and masked hypertension prevalence was 13% using the daytime threshold. These are similar to rates in the IDACO database (26) Lovibond et al. have highlighted the potential cost savings with the use of ABPM due to more appropriately targeted therapy. (6) Also the use of 24 hour ABPM may help to overcome therapeutic inertia. The Rambler Study demonstrated that the use of 24 hour ABPM impacted on GP prescribing of anti-hypertensive medication in Ireland. (27)

The method of blood pressure measurement and threshold level chosen had an impact on prevalence rates in this study. The higher sensitivity of the study blood pressure over the office blood pressure likely reflects the use of standardised methods and highlights the importance of measuring office blood pressure according to guidelines to maximise accuracy. (8) Using the recommended 24 hour threshold resulted in more people being categorised as normotensive than using the daytime threshold level or a combination of both the daytime and night-time thresholds. There has been considerable debate over diagnostic thresholds for ABPM. (28) Blood pressure, and its relationship with cardiovascular disease, is continuous and the use of diagnostic thresholds therefore has limitations, which is highlighted by our study. (29) However clinicians do require diagnostic thresholds of normality for 24 hour ABPM when treating patients but they also need to be aware of the limitations of these thresholds.

This study offers an opportunity to reflect on the use of health information technology, and electronic health records in particular, in the management of hypertension. Accurate information is essential to facilitate optimal patient care, clinical governance and healthcare planning. This is important given recently highlighted barriers to medical coding (30) and present financial constraints within healthcare systems. While the impact of health information technology on time utilisation is mixed it has been shown to improve the delivery of preventative care, improve clinical monitoring and reduce medication errors. (31) GPs generally carry out more coding than their hospital colleagues. (32) In the Irish healthcare setting

individual GPs carry out their own coding with no healthcare policy incentives or supports to do so. In our study those who were coded as hypertensive in the electronic health record were more likely to be aware of and to be on treatment for their hypertension while control rates were similar to the overall office hypertension group. These increased awareness and treatment rates needs to be translated into better control rates. In the United Kingdom the introduction of incentivised care did result in improved recording and documentation of health indicators. (33-35) Policy makers need to realise the importance of investment in information technology and supports to facilitate coding in primary and secondary care which should in turn impact on hypertension awareness, treatment and control rates.

Our study is limited by selection bias, those with a previous diagnosis of hypertension or on anti-hypertensive medication were more likely to agree to undergo 24 hour ABPM. Of the total sample 29% self-reported a previous doctor diagnosis of hypertension versus 36% of those included in this sub-sample. Therefore our findings may not be generalisable to the general population and the ABPM results may be an over-estimate of actual prevalence. However table 2.3 highlights the potential impact of ABPM on the management of both treated and untreated individuals. Our results are based on 1 ABPM recording and it is recognised that night-time blood pressure profiles in particular are not fully reproducible which may again have an impact on prevalence when blood pressure is measured by ABPM. (36) The fact that blood pressure was measured using standardised methods in a large community based sample with the availability of previously documented office blood pressure and 24 hour ABPM are major strengths of this study. The availability of hypertension coding data is a further strength as it gives deeper insight into the challenges faced in the management of hypertension in daily clinical practice.

Conclusion:

This study highlights a number of important points. Firstly, hypertension remains a public health priority. It is highly prevalent, and treatment and control rates are

suboptimal. Secondly, the use of 24 hour ABPM may not hugely impact overall population prevalence rates but at an individual level it provides a more accurate assessment of blood pressure status and therefore refines diagnosis and management of hypertension and should be considered a vital tool in the provision of care. Finally, healthcare information technology should be fully utilised so patients can receive best practice care and the burden of hypertension and its public health consequences can be reduced.

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3. Night-time blood pressure and target organ damage: A comparative analysis of absolute blood pressure and dipping status

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3.1. Abstract

Introduction

The prognostic significance of abnormal circadian blood pressure (BP) patterns is well established. Research to date has focused on both nocturnal dipping and absolute night-time BP levels, however, which of these variables should be the primary target for therapy remains unclear. The aim of this study is to determine whether dipping status or absolute night-time BP levels have a stronger association with subclinical target organ damage (TOD).

Methods

The Mitchelstown Cohort was established to examine cardiovascular health in an adult population sample recruited from primary care. Night-time BP was categorised by dipping status. Subclinical TOD was defined as Cornell Product left ventricular hypertrophy (LVH) voltage criteria on ECG and urine albumin:creatinine ratio (ACR) ≥ 1.1 mg/mmol. Multi-variable logistic regression analysis was used to assess the association between night-time BP and TOD.

Results

Of 2047 participants, 1207 (response rate 59%), under-went 24 hour ambulatory BP monitoring. We excluded 161 studies due to incomplete data. Of 1046 participants, 178 (17%) had evidence of TOD. Each 10 mmHg rise in night-time systolic BP increased the odds of TOD. Odds ratio (OR) ACR ≥ 1.1 mg/mmol 1.5 (95% CI 1.2 – 1.8) and OR LVH 1.4 (95% CI 1.1 -1.8). In multi-variable analysis neither daytime systolic blood pressure or dipping status was associated with increased risk of target organ damage.

Conclusion

Absolute BP level rather than dipping status may be a superior early marker of risk associated with night-time BP. Interventional studies are required to determine whether there is a benefit in specifically targeting absolute night-time BP levels to prevent clinically important outcomes.

3.2. Introduction

Since the introduction of 24 hour ambulatory blood pressure monitoring (ABPM) in the 1960s (1-3), much has been learned regarding the diurnal blood pressure profile. The circadian variability of blood pressure has been recognised for a number of decades. (4) The blood pressure dipping phenomenon was first described in 1988. (5) A fall of 10% or more in night-time blood pressure relative to daytime is considered optimal or normal dipping. A fall of less than 10% constitutes non-dipping while a rise in night-time blood pressure is reverse dipping or riser pattern. Non-dipping and reverse dipping patterns are associated with higher prevalence of cardiovascular risk factors. (6)

There have been numerous observational studies on the prognostic importance of night-time blood pressure and a meta-analysis confirms that night-time systolic blood pressure is a stronger predictor of clinical endpoints than daytime systolic blood pressure. (7) The definition of nocturnal hypertension using ABPM is a mean night-time blood pressure value of ≥ 120/70 mmHg. (8)

Subclinical target organ damage is a prognostic marker for future cardiovascular events. It can be detected in the heart, kidneys, brain, vasculature and retina by various methods. (9) Many studies have addressed dipping status and subclinical target organ damage (10-15) while fewer have examined nocturnal hypertension and its association with cardiovascular risk factors and subclinical target organ damage. (16, 17) Few studies have compared the relative value of dipping status versus the absolute blood pressure with respect to the association with subclinical target organ damage. (17-19)

Microalbuminuria has been shown to be a marker of future cardiovascular events. One study demonstrated increased risk at albumin:creatinine ratio (ACR) of ≥ 0.58 mg/mmol (20) while a meta-analysis in 2010 demonstrated increased risk of mortality with ACR of ≥ 1.1 mg/mmol in population based cohorts. (21) An association with adverse cardiac mechanics has also been shown with microalbuminuria within the accepted normal range. (22) Electrocardiogram (ECG)

left ventricular hypertrophy (LVH) voltage criteria is a recognised independent predictor of prognosis. (23, 24)

The Mitchelstown Cohort examines cardiovascular health in an Irish adult primary care based population sample. The objective of this study is to examine the prevalence of risk factors in subjects with subclinical target organ damage and to determine if dipping status or absolute night-time blood pressure levels have a stronger association with subclinical target organ damage.

3.3. Methods

Study Population:

Details of the Mitchelstown Cohort have previously been described. (25) In summary, patients were recruited from a single large primary care centre, the Livinghealth Clinic in Mitchelstown, a town in the south of Ireland. The practice serves a population catchment area of approximately 20,000. Those registered with the clinic in the 50-69 year old age bracket were assigned a random number. Participants were invited based on this random number in batches of 150 until the target sample size of 2000 was achieved. Those who accepted the invitation were offered 24 hour ABPM at the time of their study visit.

Baseline Assessment:
Participants self-reported a previous doctor diagnosis of hypertension, myocardial infarction, stroke, heart failure and diabetes by questionnaire. They also self-reported anti-hypertensive and cholesterol lowering medication use as well as smoking status. The International Physical Activity Questionnaire (IPAQ) was used to measure physical activity levels. (26)

A blood sample was taken after an 8 hour fast. This was analysed for glucose, lipoprotein profile, glycosylated haemoglobin (HbA1C), full blood count and biochemical profile. Subjects brought a sample of the first urine they voided on the morning of their appointment. This was analysed for ACR, sodium and potassium.

Diabetes mellitus was defined as HbA1c level greater than or equal to 6.5% (27) or self-reported doctor diagnosis of diabetes. The CKD-EPI equation was used to estimate glomerular filtration rate (eGFR) from serum creatinine. (28, 29)

A trained researcher or nurse carried out the physical measures. Height was measured without foot-ware using a Seca Leicester portable height measure. Weight was measured using a portable electronic TANITA WB100MA weighing scale. Body mass index (BMI) was then calculated.

A 12 lead ECG was obtained in the standard manner using a Siemens – Eclipse 850i machine. All ECGs were recorded at a standard 10 mm/mv. ECGs were reviewed and coded for LVH using Cornell Product voltage criteria by Dr Anne Marie O'Flynn.

Blood Pressure Measurements:

After the participant had been in a relaxed seated position for at least 5 minutes three blood pressure readings were taken on the right arm, 1 minute apart, using the OMRON Model M7 digital automatic blood pressure monitor. The average of the second and third blood pressure reading was taken as the study blood pressure.

ABPM measurements were performed using the MEDITECH ABPM-05 and data was stored using the dabl ABPM system. The monitors were programmed to record the blood pressure every 30 minutes throughout the 24 hour period. Participants kept a diary of the times they went to bed and got up. Diary times were used to calculate mean daytime and night-time blood pressures. Mean 24 hour blood pressure was calculated as the mean of all the readings throughout the 24 four hour period. Also the daytime fixed interval was defined from 9am to 9pm and the night-time fixed interval from 1am to 6am. Both diary and fixed intervals were initially used to categorise dipping patterns.

Dipping status was defined as follows (6):

(1) Dipping pattern: 10 to 20% fall in night-time systolic blood pressure

(2) Non-dipping pattern: < 10% fall in night-time systolic blood pressure

(3) Extreme dipping pattern: > 20% fall in night-time systolic blood pressure

(4) Reverse dipping pattern: Rise in night-time systolic blood pressure

Subclinical Target Organ Damage:

Subclinical microvascular disease was defined by urine ACR ≥ 1.1 mg/mmol. (21)
Subclinical cardiac disease was defined by Cornell Product ECG voltage criteria for LVH i.e. SV3 + RaVL (+6 in women) X QRS duration ≥ 2440 mm x ms. (30)

Statistical Analysis:

Statistical analysis was carried out using Stata 12. Exploratory analysis was carried out for fixed and diary intervals. Mean blood pressures for each interval were calculated. Correlations between mean diary and fixed interval blood pressures were assessed using Pearson's Correlation Coefficient. Normally distributed continuous variables were compared between groups using ANOVA and linear regression. The Kruskall-Wallis test was used for non-normally distributed variables. Proportions of categorical variables were compared using the chi-square test.

The association of dipping status and absolute night-time blood pressure levels with subclinical target organ damage was assessed using multi-variable logistic regression. In the partially adjusted models adjustments were made for sex, age, diabetes, anti-hypertensive medication, smoking and BMI. Further adjustments for absolute blood pressure levels were made in the fully adjusted models ie. absolute daytime blood pressure was further adjusted for absolute night-time blood pressure and vice versa, and, dipping status was further adjusted for absolute night-time blood pressure. Model performance was evaluated using the likelihood ratio test.

Ethical Approval:

Ethical approval for the study was obtained from the Clinical Research Ethics Committee of the Cork teaching hospitals. The study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all study participants.

3.4. Results

Of the 3051 individuals invited to participate, 2047 completed the questionnaire and physical examination components of the baseline assessment (response rate: 67%). These 2047 participants were also invited to undergo ABPM and 1207 accepted (response rate: 59%). Of these, 128 were excluded due to incomplete recordings (<14 daytime and/or <7 night-time readings (31)), 26 were excluded because they had missing data on microalbuminuria or LVH and a further 7 were excluded from the diary interval analysis due to lack of diary documentation. The analysis therefore includes 1046 participants.

Exploratory analysis using fixed intervals was initially carried out. The correlations between mean day and night blood pressures using fixed intervals and diary intervals were very high with an R > 0.99. Concordance for dipping status between diary and fixed intervals was 89.6%. Diary intervals were used for all further analysis.

The baseline characteristics of the participants by presence of subclinical target organ damage are presented in Table 3.1. A greater proportion of those with target organ damage were on anti-hypertensive treatment, approximately one half versus one third of those without evidence of target organ damage. Blood pressure levels adjusted by age and sex are presented in Table 3.2. The night-time systolic blood pressure and night-time pulse pressure of those in the 3 categories of target organ damage was significantly different from those without target organ damage.

Night-time systolic blood pressure was significantly associated with markers of target organ damage in all models. In the unadjusted model there was an approximate 50% increase in odds of target organ damage, OR of ACR ≥ 1.1 mg/mmol was 1.6 (95% CI 1.4 -1.8) and OR of LVH was 1.4 (95% CI 1.2 – 1.6) for each 10 mmHg rise in night-time systolic blood pressure. This association was somewhat attenuated in the fully adjusted model which included daytime systolic blood pressure, OR of ACR ≥ 1.1 mg/mmol was 1.5 (95% CI 1.2 – 1.8) and OR LVH 1.4 (95% CI 1.1 -1.8) (Table 3.3). The diastolic blood pressure was not associated with increased risk of LVH in any model. Adding daytime blood pressure to the

model did not significantly improve the fit. Daytime systolic blood pressure levels were also associated with target organ damage in unadjusted models. However the odds ratios were smaller than those for night-time blood pressure, OR of ACR ≥ 1.1 mg/mmol was 1.4 (95% CI 1.3 – 1.6) and OR of LVH was 1.2 (95% CI 1.0 -1.4) for each 10 mmHg rise in daytime systolic blood pressure. Findings were attenuated in adjusted models, and when night-time systolic blood pressure was also included in the models, were no longer statistically significant. (Table 3.3)

Of 576 categorised as dippers, 28% had persistent elevation in their night-time blood pressure. Of 229 non-dippers, 51% had normal night-time blood pressure (Figure 3.1). Mean blood pressures by dipping status and target organ damage are shown in Figure 3.2. In the unadjusted and partially adjusted regression models extreme dippers had reduced odds of ACR ≥ 1.1 mg/mmol, while reverse dippers had increased odds of LVH. However in the fully adjusted model which included absolute night-time systolic blood pressure the findings for reverse dippers and LVH were attenuated and no longer statistically significant (Table 3.4). When the absolute night-time blood pressure was added the model fit significantly improved. The analysis was also carried out using dipping as a continuous variable with similar findings. (Supplemental tables 3.5 and 3.6, Appendix 3).

Stratified Analysis:

The analysis was repeated after stratifying participants based on their treatment status. There were 350 (33.5%) treated participants and 670 (64%) untreated participants. Information on treatment status was missing for 26 (2.5%) participants. Night-time systolic blood pressure had a greater association with ACR ≥ 1.1 mg/mmol than daytime systolic blood pressure in both treated and untreated individuals. However in untreated individuals both night-time and daytime systolic blood pressures had similar associations with LVH and the statistical significance of the association for LVH was attenuated in fully adjusted models. (Supplemental tables 3.7 and 3.8, Appendix 3)

With respect to dipping status treated reverse dippers had increased risk of LVH in unadjusted and adjusted models (OR 4.9 (95% CI 1.0 – 23.3, p = 0.046 in fully

adjusted models including night-time systolic blood pressure). Untreated extreme dippers had reduced odds of ACR ≥ 1.1 mg/mmol in unadjusted and partially adjusted analysis. This was not statistically significant in fully adjusted models including night-time systolic blood pressure. (Supplemental tables 3.9 and 3.10, Appendix 3)

Table 3.1. Baseline characteristics by target organ damage

Total n = 1046	No LVH and ACR < 1.1 mg/mmol n =870	ACR ≥ 1.1 mg/mmol only n = 106	LVH only n = 56	LVH and ACR ≥ 1.1 mg/mmol n = 14	P-value
	n (%)/Mean (+/-SD)	n (%)/Mean (+/-SD)	n (%)/Mean (+/-SD)	n (%)/Mean (+/-SD)	
Age	59 (+/-5)	60 (+/-6)	62 (+/-5)	61 (+/-5)	<0.001*
Male	392 (45)	55 (52)	31 (55)	7 (50)	0.3
Education category					
Primary	210 (26)	41 (40)	19 (36)	7 (50)	
Secondary	414 (50)	38 (37)	30 (57)	4 (29)	
Tertiary	196 (24)	23 (23)	4 (7)	3 (21)	0.001*
IPAQ category					
Low	408 (49)	56 (57)	29 (56)	10 (77)	
Moderate	245 (30)	28 (28)	11 (22)	3 (23)	
High	175 (21)	15 (15)	11 (22)	0 (0)	0.2
Smoking Status					
Non-smoker	448 (53)	55 (53)	24 (45)	8 (57)	
Former smoker	257 (31)	35 (33)	23 (43)	5 (36)	
Current smoker	136 (16)	15 (14)	6 (11)	1 (7)	0.5

Continued…

Table 3.1. Continued

Medical History					
Hypertension	268 (32)	43 (43)	28 (53)	8 (57)	0.004*
Myocardial Infarction	16 (2)	5 (5)	4 (7)	1 (7)	0.07
Stroke	8 (1)	1 (1)	2 (4)	0 (0)	0.5
Heart failure	3 (0.4)	1 (1)	1 (2)	1 (8)	0.01*
Diabetes mellitus	72 (8)	14 (13)	5 (9)	4 (29)	0.03*
Medication					
Anti-hypertensive	269 (32)	43 (42)	31 (55)	7 (50)	0.001*
Cholesterol lowering	316 (37)	46 (44)	20 (36)	6 (43)	0.7
BMI (kg/ m^2)	29 (+/-5)	30 (+/-5)	29 (+/-5)	31 (+/-6)	0.004*
Waist circumference (cm)	96 (+/-13)	101 (+/-15)	98 (+/-13)	103 (+/-16)	0.004*
LDL (mmol/l)	3.2 (+/-0.9)	3.1 (+/-0.9)	3.4 (+/-0.7)	2.8 (+/-0.9)	0.1
Creatinine (µmol/l)	71 (+/-15)	71 (+/-17)	72 (+/-15)	77 (+/-29)	0.6
ACR (mg/mmol)	0.4 (+/-0.2)	3.0 (+/-3.8)	0.4 (+/-0.2)	7.0 (+/-11)	<0.001*
eGFR (mls/min)	89 (+/-12)	90 (+/-14)	88 (+/-12)	85 (+/-21)	0.5
Cornell Product (mm x ms)	1374 (+/-444)	1523 (+/-462)	3046 (+/-646)	3210 (+/-914)	<0.001*

LVH = Left ventricular hypertrophy; ACR = Albumin:creatinine ratio; SD = Standard deviation; IPAQ = International Physical Activity Questionnaire; BMI = Body mass index; LDL = Low density lipoprotein; eGFR = estimated glomerular filtration rate

* Statistically significant

Table 3.2. Blood Pressure levels by Target Organ Damage

	No LVH and ACR < 1.1 mg/mmol	ACR ≥ 1.1 mg/mmol only	LVH only	LVH and ACR ≥ 1.1 mg/mmol
Total n = 1046	n =870	n = 106	n = 56	n = 14
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Study systolic	133 (3)	140 (4) **	139 (3)	147 (4)*
Study diastolic	82 (0.5)	85 (0.5)*	84 (0.4)	88 (0.4)*
Day systolic	130 (3)	137 (3) ***	133 (3)	144 (3) **
Day diastolic	77 (3)	80 (3) ***	76 (3)	79 (2)
Night systolic	111 (3)	120 (3) ***	116 (3)*	130 (3) ***
Night diastolic	62 (2)	69 (2) ***	63 (2)	66 (2)
24hour systolic	123 (3)	131 (3) ***	127 (3)	139 (3) ***
24hour diastolic	72 (3)	75 (3) ***	71 (3)	74 (2)
Day pulse pressure	53 (3)	57 (3) **	57 (3)	65 (3) ***
Night pulse pressure	48 (3)	53 (3) ***	53 (3)*	64 (3) ***

LVH = Left ventricular hypertrophy; ACR = Albumin:creatinine ratio; SD = Standard deviation
Linear regression models adjusted by sex and age with p values compared to those with no target organ damage
*** p <0.001
** p <0.005
* p < 0.05

Table 3.3. Logistic regression results for absolute blood pressure and target organ damage

	ACR ≥ 1.1 mg/mmol		ECG LVH	
	Odds Ratio (95%CI)	P-value	Odds Ratio (95%CI)	P-value
Night-time SBP (+10 mmHg)	1.6 (1.4 – 1.8)	<0.001*	1.4 (1.2 – 1.6)	<0.001*
Partially adjusted	1.5 (1.3 – 1.7)	<0.001*	1.3 (1.1 – 1.5)	0.002*
Fully adjusted	1.5 (1.2 – 1.8)	<0.001*	1.4 (1.1 – 1.8)	0.009*
Night-time DBP (+5 mmHg)	1.3 (1.2 – 1.5)	<0.001*	1.1 (0.9 – 1.2)	0.5
Partially adjusted	1.3 (1.2 – 1.5)	<0.001*	1.0 (0.9 – 1.2)	0.6
Fully adjusted	1.3 (1.1 – 1.6)	0.001*	1.1 (0.9 – 1.4)	0.4
Daytime SBP (+10 mmHg)	1.4 (1.3 – 1.6)	<0.001*	1.2 (1.0 – 1.4)	0.018*
Adjusted	1.3 (1.2 – 1.6)	<0.001*	1.2 (1.0 – 1.4)	0.09
Fully adjusted	1.0 (0.8 – 1.2)	0.9	0.9 (0.7 – 1.2)	0.5
Daytime DBP (+5 mmHg)	1.2 (1.1 – 1.3)	<0.001*	1.0 (0.8 -1.1)	0.6
Adjusted	1.2 (1.1 – 1.4)	0.001*	1.0 (0.9 – 1.2)	0.9
Fully adjusted	1.0 (0.9 – 1.2)	0.8	0.9 (0.8 – 1.1)	0.5
Twentyfour hour SBP (+10 mmHg)	1.5 (1.3 – 1.8)	<0.001*	1.3 (1.1 – 1.5)	0.001*
Adjusted	1.5 (1.3 – 1.7)	<0.001*	1.3 (1.0 – 1.5)	0.017*
Twentyfour hour DBP (+5 mmHg)	1.3 (1.1 – 1.4)	<0.001*	1.0 (0.9 – 1.1)	0.9
Adjusted	1.3 (1.1 – 1.5)	<0.001*	1.0 (0.9 – 1.2)	0.8

ACR = Albumin:creatinine ratio; LVH = Left ventricular hypertrophy; CI = Confidence interval;
SBP = systolic blood pressure; DBP = diastolic blood pressure
Adjusted = sex, age, diabetes, anti-hypertensives, smoking, BMI
Fully adjusted = sex, age, diabetes, anti-hypertensives, smoking, BMI plus daytime blood pressure further adjusted for night-time blood pressure and vice versa
* Statistically significant

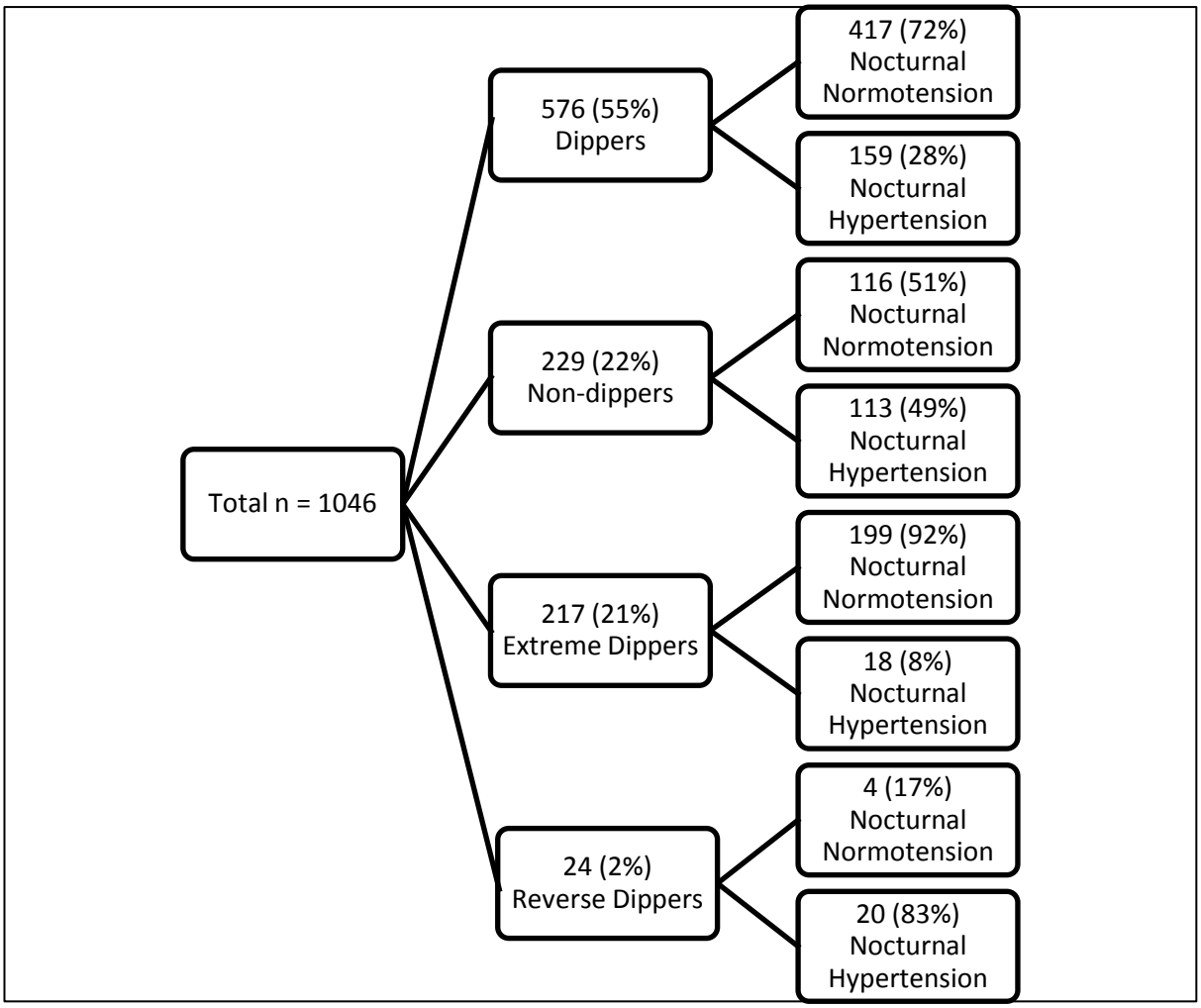


Figure 3.1. Night-time Blood Pressure Status by Dipping Status

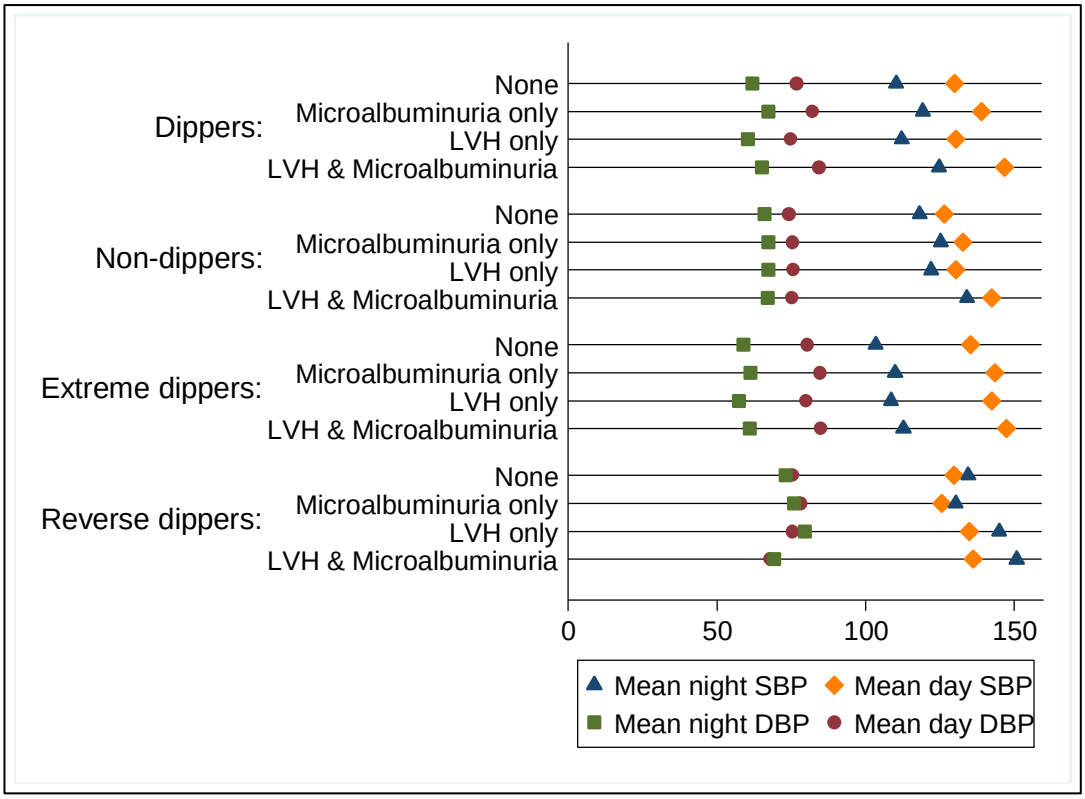


Figure 3.2. Mean blood pressures by dipping status and target organ damage

LVH = Left ventricular hypertrophy; SBP = systolic blood pressure; DBP = diastolic blood pressure

Table 3.4. Logistic regression results for dipping status and target organ damage

	ACR ≥ 1.1 mg/mmol	ECG LVH	ACR ≥ 1.1 mg/mmol		ECG LVH	
	n = 120	n = 70	OR (95%CI)	P-value	OR (95%CI)	P-value
	n	n				
Dippers	67	34	1		1	
Non-dippers	34	18	1.3 (0.8 – 2.1)	0.2	1.4 (0.8 – 2.5)	0.3
Extreme dippers	14	12	0.5 (0.3 – 0.9)	0.03*	0.9 (0.5 – 1.8)	0.8
Reverse dippers	5	6	2.0 (0.7 – 5.5)	0.2	5.3 (2.0 – 14.3)	0.001*
Partially adjusted						
Dippers			1		1	
Non-dippers			1.2 (0.8 – 2.0)	0.4	1.1 (0.6 – 2.0)	0.9
Extreme dippers			0.5 (0.3 – 1.0)	0.04*	0.9 (0.4 – 1.8)	0.7
Reverse dippers			1.8 (0.6 -5.0)	0.3	3.8 (1.4 – 11.1)	0.01*
Fully adjusted						
Dippers			1		1	
Non-dippers			0.9 (0.6 – 1.5)	0.7	0.9 (0.4 – 1.7)	0.7
Extreme dippers			0.7 (0.4 – 1.4)	0.3	1.1 (0.5 – 2.2)	0.9
Reverse dippers			0.6 (0.2 – 2.0)	0.4	2.1 (0.7 – 7.0)	0.2

ACR = Albumin:creatinine ratio; LVH = Left ventricular hypertrophy; OR = Odds ratio; CI = Confidence interval
Partially adjusted = sex, age, diabetes, anti-hypertensives, smoking, BMI
Fully adjusted = sex, age, diabetes, anti-hypertensives, smoking, BMI plus further adjusted for night-time systolic blood pressure
* Statistically significant

3.5. Discussion

This large primary care based population study describes the association between nocturnal blood pressure and subclinical target organ damage. Our findings demonstrate a significant association between the absolute night-time systolic blood pressure and LVH and ACR. The absolute daytime systolic blood pressure was associated with target organ damage in unadjusted and adjusted analysis but the odds ratios were less than those for night-time systolic blood pressure. When both daytime and night-time systolic blood pressures were included in the same models only the findings for night-time systolic blood pressure remained statistically significant. There was no association between dipping status and target organ damage in fully adjusted models. Cuspidi et al found target organ damage to be prevalent in those with nocturnal hypertension independent of dipping status. (16) Also, in dippers and non-dippers with nocturnal hypertension the prevalence of subclinical target organ damage was similar. (18) Tsioufis et al found the absolute night-time blood pressure to be better than dipping status for predicting both cardiovascular and renal outcomes in 2 systematic reviews. (32, 33) De La Sierra and colleagues reported on the prevalence of cardiovascular risk factors in patients classified by dipping and nocturnal hypertension status. (34) Those with both abnormalities had higher prevalence of additional cardiovascular risk factors. Non-dipping was better associated with reduced renal function and history of previous cardiovascular events while the absolute blood pressure was better associated with microalbuminuria. They suggest that non-dipping may be a marker of more advanced disease.

An ECG and spot urine sample are recommended as first line in the evaluation of those with hypertension. (9, 35) Both are readily available and can be measured at low cost. Therefore these were chosen as the tools to assess target organ damage in our study. The greater association of absolute night-time systolic blood pressure over daytime systolic blood pressure and dipping status with these markers of target organ damage suggest the absolute night-time systolic blood pressure is the most important parameter of the ABPM report. In addition the finding in the stratified analysis of a greater association of reverse dipping with LVH in treated

individuals adds support to the suggestion made by De La Sierra and colleagues that non-dipping may be a marker of more advanced disease.

Therefore, categorising night-time blood pressure by dipping status alone may be an inadequate approach. In our analysis there was no significant association between dipping status and subclinical target organ damage in fully adjusted models while there was for absolute blood pressure level. While a dipping pattern is considered optimal (6) we have demonstrated that dippers are a heterogeneous group. The majority of dippers had normal night-time blood pressure but over a quarter had nocturnal hypertension and therefore are likely to be at increased cardiovascular risk long-term.

A recent review discusses the complexities of dipping status versus the apparently more straightforward approach of categorising by absolute blood pressure values, with particular focus on isolated nocturnal hypertension. (36) Also, defining nocturnal blood pressure by absolute cut-offs rather than dipping status has been found to be more reproducible on follow-up ABPM. (37) Our work and evidence from the literature (18, 32, 33, 36, 37) supports the use of categories based on absolute blood pressures. It is more straightforward and it may be easier to apply in daily clinical practice. There is particularly relevant given the increasing emphasis on 24 hour ABPM in the diagnosis of hypertension. (38)

We didn't find any association between diastolic blood pressure and LVH. However, day and night pulse pressures were significantly associated with LVH in unadjusted and adjusted models which may explain this finding (Supplemental table 3.11, Appendix 3). Our sample had a large proportion of extreme dippers (21%) and over 50% of the sample had a daytime pulse pressure of 50 mmHg or more with over 40% having a night-time pulse pressure of 50 mmHg or more (data not shown). A high pulse pressure has been shown to predict cardiovascular outcomes in older adults. (39, 40) Also, a wide pulse pressure can be considered a marker for central arterial stiffness (41) and therefore subclinical target organ damage.

The use of fixed intervals or diary intervals doesn't affect the prognostic value of ABPM. (42-45) We used diary rather than fixed intervals and though this reduced

the numbers in the final analysis, carrying out the analysis using fixed intervals did not change the results (data not shown).

There are a number of limitations to our study. The cross-sectional design means we do not know the direction of the association between night-time blood pressure and target organ damage and reverse causality is a possibility. Much of the data was collected by questionnaire and as a result is subject to recall bias. However, studies have shown that self-reported history of doctor diagnosis is a valid tool for epidemiological research, in particular for hypertension, diabetes, stroke and myocardial infarction. (46)

The overall sample was similar to the background population on demographic characteristics based on census data. (25) However, it is a GP based sample which could result in bias as those who are registered with a GP may be sicker than those from a true population sample. On the other hand they could be more health conscious than those who fail to register. This selection bias could in turn impact on participant recall, for example those who had a previous ABPM with their GP may be more inclined to self-report a diagnosis of hypertension, or similarly, those with a previous history of cardiovascular disease will have had increased contact with health services and be more aware of risk factors. This may in turn have led to them being more inclined to agree to undergo ABPM for the study. Indeed those who agreed to undergo 24 hour ABPM were a higher risk group. Compared to those who didn't undergo ABPM they were a year older (60 v 59 years, $p < 0.001$), more likely to have a doctor diagnosis of hypertension (35% v 21%, $p < 0.001$), more likely to report being on anti-hypertensive medication (35% v 22%, $p < 0.001$), had a higher BMI (29 kg/m^2 v 28 kg/m^2, $p < 0.001$), a lower eGFR (89 mls/min v 91 mls/min, $p = 0.001$) and a higher Cornell Product (1511 mm x ms v 1406 mm x ms, $p < 0.001$). Also, a higher proportion of women underwent ABPM (53 % v 47%, $p = 0.007$).

Our results are based on 1 ABPM recording and it is recognised that night-time blood pressure profiles are not fully reproducible. (47) The major strengths of our

study lie in the population based sample and the relatively large number undergoing 24 hour ABPM.

Conclusion:

Based on our findings the absolute night-time systolic blood pressure is the most important parameter to consider when assessing 24 hour ABPM and may be a superior early marker of cardiovascular risk. Further research should focus on the use of absolute blood pressure categories and their application in clinical practice. Chronotherapy (the administration of antihypertensive medications in the evening to reduce night-time blood pressure) may have a benefit in reducing cardiovascular events (48, 49), however randomised controlled trials are necessary to clearly demonstrate if specifically targeting mean night-time blood pressure or restoring the normal dipping profile reduces clinically important outcomes. Our results suggest the absolute night-time systolic blood pressure rather than non-dipping status should be the primary therapeutic target for these studies.

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4.1. Isolated nocturnal hypertension and subclinical target organ damage: A systematic review

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4.1.1. Abstract

Introduction

Isolated nocturnal hypertension (INH) is associated with greater mortality and cardiovascular events compared to those who are normotensive. Subclinical target organ damage (TOD) is a prognostic marker for cardiovascular events. Our objective is to systematically summarise evidence on the association between INH and subclinical TOD.

Methods

Observational population studies were considered. INH was defined as night-time blood pressure (BP) ≥ 120/70 mmHg with daytime BP < 135/85 mmHg. We systematically searched Pubmed, EMBASE and the Cochrane Library. Abstracts were reviewed by 2 assessors. Potentially eligible articles were compared with inclusion criteria.

Results

The search yielded 954 titles, 13 abstracts were selected for review and 4 articles fulfilled inclusion criteria. INH was associated with higher ambulatory arterial stiffness index (0.4 unit v 0.35 unit, p <0.05), pulse wave velocity (16.2 m/s v 14.7 m/s, p<0.05), central (140.4% v 134.0%, p < 0.05) and peripheral (82.6% v 76.5%, p <0.01) augmentation index in a Chinese study. In the same population there was no association with left ventricular hypertrophy (LVH) documented by electrocardiogram. Central aortic diastolic BP (75.9 mmHg v 69.4 mmHg, p =0.02) was higher in those with INH in a Swedish study. An American study demonstrated higher left ventricular mass (153.46 g v 136.16 g, p = 0.01) and greater odds of LVH (OR 3.03, 95% CI 1.02 – 9.05) in unadjusted analysis. There was no association with proteinuria.

Discussion

Evidence is inconclusive regarding the association between INH and subclinical TOD. Future research should focus on trying to elucidate the mechanisms that

generate INH and contribute to the higher mortality associated with this BP pattern.

4.1.2. Introduction

Twenty four hour ambulatory blood pressure monitoring (ABPM) enables blood pressure to be recorded throughout the day and night away from the medical setting as a person carries out their usual activity. This provides more reliable assessment of blood pressure. (1) The National Institute of Health and Care Excellence in the United Kingdom now recommend 24 hour ABPM for the diagnosis of hypertension (2), while the JNC 7 and the European guidelines recommend 24 hour ABPM in certain clinical situations such as suspected white coat hypertension, drug resistance, hypotensive symptoms and others. (1, 3) The European guidelines also give assessment of night-time blood pressure a specific indication for ABPM.

Since the introduction of 24 hour ABPM much has been learned regarding the diurnal blood pressure profile. The prognostic importance of night-time blood pressure is recognised. (4) The dipping phenomenon and nocturnal hypertension have been the focus of much research. (5-8) Isolated nocturnal hypertension was first described in 2007 and describes elevated night-time blood pressure in the presence of normal daytime blood pressure i.e. night-time systolic blood pressure ≥ 120 mmHg and/or night-time diastolic blood pressure ≥ 70 mmHg with daytime blood pressure of < 135/85 mmHg on ABPM. (9) Fan et al have demonstrated a higher risk of mortality and cardiovascular events in those with isolated nocturnal hypertension. (10)

Subclinical target organ damage is a prognostic marker for future cardiovascular events. (11-14) It is recognised that the presence of organ damage refines cardiovascular risk assessment. (15, 16) It is recommended that all patients with hypertension undergo a physical examination to assess for organ damage. It can be considered an intermediate in the development of cardiovascular disease and can be detected in the heart, kidneys, brain, vasculature and retina by various methods. (1)

Given the greater prognostic significance of night-time blood pressure we postulate that those with isolated nocturnal hypertension have more target organ damage. The objective of this paper is to systematically review available evidence on the

association between isolated nocturnal hypertension and subclinical target organ damage.

4.1.3. Methods

Inclusion Criteria:

Study type

Original observational population based research studies.

Study Population

Those recruited to population based observational studies undergoing 24 hour ABPM and an assessment of any target organ.

Definition of isolated nocturnal hypertension

Elevated night-time systolic blood pressure ≥ 120 mmHg and/or night-time diastolic blood pressure ≥ 70 mmHg and normal daytime blood pressure (< 135/85 mmHg) measured by ABPM.

Comparison group

Those with isolated nocturnal hypertension compared to a group who were normotensive by day and night.

Subclinical target organ damage

Recognised markers of subclinical damage in any target organ.

Search Methods:

We developed the search strategy for PubMed and adapted it for use in the other databases. We systematically searched Pubmed, EMBASE and the Cochrane Library. The following search terms were used as keywords and/or MESH terms: (((((isolated OR masked) AND (nocturnal OR night-time OR nighttime OR night time) AND hypertension)) OR (((Hypertension) AND "Blood Pressure Monitoring, Ambulatory") AND "Circadian Rhythm"))) AND ((((((((((((((((((microalbuminuria) OR (Left AND ventricular AND hypertrophy)) OR (Left AND ventricular AND mass)) OR electrocardio*) OR echocardio*) OR (arterial AND stiffness)) OR (augmentation AND index)) OR (Pulse AND wave AND velocity))

OR (carotid AND ultrasound)) OR (carotid AND intima AND media AND thickness)) OR CIMT) OR (asymptomatic AND carotid AND stenosis)) OR (ankle AND brachial AND index)) OR (flow AND mediated AND dila*)) OR (endothelial AND dysfunction)) OR (((((((magnetic AND resonance AND imaging)) OR (computed AND tomography)) OR MRI) OR CT)) AND (((white AND matter AND hyperintensities)) OR (white AND matter AND lesions)))) OR retinopathy) OR (retinal AND photography)) OR (Coronary AND calcium AND score))) OR ((end OR target) AND organ AND (damage OR disease)))

Potentially relevant articles were identified. Duplicates were removed. Two independent reviewers reviewed selected abstracts and the full text of relevant papers was obtained. These were compared against the inclusion criteria and assessed for quality using guidelines recommended by Hayden et al for quality appraisal in systematic reviews of prognostic studies, (17) (Table 4.1.1). The references of relevant articles were searched for further potential studies.

There was one non-English article included. The authors were contacted for an English translation which wasn't available. The article was translated with an online translation programme and this was checked with a native speaker.

Because of heterogeneity in the outcomes assessed, pooling of results or meta-analysis was not carried out.
(Appendix 3. MOOSE Checklist for Search Strategy)(18)

4.1.4. Results

Figure 4.1.1 demonstrates the results of the literature search. The electronic search yielded 954 titles. On screening the titles 18 were considered potentially relevant. Duplicates were removed and 13 abstracts were selected for review. Of these 5 were excluded and the full text of 8 articles was obtained. A further 4 were excluded at this point. One was a duplicate study, 1 was a review article and 2 didn't assess isolated nocturnal hypertension.

Four studies are included in this narrative review. The design of these are summarised in Table 4.1.2. No single measure of subclinical target organ damage

was assessed by all 4 studies. The number of patients with isolated nocturnal hypertension in each study varied from 15 to 81 (Table 4.1.3).

Li et al first described isolated nocturnal hypertension in 2007. (9) They studied a population based sample from rural China. Of 677 participants, 74 (10.9%) had isolated nocturnal hypertension. They excluded patients who had either a normal daytime or night-time blood pressure and were also on anti-hypertensive medications, as they couldn't ascertain what category they would have fitted into in the untreated condition.

They assessed arterial properties using radial and central augmentation indexes, ambulatory arterial stiffness index and brachial-ankle pulse wave velocity. They found all markers of arterial stiffness were significantly higher in those with isolated nocturnal hypertension compared to those who were normotensive with adjustments applied for sex, age, height and pulse rate (Table 4.1.3).

Lu et al examined the relationship between isolated nocturnal hypertension and left ventricular hypertrophy documented by electrocardiography (ECG) in the same Chinese population. (19) They used Sokolow-Lyon voltage and Cornell Product criteria to define left ventricular hypertrophy.

They found that those with isolated nocturnal hypertension had higher Sokolow-Lyon voltage and Cornell Product compared to normotensive participants. However following adjustment for sex, age, BMI, alcohol, smoking status, cholesterol, fasting glucose and anti-hypertensive medications these findings were no longer statistically significant. The prevalence of left ventricular hypertrophy by cut-offs was not statistically different between those with isolated nocturnal hypertension and normotension (23.6% v 17.4%, $p = 0.24$) (Table 4.1.3).

Wijkman et al examined isolated nocturnal hypertension in middle aged people with type 2 diabetes from 15 different primary healthcare centres in Sweden. (20) They defined isolated nocturnal hypertension as clinic blood pressure < 130/80 mmHg, daytime ABPM blood pressure < 135/85 mmHg and night-time ABPM blood pressure ≥ 120/70 mmHg. Of a total sample of 414, 15 (3.6%) patients fulfilled this definition. They assessed arterial properties by measuring the central augmentation

index and carotid femoral pulse wave velocity. Left ventricular mass index was determined by echocardiography.

They found no statistical difference in central pulse pressure, central augmentation index or aortic pulse wave velocity. Similarly there was no statistically significant difference in left ventricular mass between the isolated nocturnal hypertensive group and the normotensive group (Table 4.1.3).

Ogedegbe et al examined isolated nocturnal hypertension in an African American sample of the Jackson Study. (21) The sample size was 425 and 81 (19.1%) had isolated nocturnal hypertension. The authors excluded those on anti-hypertensive therapy. Two-D and m-mode echocardiography was carried out and left ventricular mass and mass index calculated. Spot urinary albumin:creatinine ratio (ACR) was used to document proteinuria.

They found higher left ventricular mass in those with isolated nocturnal hypertension in unadjusted models and in models adjusted for age and gender. This was not seen in fully adjusted models which included diabetes, cholesterol, metabolic syndrome, urinary sodium:creatinine ratio, daytime pulse pressure and alcohol. The odds ratio (OR) for left ventricular mass index ≥ 51 g/m^2 was greater in unadjusted models for the isolated nocturnal hypertension group (OR 3.03, 95% CI 1.02 – 9.05). However, the adjusted models were not statistically significant (OR 2.58, 95% CI 0.75 – 8.94). This was the only study to examine proteinuria. There was no increased risk of proteinuria in those with isolated nocturnal hypertension in either unadjusted or adjusted analysis (Table 4.1.3).

Table 4.1.1. Quality assessment of included studies

Author	Li et al	Lu et al	Wijkman et al	Ogedegbe et al
Study Participation The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results.	Yes	Yes	Partly Isolated nocturnal hypertension study sample characteristics not adequately described	Yes
Study Attrition Loss to follow-up (from sample to study population) is not associated with key characteristics (i.e. the study data adequately represent the sample), sufficient to limit potential bias	Partly No description of characteristics of non-responders	Partly No information on response rate and non-responders	Partly No information on response rate and non-responders	Yes
Prognostic Factor Measurement /Outcome Measurement The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias	Yes	Yes	Yes	Yes
Confounding Measurement and Account Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Partly	Partly	No	Yes
Analysis The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results	Yes	Yes	Yes	Yes

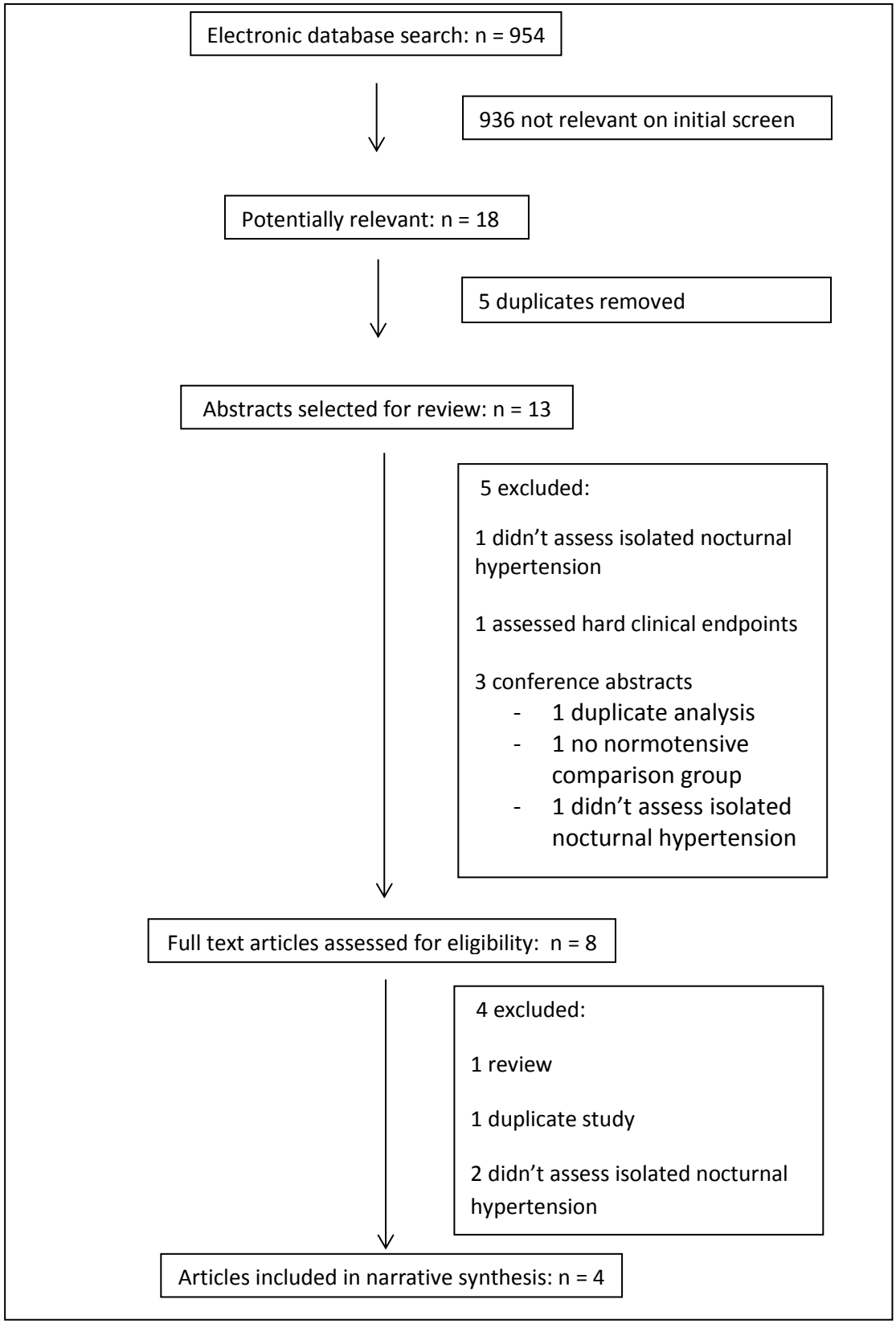


Figure 4.1.1 Flow chart of the systematic review search

Table 4.1.2. Design of included studies

Author, publication date	Setting	Participants	Study Design	Sampling	Cases Excluded	Subclinical cardiovascular disease measure	Confounders
Li et al, 2007	14 villages in the JingNing county, a rural area approx. 500 km south of Shanghai, China	Population based participants aged > 12 years	Cross-sectional	2059 villagers invited to participate 1490 (72.4%) gave informed consent 733 (49%) underwent ABPM	17 excluded due to lack of valid ABPM readings 14 excluded due to lack of measurement of arterial properties 25 excluded with either a normal day-time or night-time blood pressure on antihypertensive treatment	Central and peripheral augmentation index Ambulatory arterial stiffness index Pulse wave velocity	Sex, age, body height and pulse rate
Lu et al, 2008	14 villages in the JingNing county, a rural area approx. 500 km south of Shanghai, China	Population based participants aged > 12 years	Cross-sectional	Total numbers screened not stated 697 underwent ABPM	8 under 18 years excluded 17 excluded due to lack of valid ABPM readings 25 excluded with either a normal day-time or night-time blood pressure on antihypertensive treatment	Sokolow Lyon and Cornell Product LVH criteria on 12 lead ECG	Sex, age, BMI, alcohol, smoking status, cholesterol, fasting glucose and anti-hypertensive medications

Continued…

Table 4.1.2. Continued							
Wijkman et al, 2009	15 different primary healthcare centres in the counties of Östergötland and Jönköping, Sweden	Patients with type 2 diabetes aged 55-65 years	Cross-sectional	Participants in the Cardiovascular Risk factors in Patients with Diabetes – a Prospective study in Primary care (CARDIPP) Total numbers screened not stated 414 underwent ABPM	314 excluded with clinic blood pressure ≥ 130/80 mmHg 25 excluded due to elevated daytime ambulatory blood pressure	Central aortic BP Central pulse pressure Central augmentation index Pulse wave velocity LVMI by echocardiography	No adjustment for confounders
Ogedegbe et al, 2013	Jackson, Mississippi, USA	Non-institutionalised African American adults aged 21 – 94 years	Cross-sectional	Participants of the Jackson Heart Study were invited to undergo 24 hour ABPM 5301 invited to participate 1150 (21.6%) agreed	327 due to lack of valid ABPM readings 398 excluded due to antihypertensive use	LV mass and LVMI by echocardiography Urinary albumin:creatinine ratio > 30 mg/g	Age, gender, diabetes, cholesterol, metabolic syndrome, urinary sodium:creatinine ratio, daytime pulse pressure and alcohol

ABPM = Ambulatory Blood Pressure Monitoring; INH = Isolated nocturnal hypertension; BP = blood pressure ; LV = left ventricular; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index

Table 4.1.3. Results of included studies

Author, publication date	Number of participants INH/Total(%)	Results		Summary of Findings
Li et al, 2007	74/677 (10.9%)	Central augmentation index, % Peripheral augmentation index, % Ambulatory arterial stiffness index, units Brachial-ankle pulse wave velocity, m/s	140.4 v 134.0, p < 0.05 82.6 v 76.5, p < 0.01 0.4 v 0.35, p < 0.05 16.2 v 14.7, p < 0.05	INH group showed significant increases in all 4 measured indexes of arterial stiffness compared to normotensive group
Lu et al, 2008	72/647 (11.1%)	Sokolow Lyon and Cornell Product LVH criteria	23.6% v 17.4%, p = 0.24	No difference in prevalence of LVH in those with INH from normotensives
Wijkman et al, 2009	15/414 (3.6%)	Central aortic diastolic BP, mmHg	75.9 v 69.4, p = 0.02	Central aortic diastolic BP higher in those with INH compared to normotensives
		Central aortic systolic BP, mmHg Central pulse pressure Central augmentation index Aortic pulse wave velocity, m/s LVMI	116.6 v 109.8, p = 0.15 Figures not provided Figures not provided 10.3 v 9.3, p = 0.06 Figures not provided	No difference in central aortic systolic BP, central pulse pressure, central augmentation index, aortic pulse wave velocity or LVMI
Ogedegbe et al, 2013	81/425 (19.1%)	Unadjusted LV mass (g) Age and gender adjusted LV mass (g) Multivariable adjusted LV mass (g)	153.46 v 136.16, p = 0.01 152.32 v 137.42, p = 0.02 147.54 v 136.32, p = 0.12	Higher LV mass in the INH group compared to normotensive group in unadjusted and age and gender adjusted model. Not seen in fully adjusted models.
		Unadjusted LVH (OR LVMI ≥ 51g/m^2) Age and gender adjusted LVH (OR LVMI ≥ 51g/m^2) Multivariable adjusted LVH (OR LVMI ≥ 51g/m^2)	3.03 (95% CI 1.02 – 9.05, p = 0.05) 2.89 (95% CI 0.96 – 8.69, p = 0.06) 2.58 (95% CI 0.75 – 8.94, p = 0.13)	INH group greater odds of LVH in unadjusted model only
		Unadjusted proteinuria (OR UACR > 30mg/g) Age and gender adjusted proteinuria (OR UACR > 30mg/g) Multivariable adjusted proteinuria (OR UACR > 30mg/g)	3.34 (95% CI 0.91 – 12.28, p = 0.07) 3.29 (95% CI 0.89 – 8.22, p = 0.08) 1.95 (95% CI 0.46 – 8.22, p = 0.37)	No increased risk of proteinuria

INH = isolated nocturnal hypertension; BP = blood pressure; LV = left ventricular; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; OR = Odds Ratio; UACR = Urinary Albumin Creatinine Ratio

4.1.5. Discussion

There is relatively little literature regarding the association of isolated nocturnal hypertension with subclinical target organ damage. Available evidence is inconclusive on this subject. Just 4 papers satisfied the inclusion criteria. No single measure of target organ damage was assessed by all of these. The studies included were cross-sectional in design and each had some weaknesses which further limits the capacity to draw inference.

The Li et al study from China suggests an association with increased arterial stiffness but the issue of residual confounding remains in this study. They did not adjust for potential important confounders such as diabetes and renal disease. This isn't addressed and is a potential source of bias. They do discuss other potential limitations such as the reproducibility of isolated nocturnal hypertension and the use of short fixed time intervals rather than diary intervals to analyse the ABPM results.

On the other hand, Lu et al didn't find any increased risk of left ventricular hypertrophy documented by ECG in the same population. They do adjust for confounders, but diabetes and renal disease are omitted. They discuss the limited reproducibility of night-time blood pressure and also acknowledge the limited sensitivity and specificity of the ECG. However, despite the recognised weaknesses of the ECG (22), it is a cheap investigation which is readily available to most practitioners and is a recognised independent predictor of prognosis, (12, 23) which makes it important to consider in research questions.

The Wikjman et al study found the markers of arterial stiffness to be no different from those in the normotensive group. The small numbers included in this analysis limits interpretation. Also, limited information is provided on the study sample. We contacted the study authors for this information but this was unavailable.

The primary focus of this paper was to evaluate the impact of masked nocturnal hypertension, defined as a clinic blood pressure < 130/80 mmHg and night-time blood pressure ≥ 120/70 mmHg, on arterial stiffness and central blood pressure. The numbers included in the analysis for isolated nocturnal hypertension were

small as they extended the definition for masked nocturnal hypertension to include those who had normal daytime blood pressure on ABPM. The clinic blood pressure is not usually included in the definition for isolated nocturnal hypertension. They may have had higher numbers in their analysis had they used the usual definition. As a result of the small numbers adjustment for confounding was not possible in the isolated nocturnal hypertension analysis.

Also, those on anti-hypertensive medication were not excluded which could also have had an impact on blood pressure categorisation. This is addressed in the discussion by the authors. A number of other limitations are also considered including the use of a single ABPM recording, the potential impact of obstructive sleep apnoea on night-time blood pressure and the influence of sleep depth which they couldn't address.

In the Ogedegbe et al study, just 21.7% of invited Jackson Study participants agreed to undergo ABPM. The authors do address this potential source of bias and report the differences between those who did and did not undergo 24 hour ABPM. They were younger (53.2 v 57.1 years, $p < 0.01$) and more likely to be male (67.9% v 61.6%, $p < 0.01$). They also raise the issue of the sample size which may not have had sufficient power to detect differences between isolated nocturnal hypertension and normotension. The limited reproducibility of night-time blood pressure patterns and the fact that their results are based on one ABPM recording are discussed. Sleep quality and the impact of this on night-time blood pressure are also considered.

Generalisability of the findings of all the studies is a potential issue when the numbers in each study who actually underwent 24 hour ABPM is considered. The only study to address this is that by Ogedegbe et al as outlined above. Li et al do provide the numbers screened and those undergoing ABPM but fail to discuss the potential impact of this on the generalisability of their findings. Lu et al and Wijkman et al fail to provide the total numbers screened for inclusion in their studies and there is no discussion on the generalisability of the findings. All authors acknowledge the potential limited reproducibility of the isolated nocturnal hypertension pattern. Analysis in all 4 of the studies was based on 1 ABPM

recording. Night-time blood pressure patterns are not always reproducible although using absolute values rather than dipping status was found to result in more reproducible results. (24) Li et al carried out a follow-up study on 30 participants with isolated nocturnal hypertension with a mean follow-up time of 3.5 years. They found that 33% still had isolated nocturnal hypertension, 33% developed day-night hypertension, while 27% were normotensive and 7% had isolated daytime hypertension. (9)

Categorising a normally distributed continuous variable such as blood pressure impacts power to detect real associations. (25, 26) However, clinicians need a diagnostic reference with thresholds that define normal and abnormal when managing patients. Therefore, from a practical perspective, there are advantages to using categories. The numbers of patients with isolated nocturnal hypertension in the 4 studies were not large which further reduces power to detect a true association.

Studies that included participants taking anti-hypertensive medications were not excluded from the review. Anti-hypertensive medications potentially influence blood pressure categorisation. Those on treatment may demonstrate isolated nocturnal hypertension but in the untreated state they may have demonstrated a sustained hypertension pattern. This is only really relevant for the Wikjman et al study as the Chinese studies excluded those on medications with either a normal daytime or night-time blood pressure and the Ogedegbe et al study excluded those on medications altogether. Given the small numbers in the Wikjman et al study this is unlikely to have had an impact on the overall findings.

The prevalence of isolated nocturnal hypertension is 6% in Western Europe and 7.9% in Eastern Europe which is significantly lower than that in Asia (10.9% in China and 10.2% in Japan), South Africa (10.2%) (27) or in African Americans (19.1%). (21) The mechanisms underlying the differences in prevalence rates and the increased risk associated with isolated nocturnal hypertension are not clear. Documenting changes in the cardiovascular system prior to the development of clinical disease may help us to further understand these potential mechanisms. Blunted sodium

metabolism, obstructive sleep apnoea and reverse causality have been proposed. (27) The outcomes assessed in this review can be considered surrogate markers. The use of surrogate markers is not without controversy. (28, 29) They need to accurately measure disease and predict future events while measurement needs to be meticulous.(30) However, the measures used in the 4 studies in this review all have a weight of literature behind them and are recognised as valid tools. (30, 31)

The strengths of this review include a focused question with relative paucity of information and it identifies an evidence gap as the question isn't answered by the available literature. The inclusion of non-English articles makes it likely that all relevant studies were identified. However, as with any systematic review there is always the possibility of missed studies.

Conclusion:

The evidence is inconclusive with respect to the association between isolated nocturnal hypertension and subclinical target organ damage. Future research should focus on elucidating the mechanisms that generate isolated nocturnal hypertension and the higher mortality risk associated with it demonstrated by Fan et al. (10) The reproducibility of this particular blood pressure pattern also needs to be elucidated. Specifically, research should focus on whether normalising isolated nocturnal hypertension in prospective studies reduces cardiovascular events.

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4.2. Isolated nocturnal hypertension and subclinical target organ damage in the Mitchelstown Cohort Study: A short report

Anne Marie O'Flynn

Ronan J Curtin

Patricia M Kearney

4.2.1. Introduction

Isolated nocturnal hypertension was first described in 2007 and describes elevated night-time blood pressure with normal daytime blood pressure. (1) In a systematic review of the literature we found the association between isolated nocturnal hypertension and subclinical target organ damage to be inconclusive. (2) However those with this blood pressure phenotype have higher mortality risk compared to those who are normotensive as demonstrated by the IDACO investigators. (3) Given the knowledge deficit identified in our systematic review the aim of this study is to examine the association between isolated nocturnal hypertension and target organ damage in the Mitchelstown Cohort Study.

4.2.2. Methods

Details of the Mitchelstown Cohort have previously been described. (4)

Blood Pressure Assessment:
After the participant had been in a relaxed seated position for at least 5 minutes three blood pressure readings were taken on the right arm, 1 minute apart, using the OMRON Model M7 digital automatic blood pressure monitor. The average of the second and third blood pressure reading was taken as the study blood pressure.

Those recruited were also offered 24 hour ambulatory monitoring and 1207 (59%) agreed. ABPM measurements were performed using the MEDITECH ABPM-05 and data was stored using the dabl ABPM system. The monitors were programmed to record the blood pressure every 30 minutes throughout the 24 hour period. Participants kept a diary of the times they went to bed and got up. Diary times were used to calculate mean daytime and night-time blood pressures. Based on the ABPM results the sample was divided into 4 groups: normotension, isolated nocturnal hypertension, isolated daytime hypertension and day-night hypertension. We excluded those on treatment.

Target Organ Damage:

Subjects brought a sample of the first urine they voided on the morning of their baseline appointment. This was analysed for albumin:creatinine ratio (ACR) which was used to document subclinical microvascular disease. A 12 lead ECG was obtained in the standard manner using a Siemens – Eclipse 850i machine. All ECGs were recorded at a standard 10 mm/mv. ECGs were reviewed and coded for Cornell Product voltage criteria by Dr Anne Marie O'Flynn (i.e. SV3 + RaVL (+6 in women) X QRS duration ≥ 2440 mm x ms). This was used to document subclinical cardiac disease.

Statistical Analysis:

Statistical analysis was carried out using Stata 12. Baseline characteristics are presented as absolute numbers with corresponding percentages for categorical variables and as means with standard deviations for continuous variables. Normally distributed continuous variables were compared between groups using ANOVA. The Kruskall-Wallis test was used for non-normally distributed variables. Proportions of categorical variables were compared using the chi-square test. The association between blood pressure patterns and target organ damage was assessed by ANOVA and linear regression. Multivariable models were adjusted for sex, age, diabetes mellitus, smoking and BMI.

4.2.3. Results

Of 1207 who underwent ABPM, 128 were excluded due to incomplete recordings (<14 daytime and/or <7 night-time readings), 26 were excluded because they had missing data on microalbuminuria or LVH and a further 7 were excluded from the diary interval analysis due to lack of diary documentation. In addition we excluded those on treatment or those whose treatment status was unclear from the questionnaire. The analysis therefore includes 685 participants.

Of 685 participants included, 29 (4%) had isolated nocturnal hypertension and 399 (58%) were normotensive by day and night. There were 121 (18%) participants with isolated daytime hypertension and 136 (20%) with sustained day-night hypertension. The baseline characteristics by these blood pressure phenotypes are

presented in table 4.2.1. Blood pressure levels of the different groups are presented in table 4.2.2.

In unadjusted analysis only those with sustained day-night hypertension had a statistically significant higher ACR compared to those who were normotensive (1.21 mg/mmol v 0.52 mg/mmol, $p < 0.001$). Findings were similar in sex and age adjusted and multivariable adjusted models. The difference between those with isolated nocturnal hypertension and normotension was not statistically significant (1.01 mg/mmol v 0.52 mg/mmol, $p = 0.1$). Both those with sustained day-night hypertension and those with isolated daytime hypertension had statistically higher Cornell Product voltage than those who were normotensive. The findings for isolated nocturnal hypertension were not statistically significant (1525 mm x ms v 1332 mm x ms, $p = 0.08$). Findings were similar in sex and age adjusted and multivariable adjusted models (Table 4.2.3).

Table 4.2.1. Baseline characteristics by blood pressure status in untreated participants

n=685	Normotensive n = 399 (58%) mean(+/-SD)/n(%)	Isolated Daytime Hypertension n = 121 (18%) mean(+/-SD)/n(%)	Isolated Nocturnal Hypertension n = 29 (4%) mean(+/-SD)/n(%)	Day-night Hypertension n = 136 (20%) mean(+/-SD)/n(%)	P-value
Age	59 (+/-5)	58 (+/-6)	59 (+/-5)	60 (+/-6)	0.8
Male	161 (40)	61 (50)	19 (66)	84 (62)	<0.001*
Education category					
Primary	91 (24)	32 (28)	6 (21)	33 (25)	0.2
Secondary	203 (54)	54 (47)	13 (45)	58 (43)	
Tertiary	82 (22)	28 (25)	10 (34)	43 (32)	
IPAQ category					
Low	166 (43)	62 (54)	12 (41.5)	72 (56)	0.02*
Moderate	122 (32)	33 (29)	5 (17)	34 (26)	
High	95 (25)	19 (17)	12 (41.5)	23 (18)	
Smoking Status					
Non-smoker	224 (57.5)	46 (39)	17 (61)	65 (49)	0.02*
Former smoker	103 (26.5)	47 (40)	9 (32)	43 (32)	
Current smoker	63 (16)	24 (21)	2 (7)	26 (19)	

Continued…

Table 4.2.1. Continued					
Medical History					
Hypertension	9 (2)	6 (5)	2 (7)	13 (10)	0.03*
Myocardial Infarction	2 (0.5)	0 (0)	1 (3)	1 (0.7)	0.4
Stroke	3 (0.8)	1 (0.8)	0 (0)	0 (0)	0.9
Heart failure	1 (0.3)	1 (0.9)	0 (0)	0 (0)	0.8
Diabetes	18 (5)	5 (4)	12 (9)	4 (14)	0.05
Medication					
Cholesterol lowering	104 (26)	35 (29)	7 (24)	41 (30)	0.8
BMI (kg/m^2)	27 (+/-4)	29 (+/-4)	29 (+/-4)	30 (+/-4)	<0.001*
Waist circumference (cm)	92 (+/-12)	98 (+/-11)	97 (+/-11)	102 (+/-13)	<0.001*
LDL (mmol/l)	3.4 (+/-0.8)	3.3 (+/-0.8)	3.4 (+/-1.0)	3.4 (0.9)	0.8
Creatinine (µmol/l)	69 (+/-13)	69 (+/-13)	75 (+/-15)	73 (+/-14)	0.01*
eGFR (mls/min)	91 (+/-11)	93 (+/-11)	89 (+/-10)	89 (+/- 12)	0.05
ACR (mg/mmol)	0.5 (+/-0.9)	0.5 (+/-0.5)	1.0 (+/-2.3)	1.2 (+/-3.1)	<0.001*
Cornell Product (mm x ms)	1332 (+/-557)	1480 (+/-623)	1524 (+/-400)	1585 (+/-549)	<0.001*
ECG LVH	15 (4)	8 (7)	0 (0)	10 (7)	0.2

* Statistically significant

Table 4.2.2. Blood pressure levels				
n=685	Normotensive mean(+/-SD)	Isolated Daytime Hypertension mean(+/-SD)	Isolated Nocturnal Hypertension mean(+/-SD)	Day-night Hypertension mean(+/-SD)
Clinic systolic BP mean (SD)	124 (+/-14)	142 (+/-14)***	132 (+/-11)**	148 (+/-16)***
Clinic diastolic BP mean (SD)	78 (+/-9)	87 (+/-8)***	83 (+/-8)**	91 (+/-8)***
Day systolic mean (SD)	121 (+/-8)	140 (+/-6)***	128 (+/-5)***	148 (+/-13)***
Day diastolic mean (SD)	73 (+/-7)	83 (+/-6) ***	78 (+/-5) ***	87 (+/-9) ***
Night systolic mean (SD)	103 (+/-8)	110 (+/-7) ***	121 (+/-5) ***	129 (+/-12) ***
Night diastolic mean (SD)	58 (+/-5)	61 (+/-5) ***	70 (+/-5) ***	73 (+/-8) ***
24hr systolic mean (SD)	114 (+/-8)	129 (+/-6) ***	125 (+/-4) ***	141 (+/-11) ***
24hr diastolic mean (SD)	67 (+/-6)	75 (+/-5) ***	75 (+/-5) ***	82 (+/-8) ***
Significance of the difference with the normotensive comparison group **<0.01 ***<0.001				

Table 4.2.3. Target organ damage by blood pressure status

	Normotensive	Isolated Daytime Hypertension	Isolated Nocturnal Hypertension	Day-night Hypertension
Urine ACR n = 678	**(mg/mmol)**	**(mg/mmol)**	**(mg/mmol)**	**(mg/mmol)**
Model 1: Unadjusted	0.52	0.49	1.01	1.21***
Model 2: Sex and age adjusted	0.52	0.49	1.01	1.21***
Model 3: Multivariable adjusted	0.53	0.50	1.04	1.20***
Cornell Product Voltage n = 684	**(mm x ms)**	**(mm x ms)**	**(mm x ms)**	**(mm x ms)**
Model 1: Unadjusted	1332	1480*	1525	1586***
Model 2: Sex and age adjusted	1332	1479**	1525	1586***
Model 3: Multivariable adjusted	1327	1468*	1520	1585**

Model 1: unadjusted
Model 2: adjusted for sex and age
Model 3: adjusted for sex, age, diabetes mellitus, smoking and BMI

Significance of the difference with the normotensive comparison group
*<0.05
**<0.01
***<0.001

4.2.4. Discussion

This short report did not find a statistically increased risk of target organ damage documented by ACR and ECG Cornell Product voltage criteria in those with isolated nocturnal hypertension compared to those who are normotensive. However this was a small study with just 29 participants fulfilling the criteria for isolated nocturnal hypertension so statistical power is a significant issue, as it was in the 4 studies included in the systematic review. Isolated nocturnal hypertension is more prevalent in in those of Asian and African ethnicity. (1) Therefore future research into this blood pressure profile should focus on such populations to avoid further underpowered studies.

We excluded those on anti-hypertensive medication from this analysis as treatment status has a confounding effect on night-time blood pressure profiles as already discussed. The prevalence of isolated nocturnal hypertension in the untreated group included in this analysis was 4% versus 9% in those who were on treatment. This highlights the potential significance of this confounding effect. Therefore we recommend that future research examining isolated nocturnal hypertension exclude those on anti-hypertensive medication.

Conclusion:

The result of this analysis does not address the knowledge deficit identified in our systematic review and further research is required. This research should focus on untreated individuals in geographical areas where isolated nocturnal hypertension is most prevalent.

4.2.5. References

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5. Imaging protocols and quality control methods for speckle tracking echocardiography and carotid intima media thickness acquisition and analysis

Anne Marie O'Flynn

Emily Ho

Ronan J Curtin

Patricia M Kearney

5.1. Abstract

Introduction

Valid measurement of target organ damage in epidemiological studies is essential to avoid measurement bias. We designed an epidemiological study to assess the association of night-time systolic blood pressure with ultrasound markers of vascular and cardiac damage. The aim of this study is to describe the quality assurance measures applied in order to minimise potential measurement error, including description of the ultrasound image acquisition protocol, device and personnel evaluation.

Methods

Carotid ultrasound and cardiac echocardiogram image acquisition and measurement protocols are described. Details of ultrasound phantom scans are described. Ten healthy volunteers underwent a carotid ultrasound twice within the same week by the same investigator. Carotid intima media thickness (CIMT) was measured from the acquired images by the same investigator for intra-observer reproducibility. An independent investigator analysed the second set of images for inter-observer reproducibility. The images of 10 outpatients undergoing routinely indicated echocardiography were analysed by speckle tracking analysis. All echocardiograms were carried out by the same operator. Speckle tracking analysis was carried out offline to measure global longitudinal strain (GLS). This was repeated by the same investigator for intra-observer reproducibility. An independent investigator also analysed the images for inter-observer reproducibility. Intra- and inter-observer reproducibility was assessed by Bland Altman Plots and intra-class correlation coefficients.

Results

The intra-observer intra-class coefficient (ICC) for CIMT was 0.91 (95% CI 0.69 – 0.98). The inter-observer ICC for CIMT was 0.97 (95% CI 0.88 -0.99). The intra-observer ICC for GLS was 0.93 (95% CI 0.70 - 0.98). The inter-observer ICC for GLS was 0.86 (95% CI 0.51 – 0.96).

Discussion

We have demonstrated good intra- and inter-observer reproducibility of CIMT and GLS results with standardised imaging and reading protocols. Our findings suggest our measurement methods are valid and suitable to be applied in an epidemiological study.

5.2. Introduction

The cardiovascular disease continuum highlights the importance of documenting target organ damage and clinical trials have clearly demonstrated that intervening on risk factors interrupts the continuum and improves clinical outcomes. (1) Documenting subclinical stages of organ damage helps to identify individuals who will get greater benefit from risk reduction therapy. (2) These intermediate surrogate markers must be meticulously measured to ensure accuracy of data.

Carotid intima media thickness (CIMT) measurement by ultrasound is used to document subclinical disease in the carotid vasculature. There is evidence for the validity of CIMT as a surrogate measure of atherosclerotic disease. (3, 4) CIMT is recognised to be associated with the incidence of myocardial infarction and stroke. (5, 6) The detection of plaques is also important as it improves the predictive performance of CIMT. (7)

Cardiac echocardiography can detect subclinical changes in the heart such as left ventricular hypertrophy, left atrial enlargement and early diastolic dysfunction. More recently the development of speckle tracking echocardiography has also allowed the detection of subtle myocardial dysfunction. (8) The principle of speckle tracking echocardiography is the scattering of sound waves by the myocardium which generates speckles specific for an area of myocardium. These blocks of speckles or kernels can be tracked from frame to frame and provide information on deformation or contraction and relaxation (Figure 5.1). Global Longitudinal Strain (GLS) is a measure of the myocardial systolic deformation over the longitudinal axis measured from the apical views.

Measurement bias occurs when measurement methods systematically over- or under-estimate the actual measurement. We designed a study to assess the association of night-time blood pressure with surrogate markers of cardiovascular disease including CIMT and GLS in a sample of participants of the Mitchelstown Cohort Study. (9) Quality assurance for such a study is essential to ensure valid and reliable measurement of target organ damage without systematic error. The aim of this manuscript is to describe the quality control measures applied in our study in

order to minimise potential measurement error, including description of the ultrasound image acquisition protocol, device and personnel evaluation.

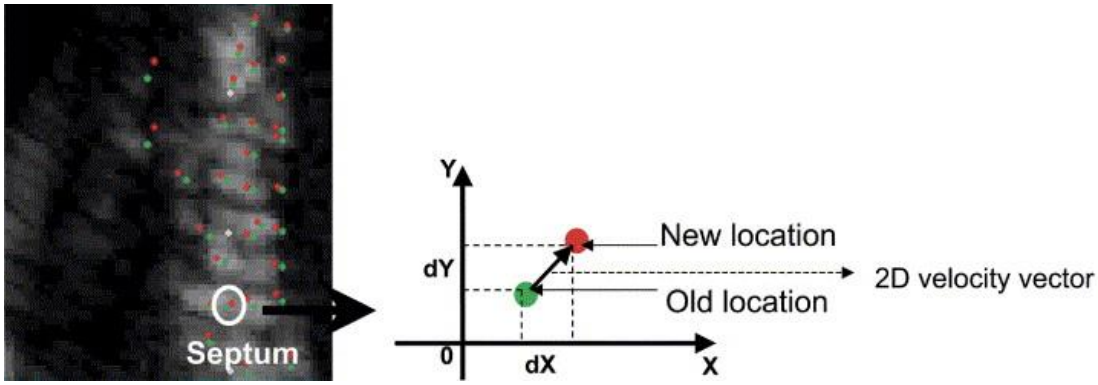


Figure 5.1. Tracking of acoustic speckles from frame to frame. Thomas H. Marwick. JACC 2006. Reproduced with permission. (10)

5.3. Methods

Carotid ultrasound protocol:

A Philips Cx50 ultrasound machine and a L12-3 3 to 12 MHz extended frequency range linear array transducer were used for image acquisition. Subjects were examined in the supine position with their head tilted to the opposite side. A Meijer arc was used to ensure optimal positioning (Figure 5.2). All imaging was carried out at 4 cm depth where possible. A full transverse and longitudinal scan of the extra-cranial carotid arteries was carried out to assess for the presence of atherosclerotic plaques. Ultrasound images of the distal portion of the far wall of both common carotid arteries were obtained for assessment of CIMT. Far wall still frames were taken from anterior, lateral and posterior angles. Three still frame images were taken from each angle. (11)

The acquired images were saved using digital media and measurement was carried out offline using Philips QLAB cardiac and vascular ultrasound quantification border detection software version 9.0. This software automatically detects the CIMT borders but does allow manual manipulation in cases of suboptimal detection. Measurements were made on the 3 still frame images from each angle over a length of 1 cm at the distal common carotid artery (CCA) (Figure 5.3). The reference point for the commencement of the measurement was where the CCA began to

dilate prior to the bifurcation. A mean measurement from the 3 frames for each angle was obtained. The mean of these means was obtained to give the measurement for each side. The mean of the left and right was used to estimate the CIMT. The presence of plaques in the extra-cranial carotid arteries was recorded as a binary variable. A plaque was defined according to the Mannheim Consensus as a focal protrusion into the blood vessel ≥ 50% of the thickness of the adjacent IMT or focal IMT > 1.5 mm. (12)



Figure 5.2. The Meijer Arc. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER et al. Journal of the American Society of Echocardiography 2008. Reproduced with permission. (11)



Figure 5.3. Measurement of CIMT at distal 1 cm of CCA

Cardiac echocardiography protocol:

A Philips iE33 ultrasound machine and a S5-1 1 to 5 MHz extended frequency range phased array transducer were used for image acquisition. A standard echocardiogram protocol was used. Parasternal long and short axis, apical 4-, 2- and 3-chamber views were obtained. Optimisation of frame rate was carried out by reducing the sector depth and width and was above 50 frames/sec in all cases.

The acquired images were saved using digital media and GLS analysis was carried out offline from apical 4-, 2- and 3- chamber views using Philips QLAB cardiac and vascular ultrasound quantification software version 9.0. The region of interest was selected by the identification of 3 points, one on either side of the mitral valve annulus and one at the apex for each view. Adequate tracking was confirmed visually and if deemed inadequate the region of interest was edited. GLS average was obtained from 17 ventricular segments represented on a bulls-eye plot from apical 4-, 2- and 3- chamber views. (Figure 5.4)

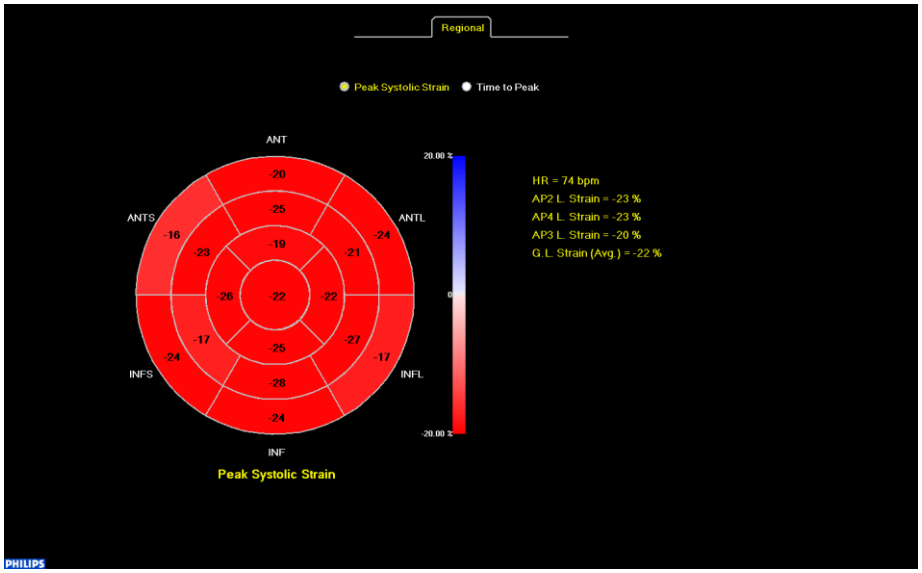


Figure 5.4. Bullseye plot of global longitudinal strain averaged from apical 4-, 2- and 3-chamber views

Ultrasound Phantom scans:

Routine equipment maintenance was carried out during the scanning period. An ultrasound phantom mimics the acoustic properties of tissues and enables measurement of ultrasound system accuracy and performance in a standardised manner. For this study a general purpose urethane ultrasound phantom (CIRS Tissue Simulation & Phantom Technology Model 042 (Figure 5.5)) was used to assess ultrasound image quality and distance calibration. It consists of series of wires embedded in tissue mimicking gel. Image uniformity was inspected. Vertical and horizontal target distances were measured. Lateral and axial resolution targets were inspected. Follow-up phantom scans were performed at 6 month intervals throughout the study period to ensure there was no drift in results.



Figure 5.5. General purpose urethane ultrasound phantom

Intra- and inter-observer reproducibility:
Ten healthy volunteers had a carotid ultrasound twice within the same week in 2013 carried out by the same investigator (AMOF) who analysed both sets of images and compared them for intra-observer reproducibility. An independent investigator (EH) analysed the second set of images for inter-observer reproducibility.

Ten outpatients undergoing routinely indicated echocardiography in Cork University Hospital in 2013 were asked to consent to have their images analysed by speckle tracking analysis. All echocardiograms were carried out by the same operator (IB). Speckle tracking analysis was carried out offline by AMOF and repeated for intra-observer reproducibility. An independent investigator (EH) also analysed the images for inter-observer reproducibility.

AMOF received formal training in CIMT image acquisition. IB is accredited in transthoracic echocardiography by the British Society of Echocardiography. Both AMOF and EH had formal training in CIMT and speckle tracking echocardiography analysis.

Statistical analysis:
All statistical analysis was carried out using Stata 12. Mean CIMT and GLS measured by AMOF and EH were compared and inspected visually by scatter plots. Mean differences were compared using paired t-tests. Exploratory analysis for intra- and inter-observer reproducibility was then carried out by Bland Altman Plots. Intra-

class correlation coefficients for intra- and inter-observer reproducibility were also calculated.

Ethical approval for the study was obtained from the Clinical Research Ethics Committee of the Cork Teaching Hospitals and all participants provided written informed consent.

5.4. Results

The phantom scan results are presented in Table 5.1. There was no drift in results over the study period. CIMT results of the healthy volunteers who underwent carotid ultrasound are presented in Table 5.2. GLS results for the patients undergoing echocardiography are presented in Table 5.3.

Scatter plots of the CIMT and GLS results are presented in figures 5.6-5.9. The mean difference in CIMT between examinations observed by investigator 1 was -0.0004mm ($p = 1.0$). The mean difference in CIMT between observers was 0.004 mm ($p = 0.2$). The mean difference in GLS observed by investigator 1 was -0.82% ($p = 0.07$). The mean difference in GLS between observers was -1.04% ($p = 0.09$).

Bland Altman Plots for intra- and inter-observer reproducibility are presented in figures 5.10-5.13. The intra-observer intra-class correlation coefficient (ICC) for CIMT was 0.91 (95% CI 0.69 – 0.98). The inter-observer ICC for CIMT was 0.97 (95% CI 0.88 -0.99). The intra-observer ICC for GLS was 0.93 (95% CI 0.70 - 0.98). The inter-observer ICC for GLS was 0.86 (95% CI 0.51 – 0.96).

Table 5.1. Phantom ultrasound scan results			
Cx50 ultrasound machine and L12-3 linear array transducer			
	Scan 1	Scan 2	Scan 3
Uniformity	Consistent	Consistent	Consistent
Vertical distance	2.01 cm	2.01 cm	2.01 cm
Horizontal distance	1.88 cm	1.88 cm	1.88 cm
Axial resolution	0.5-1 mm	0.5-1 mm	0.5-1 mm
Lateral resolution	3 mm	3 mm	3 mm
iE33 ultrasound machine and S5-1 1 phased array transducer			
	Scan 1	Scan 2	Scan 3
Uniformity	Consistent	Consistent	Consistent
Vertical distance	2.01 cm	2.01 cm	2.01 cm
Horizontal distance	2 cm	2 cm	2 cm
Axial resolution	0.5-1 mm	0.5-1 mm	0.5-1 mm
Lateral resolution	2 mm	2 mm	2 mm

Table 5.2. CIMT results					
Subject	**Sex**	**Age**	**CIMT mm (Investigator 1)**	**CIMT mm (Investigator 1)**	**CIMT mm (Investigator 2)**
1	Female	28	0.4628	0.4381	0.4136
2	Male	19	0.4767	0.4939	0.4961
3	Male	26	0.5861	0.5411	0.5511
4	Male	30	0.4783	0.4906	0.4942
5	Female	25	0.3811	0.3883	0.3697
6	Female	34	0.4917	0.4878	0.4811
7	Male	35	0.4511	0.4689	0.4550
8	Female	33	0.4500	0.4678	0.4678
9	Female	28	0.4494	0.4500	0.4500
10	Male	25	0.4356	0.4400	0.4439
CIMT = Carotid Intima Media Thickness Investigator 1 = Anne Marie O'Flynn Investigator 2 = Emily Ho					

Table 5.3. Global longitudinal strain results

Subject	Sex	Age	Clinical information	GLS % (Investigator 1)	GLS % (Investigator 1)	GLS % (Investigator 2)
1	Male	67	Mild aortic stenosis	-22.0	-21.2	-19.6
2	Male	27	Dilated aortic root	-22.1	-22.0	-17.9
3	Male	62	Mechanical aortic valve and left ventricular ejection fraction 40-50%	-16.7	-15.1	-14.8
4	Female	60	Murmur on clinical examination	-19.0	-17.5	-15.9
5	Male	51	History of non ST elevation myocardial infarction	-23.5	-20.1	-22.0
6	Male	77	Left ventricular ejection fraction 25-35%	-14.9	-14.6	-14.0
7	Male	55	Bicuspid aortic valve	-12.7	-11.2	-12.4
8	Male	45	Dyspnoea with previous chemotherapy	-16.0	-16.6	-14.1
9	Male	29	Hypertension	-17.6	-18.6	-17.2
10	Male	35	Bicuspid aortic valve	-24.1	-23.5	-22.1

GLS = Global longitudinal strain
Investigator 1 = Anne Marie O'Flynn
Investigator 2 = Emily Ho

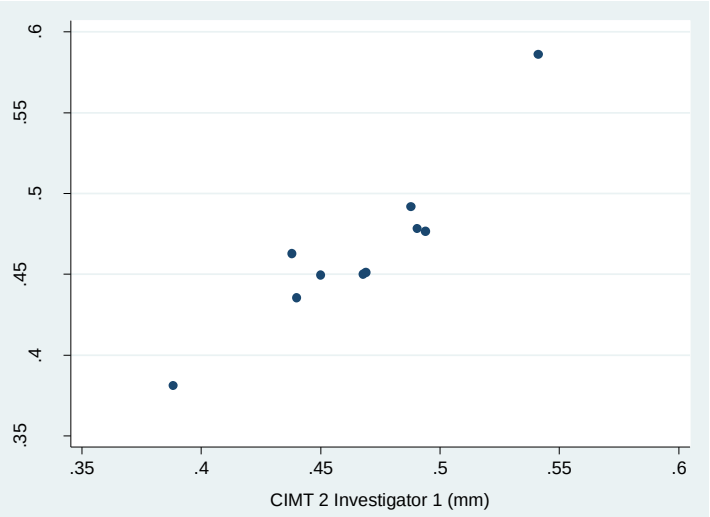


Figure 5.6. Scatter plot of CIMT measured by investigator 1

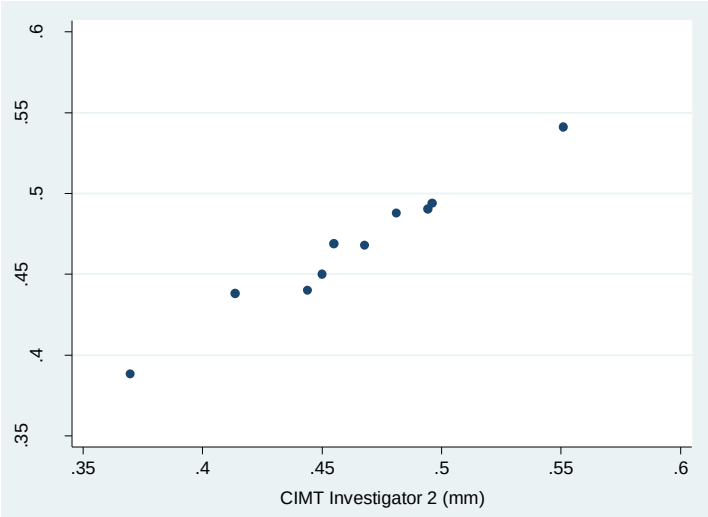


Figure 5.7. Scatter plot of CIMT measured by investigators 1 and 2

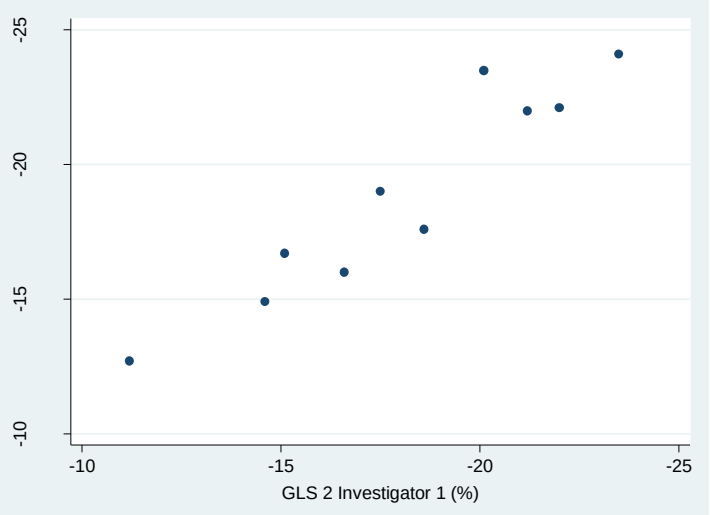


Figure 5.8. Scatter plot of GLS measured by investigator 1

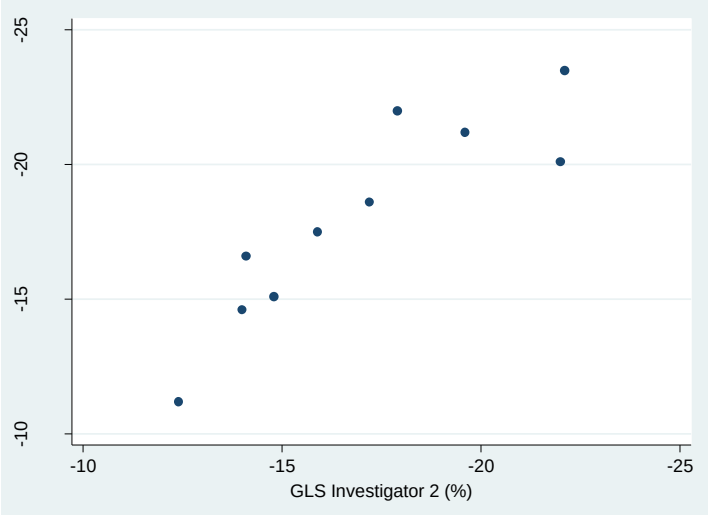


Figure 5.9. Scatter plot of GLS measured by investigators 1 and 2

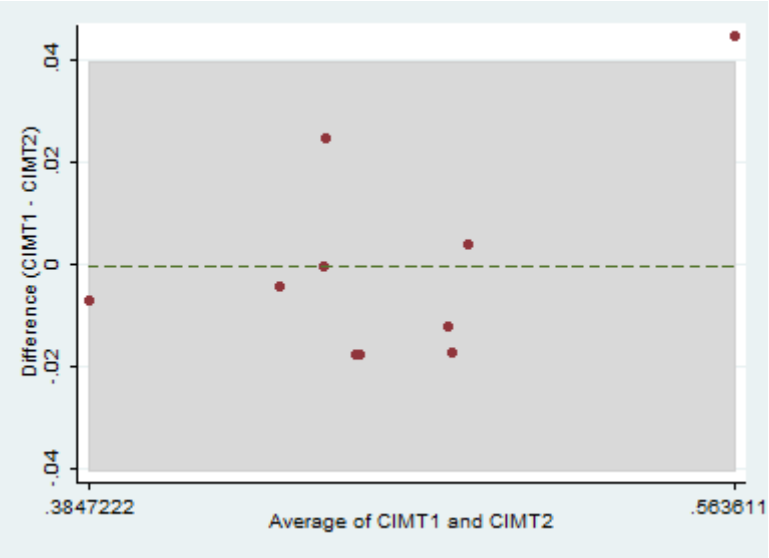


Figure 5.10. Bland Altman plot for CIMT intra-observer reproducibility

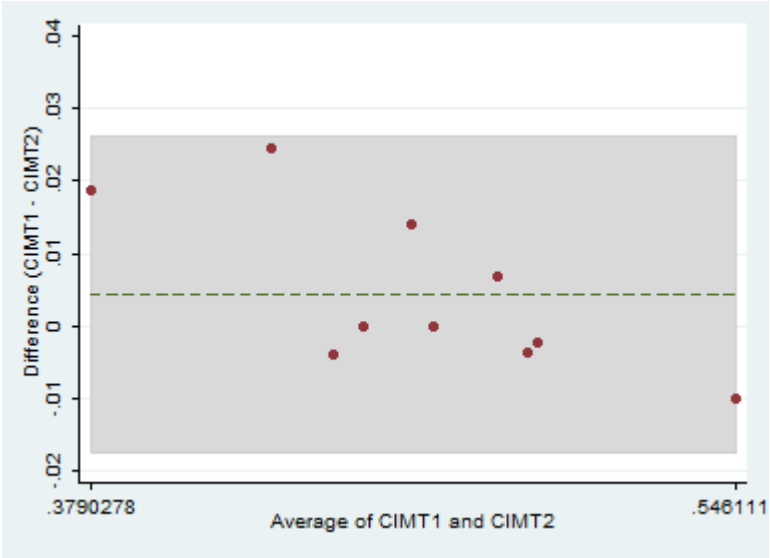


Figure 5.11. Bland Altman plot for CIMT inter-observer reproducibility

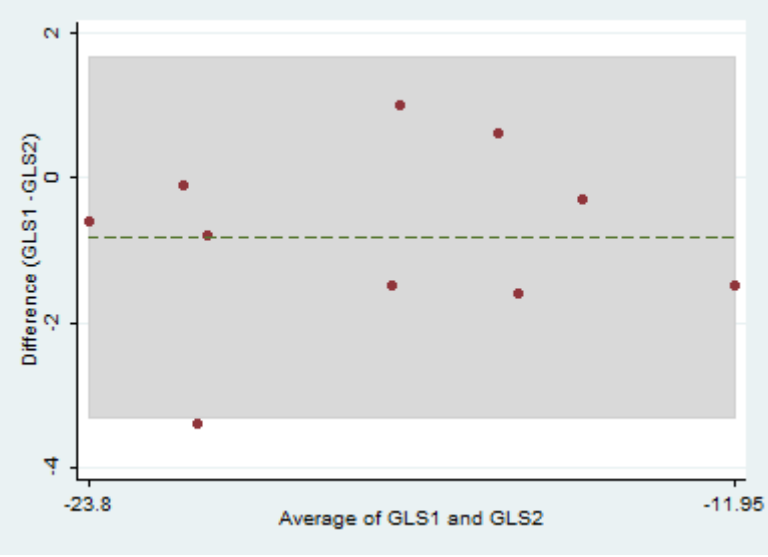


Figure 5.12. Bland Altman plot for GLS intra-observer reproducibility

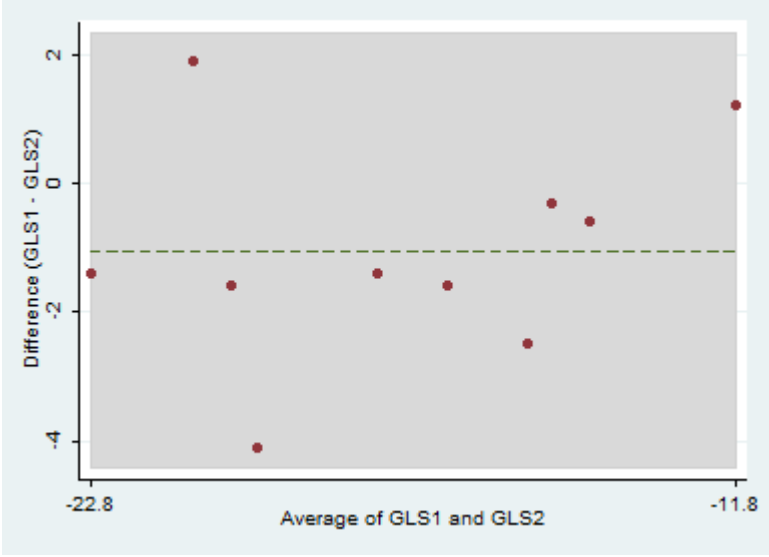


Figure 5.13. Bland Altman plot for GLS inter-observer reproducibility

5.5. Discussion

We have demonstrated good reproducibility of CIMT and GLS with standardised imaging and reading protocols. We found high levels of agreement within and between investigators with intra-observer and inter-observer ICCs above 0.9 for CIMT and intra-observer and inter-observer ICCs above 0.85 for GLS.

Validity is the degree to which an instrument truly measures that which it is supposed to measure while reliability is defined as the degree to which a measurement is free from measurement error. A measurement can be valid but unreliable and vice versa. (13) Concerns exist regarding measurement quality with respect to CIMT. (14) This contributed to the decision not to recommend CIMT in routine clinical practice for the assessment of cardiovascular risk in American guidelines. (15)

However, standardised protocols which take multiple measurements increase the validity of measurements. (13) Medical residents can be trained to measure CIMT using an abbreviated version of the American Society of Echocardiography protocol. (16) We have used a standardised CIMT imaging protocol with multiple measurements made from different angles on both sides to maximise the likelihood of a valid mean estimate and limit measurement error.

Automated measurements result in less variability of CIMT. (17) Automated ultrasound makes it possible for novice operators to accurately assess CIMT after a short training period. (18) Automated border detection programmes produce valid and reproducible measurements. (19, 20) We used a semi-automated border detection programme to detect the CIMT border as recommended by the American Society of Echocardiography CIMT task force. (11)

Our reproducibility results for CIMT are comparable to those reported by others in the literature. In the SALPALDIA Cohort Study in Switzerland, Caviezel et al reported ICCs of 0.87 to 0.91 for CIMT measured at the distal 1 cm of the CCA far wall and read using an automatic border detection programme. (21) An ICC of 0.74 was reported for the Rotterdam Study where both near and far wall CIMT of the distal

CCA was measured. (22) In the MESA (Multi-Ethnic Study of Atherosclerosis) study intra-observer rescan ICC was 0.95 and inter-observer ICC was 0.87. They measured the mean of the maximal CIMT of the near and far wall of the distal 1 cm of the CCA. (23) The ARIC (Atherosclerosis Risk in Communities) study, on which our image acquisition protocol is based, has reported a reliability coefficient of 0.77 for the mean CIMT of the distal 1 cm of the CCA. (7)

Speckle tracking echocardiography myocardial strain is an accurate and angle independent measurement of myocardial function and has been validated against sonomicrometry and magnetic resonance imaging. (24) GLS appears to be the most robust strain measurement. (25) It is also more reproducible than ejection fraction and other conventional echocardiographic parameters. (26) It also provides superior prognostic information to ejection fraction. (27) To maximise validity we used a standardised protocol to acquire the echocardiogram images. As per recommendations we ensured a frame rate above 50 frames/sec. (8, 28) In addition GLS was averaged from 3 apical views.

Our GLS reproducibility results compare favourably with those reported in the literature. Oxborough et al reported an ICC of 0.807 for intra-observer reliability of longitudinal strain measured from the apical 4 chamber view in healthy young adults. (29) At the 25 year follow-up examination of the CARDIA (Coronary Artery Risk Development in Young Adults) Study Armstrong et al reported an ICC of 0.71 for 2 chamber longitudinal strain and 0.55 for 4 chamber longitudinal strain for inter-reader reproducibility while the ICC values for intra-reader reproducibility were 0.87 and 0.79 respectively. (30) Russo et al reported an ICC of 0.85 for inter-observer reproducibility of GLS measured from 2 and 4 chamber views in a random sample of 20 older community based participants of the CABL (Cardiovascular Abnormalities and Brain Lesion) Study. (31) In the Framingham Offspring Study Cheng et al reported an ICC of 0.89 for 2 chamber longitudinal strain and 0.84 for 4 chamber longitudinal strain for inter-observer reproducibility in middle-aged to older adults. For intra-observer reproducibility the ICC for 2 chamber longitudinal strain was 0.92 and for 4 chamber longitudinal strain was also 0.92. (32)

Inter-vendor variation also needs to be considered in the interpretation of GLS studies. Takigiku et al demonstrated poor inter-vendor agreement, however GLS reproducibility was better than radial or circumferential strain. Also Philips Medical, the vendor used in our work, demonstrated GLS results more in line with results from the GE Healthcare system (ICC 0.63) than that of Toshiba (ICC 0.2). (33) Other investigators have similarly found GLS to be more reproducible than radial, circumferential or transverse strain. (25) A joint initiative from the European Association of Cardiovascular Imaging (EACVI), the American Society of Echocardiography (ASE) and an industry task force have looked at this in 62 subjects using 7 ultrasound machine vendors and 2 software vendors. They found endocardial GLS reproducibility to be superior to that of other echocardiographic parameters. (26) However there was variability between vendors with a maximum absolute difference between vendors of 3.7%. Philips, the vendor used in our work, had a maximum absolute difference of 2.7% and correlation coefficients above 0.81 when compared to the other 8 vendors. Also inter- and intra-observer mean errors for endocardial GLS averaged from 2 or 3 apical views were less than that measured from the 4 chamber view alone. Software differences have been suggested to be the main source of the variation between vendors. (26, 34)

Ultrasound quality assurance programmes and the use of phantoms to assess image based performance measurements is recommended by most authorities including the Irish Faculty of Radiologists, Royal College of Surgeons in Ireland. (35-37) In addition to routine equipment maintenance we also used an ultrasound phantom regularly throughout the study period. This gives an objective assessment of image quality and measurement accuracy and our results demonstrate that our equipment operated consistently.

Limitations:

We designed a study to assess the association of night-time blood pressure with CIMT and GLS in a sample of participants from the Mitchelstown Cohort Study. Our reproducibility data for CIMT is from a sample of healthy controls (mean age 28, 50% male) while that for GLS is from a sample of patients referred for clinically indicated echocardiography (mean age 51, 90% male). Therefore neither sample in

the reproducibility analysis is representative of the Mitchelstown Cohort Study participants (mean age 60, 52% male). This approach was taken so we could demonstrate sound measurement methods prior to inviting participants to take part in the formal study as they had to travel a significant distance to a tertiary clinical centre in order to do so.

Conclusion:

We have described the imaging and reading protocols and equipment quality control measures including the use of phantom ultrasound scans to maximise validity of our results. We have also demonstrated good intra- and inter-observer reproducibility of CIMT and GLS results. Our findings suggest our measurement methods are valid and reliable and suitable to be applied in an epidemiological study.

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6. The association of night-time systolic blood pressure with ultrasound markers of subclinical cardiac and vascular disease

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6.1. Abstract

Introduction

Ambulatory blood pressure monitoring (ABPM) measures blood pressure (BP) over a prolonged period and has been shown to be superior to office BP for the prediction of clinical events. In particular, night-time systolic BP is a stronger predictor than daytime systolic BP. It is not yet clear if night-time BP should be a specific therapeutic target although some studies have demonstrated promising results. Subclinical cardiovascular disease is a prognostic marker for future cardiovascular events. Our aim is to examine the association of night-time systolic BP with subclinical cardiac dysfunction measured by global longitudinal strain (GLS) and subclinical vascular damage measured by carotid intima media thickness (CIMT) and carotid plaques.

Methods

In 2014 a random sample of 80 individuals, stratified by BP status at baseline recruitment to the Mitchelstown Cohort Study, were invited to undergo echocardiogram and carotid ultrasound. GLS was measured by speckle-tracking analysis of echocardiogram images carried out on a Philips iE33 ultrasound machine. Mean CIMT was measured at the distal 1 cm of the common carotid artery. Still images were taken from 3 angles on both sides of the neck using a Philips Cx50 ultrasound machine. The presence of carotid plaques was recorded. Philips QLAB cardiac and vascular ultrasound quantification software was used for analysis. The association of night-time systolic BP with GLS, CIMT and carotid plaques was assessed using linear and logistic regression.

Results

Fifty (response rate 63%) individuals took part in this study. In univariable models night-time systolic BP was significantly associated with GLS (beta coefficient 0.85 for every 10 mmHg rise, 95% CI 0.3 – 1.4) and carotid plaques (OR 1.9 for every 10 mmHg rise, 95% CI 1.1 – 3.2). Univariable analysis of daytime systolic BP did not demonstrate any statistically significant associations. In age and sex adjusted models, the association for night-time systolic BP and GLS remained significant

(beta coefficient 0.68 for every 10 mmHg rise, 95% CI 0.1 – 1.3). The association for carotid plaques was no longer statistically significant. In multivariable models findings were diminished.

Discussion

Our results support an association between night-time systolic BP and subclinical cardiac and vascular disease. However this is a small study and the sample size may have provided insufficient power to detect true associations between night-time systolic BP and target organ damage in multivariable models and for CIMT in particular. When assessing ABPM results the absolute night-time BP seems to be the most important parameter but ultimately a large randomised controlled trial involving chronotherapy is necessary to fully address this.

6.2. Introduction

Cardiovascular disease remains the leading cause of mortality worldwide (1) and hypertension is the risk factor with the greatest population attributable risk. (2, 3) Prevalence rates of hypertension are high while control rates are low. (4) Ambulatory blood pressure monitoring (ABPM) measures blood pressure over 24 to 48 hours and has been shown to be superior to office blood pressure for the prediction of clinical events. (5, 6) Night-time systolic blood pressure is a stronger predictor of events than daytime systolic blood pressure. (7)

Though it is unclear if night-time blood pressure should be a specific therapeutic target, chronotherapy has demonstrated some promising results. In one study patients were randomised to either take all of their anti-hypertensive medications in the morning or to take at least 1 of them at night. The decrease in nocturnal blood pressure was associated with a reduced risk of total cardiovascular events. Similarly patients with chronic kidney disease who took at least one anti-hypertensive at night had a lower hazard ratio of total cardiovascular events than those taking all of their medications in the morning. (8, 9)

The association of night-time blood pressure with subclinical target organ damage has been investigated. (10, 11) This would seem intuitive given the greater association of night-time blood pressure with clinical events, the continuum of cardiovascular disease, (12) and subclinical disease being a prognostic marker for future cardiovascular events. (13) Many studies have focused on dipping status rather than the absolute blood pressure level. (14-16) We have previously shown that absolute night-time systolic blood pressure is better associated than dipping status with subclinical cardiac and vascular damage documented by electrocardiogram left ventricular hypertrophy voltage criteria and microalbuminura in the Mitchelstown Cohort Study . (17)

Echocardiography can measure the subclinical cardiac consequences of hypertension such as increased left atrial (LA) size and left ventricular hypertrophy (LVH). Speckle tracking echocardiography has enabled the quantification of strain which is a dimensionless measure of myocardial deformation. Global longitudinal

strain (GLS) is a measure of the myocardial systolic deformation over the longitudinal axis. (18) There is emerging evidence for the prognostic importance of this measure. (19, 20) It offers incremental prognostic information in the assessment of left ventricular function particularly when the ejection fraction is near normal. (21) Few studies have examined the association of night-time blood pressure and GLS measured by speckle tracking analysis. (22, 23)

Carotid intima-media thickness (CIMT) measured by ultrasound is a marker of subclinical vascular damage and is recognised to be associated with cardiovascular risk factors and with the incidence of myocardial infarction and stroke. (24, 25) There is evidence for the validity of CIMT as a suitable surrogate measure of atherosclerotic disease. (26, 27) The addition of carotid plaques to risk prediction models including CIMT improves performance. (28, 29)

The present study aims to build on previous work by examining the association of night-time systolic blood pressure with ultrasound markers of subclinical cardiovascular disease including abnormal GLS, CIMT and carotid plaques in a sample from the Mitchelstown Cohort Study.

6.3. Methods

In 2010 the Mitchelstown Cohort Study recruited 2047 participants from a single large primary care centre, the Livinghealth Clinic in Mitchelstown, a town in the south of Ireland. (30) Of these, 1207 (response rate 59%) also underwent 24 hour ambulatory blood pressure monitoring (ABPM). These individuals provide the sample for the present study. Based on the initial ABPM results the sample was divided into 4 groups: normotension, isolated daytime hypertension, isolated nocturnal hypertension and day-night hypertension. Twenty participants were randomly selected from each group and invited to attend for echocardiogram and carotid ultrasound in 2014. This study therefore includes analysis of baseline ABPM data and follow-up imaging data.

Height and weight measurements:

A trained researcher carried out the physical measures. Height and weight were measured without foot-ware using a Seca measuring and weighing station. Body mass index (BMI) and body surface area (BSA) were calculated.

Study blood pressure:

At the baseline visit after the participant had been in a relaxed seated position for at least 5 minutes three blood pressure readings were taken on the right arm, 1 minute apart, using an OMRON M7 digital automatic blood pressure monitor. The average of the second and third blood pressure reading was defined as the study blood pressure.

ABPM:

ABPM measurements were performed at baseline using the MEDITECH ABPM-05 and data was stored using the dabl ABPM system. The monitors were programmed to record the blood pressure every 30 minutes throughout the 24 hour period. Participants kept a diary of the times they went to bed and got up. Diary times were used to calculate mean daytime and night-time blood pressures. Mean 24 hour blood pressure was calculated as the mean of all the readings throughout the 24 hour period.

Echocardiography:

A Philips iE33 ultrasound machine and a S5-1 phased array transducer were used for image acquisition. All scans were carried out by the same operator (IB). IB is accredited in transthoracic echocardiography by the British Society of Echocardiography. A standard echocardiogram protocol was used. Parasternal long and short axis, apical 4-, 2- and 3-chamber views were obtained. Optimisation of frame rate was carried out by reducing the sector depth and width.

Left ventricular (LV) wall thickness and diameters were measured from the parasternal long axis view. LV mass was calculated using the Devereux formula. (31) LV mass was indexed for BSA. LVH was defined as LV mass > 115 g/m^2 in males and > 95 g/m^2 in females. (32) LV volumes and ejection fraction were calculated from the apical 4 chamber view using the single plane method of discs. (33) LV volumes

were indexed for body surface area. LA volume was calculated from the apical 4 chamber view using the single plane method of discs. LA volume was indexed for body surface area. (32)

Diastolic function parameters were measured in the apical 4 chamber view. Mitral inflow early (E) and late (A) velocities and E wave deceleration time were obtained by pulse-wave Doppler with the sample volume at the mitral valve tips. Peak diastolic mitral annular (e') velocity was measured from the septal and lateral mitral annulus and averaged. The E/e' ratio was then calculated. Diastolic dysfunction was defined as E/A ≤ 0.7 or deceleration time > 260 ms; or E/A ratio > 0.7 and ≤ 1.5 and e' velocity < 7 cm/s; or E/A ratio > 1.5 and e' velocity < 7 cm/s or deceleration time < 140 ms. (34)

The acquired images were saved using digital media and speckle tracking GLS analysis was carried out offline by a single reader (AMOF) from apical 4-, 2- and 3-chamber views using Philips QLAB cardiac and vascular ultrasound quantification software version 9.0. The region of interest was identified by the selection of 3 points, one on either side of the mitral valve annulus and one at the apex for each view. Adequate tracking was confirmed visually and if deemed inadequate the region of interest was edited. If inadequate tracking persisted problematic segments were excluded. If more than 2 segments in a single view had to be excluded the entire study was excluded from speckle tracking analysis. (32) GLS average was obtained from 17 ventricular segments represented on a bulls-eye plot from apical 4-, 2- and 3- chamber views. Normal cut-off was taken as -19.7%. (35)

Carotid ultrasound:

A Philips Cx50 portable ultrasound machine and a L12-3 linear array transducer were used for image acquisition. All scans were carried out by the same operator (AMOF). AMOF received formal training in CIMT image acquisition. Subjects were examined in the supine position with their head tilted to the opposite side. A Meijer arc was used to ensure optimal positioning. A thorough transverse and longitudinal scan of the extra-cranial carotid arteries was carried out to evaluate for the presence of atherosclerotic plaques. Ultrasound images of the distal portion of the

far wall of both common carotid arteries were obtained for assessment of CIMT. Far wall still frames were taken from anterior, lateral and posterior angles. Three still frame images were taken from each angle. (36)

The acquired images were saved using digital media and measurement was carried out offline by a single reader (AMOF) using Philips QLAB cardiac and vascular ultrasound quantification software version 9.0. Measurements were made on the 3 still frame images from each angle over a length of 1 cm at the distal common carotid artery (CCA). The reference point for the commencement of the measurement was where the CCA began to dilate prior to the bifurcation. A mean measurement from each angle was obtained. The mean of these means was obtained to give the measurement for each side. The mean of the left and right was then taken as the CIMT. Normal cut-off was taken as the 75th percentile. (37) The presence of plaques in the extra-cranial carotid arteries was recorded as a binary variable. A plaque was defined according to the Mannheim Consensus as a focal protrusion into the blood vessel ≥ 50% of the thickness of the adjacent IMT or focal IMT > 1.5 mm. (38)

Reproducibility:
Intra- and inter-observer reproducibility was assessed prior to undertaking the study. Ten patients undergoing routinely indicated echocardiography were asked to consent to have their images analysed by speckle tracking analysis. All echocardiograms were carried out by the same operator (IB). Speckle tracking analysis was carried out offline by AMOF and repeated for intra-observer reproducibility. An independent observer (EH) also analysed the images for inter-observer reproducibility. Ten healthy volunteers had a carotid ultrasound twice within the same week carried out by the same investigator (AMOF) who also analysed the images for intra-observer reproducibility. An independent observer (EH) analysed the second set of images for inter-observer reproducibility.

The intra-observer intra-class coefficient (ICC) for GLS was 0.93 (95% CI 0.70 - 0.98). The inter-observer ICC was 0.86 (95% CI 0.51 – 0.96). The intra-observer ICC for

CIMT was 0.91 (95% CI 0.69 – 0.98). The inter-observer ICC was 0.97 (95% CI 0.88 - 0.99).

Statistical analysis:
Statistical analysis was carried out using Stata 12. Continuous variables are described by means +/- standard deviation. Categorical variables are described using proportions.

The association of baseline night-time, daytime and study systolic blood pressure with GLS and CIMT was assessed using univariable and multi-variable linear regression. The association of baseline night-time, daytime and study systolic blood pressure with carotid plaques was assessed using logistic regression. Regression models were initially adjusted for sex and age. Multi-variable regression analysis was also carried out with adjustments applied for sex, age, BMI, smoking status, diabetes mellitus and total cholesterol. Interaction terms including antihypertensive medications with night-time, daytime and study systolic blood pressures respectively were also included in the models.

6.4. Results

Fifty individuals took part in this study (Overall response rate 63%). The mean period of follow up was 3.9 years. The mean age of participants was 60 and 26 (52%) were male. Baseline characteristics are presented in table 6.1 together with the baseline characteristics of the full cohort and those who underwent ABPM.

The echocardiogram and carotid ultrasound findings by blood pressure strata are presented in table 6.2. Speckle tracking echocardiography analysis was not possible in 1 study due to poor image quality. In univariable models night-time systolic blood pressure was significantly associated with GLS (beta coefficient 0.85 for every 10 mmHg rise, 95% CI 0.3 – 1.4) and carotid plaques (OR 1.9 for every 10 mmHg rise, 95% CI 1.1 – 3.2). Univariable analysis of daytime systolic blood pressure did not demonstrate any statistically significant associations. Table 6.3. In age and sex adjusted models, the association for night-time systolic blood pressure and GLS remained significant (beta coefficient 0.68 for every 10 mmHg rise, 95% CI 0.11 – 1.25). The association for carotid plaques was no longer statistically significant.

Table 6.4. In multivariable models findings were attenuated. Table 6.5. Interaction terms including antihypertensive medications with night-time, daytime and study systolic blood pressures respectively were included in the models but were not statistically significant (data not shown).

Table 6.1. Baseline characteristics

	Total cohort n =2047 N (%) /mean +/-SD	Sample with satisfactory ABPM n =1072 N (%) /mean +/-SD	Sample n =50 N (%) /mean +/-SD
Age	59 (+/-6)	60 (+/-6)	60 (+/-5)
Male	1008 (49)	567 (47)	26 (52)
Education category			
Primary	537 (28)	335 (30)	7 (15.5)
Secondary	936 (49)	547 (48)	22 (49)
Tertiary	435 (23)	253 (22)	16 (35.5)
IPAQ category			
Low	932 (49)	571 (50)	31 (62)
Moderate	566 (30)	318 (28)	19 (38)
High	420 (22)	248 (22)	0 (0)
Smoking Status			
Non-smoker	1002 (51)	615 (53)	27 (54)
Former smoker	671 (34)	378 (32)	18 (36)
Current smoker	292 (15)	175 (15)	5 (10)
Medical History			
Hypertension	567 (29)	407 (34)	19 (40)
Myocardial Infarction	49 (2)	33 (3)	2 (4)
Stroke	22 (1)	13 (1)	0 (0)
Heart failure	8 (0.4)	6 (0.5)	1 (2)
Diabetes	174 (9)	114 (10)	5 (10)
Medication			
Anti-hypertensive	584 (29)	405 (35)	21 (42)
Cholesterol lowering	711 (36)	457 (39)	21 (42)
BMI (kg/ m2)	29 (+/-5)	30 (+/-5)	29 (+/-5)
Waist circumference	97 (+/-13)	97 (+/-14)	100 (+/-13)
LDL (mmol/l)	3.2 (+/-0.9)	3.2 (+/-0.9)	3.2 (+/-0.8)
Creatinine (µmol/l)	71 (+/-16)	72 (+/-16)	74 (+/-17)
ACR (mg/mmol)	0.7 (+/-2.1)	0.8 (+/-2.1)	0.6 (+/-0.7)
eGFR (mls/min)	90 (+/-13)	89 (+/-13)	87 (+/-13)
Cystatin C	0.83 (+/-0.18)	0.83 (+/-0.18)	0.87 (+/-0.14)
Study systolic	130 (+/-17)	134 (+/- 18)	134 (+/-16)
Study diastolic	80 (+/-10)	83 (+/- 10)	82 (+/-10)
Daytime systolic		131 (+/-14)	132 (+/-12)
Daytime diastolic		77 (+/-9)	78 (+/-9)
Night-time systolic		112 (+/-14)	117 (+/-14)
Night-time diastolic		63 (+/-8)	66 (+/-9)
Twenty four systolic		124 (+/-13)	126 (+/- 11)
Twenty four diastolic		72 (+/-8)	74 (+/- 8)

Note some missing data

Table 6.2. Echocardiogram and carotid ultrasound characteristics

	Total sample n= 50 mean (+/- SD)/ n(%)	Normotension n=11 mean (+/- SD)/ n(%)	Isolated daytime hypertension n=14 mean (+/- SD)/ n(%)	Isolated nocturnal hypertension n=14 mean (+/- SD)/ n(%)	Sustained day-night hypertension n=11 mean (+/- SD)/ n(%)
Echocardiogram					
LA volume index, ml/m2	32.0 (+/-9.4)	27.7 (+/-7.3)	31.3 (+/-7.7)	32.6 (+/-9.7)	36.2 (+/-12.0)
LV mass index , g/m2	99.3 (+/-24.2)	85.5 (+/-19.7)	97.8 (+/-17.5)	101.5 (+/-24.7)	112.4 (+/-29.9)
Left ventricular hypertrophy	16 (32)	2 (18)	4 (29)	5 (36)	5 (45)
LV end diastolic volume, ml/m2	48.3 (+/-8.4)	45.8 (+/-7.6)	48.2 (+/-7.0)	48.6 (+/-10.3)	50.5 (+/-8.7)
LV end systolic volume, ml/m2	17.2 (+/-5.2)	17.7 (+/-6.8)	16.3 (+/-2.9)	17.5 (+/-7.0)	17.6 (+/-3.6)
LV ejection fraction, %	65.1 (+/-6.2)	64.5 (+/-7.2)	66.0 (+/-5.0)	64.9 (+/-7.5)	65.0 (+/-5.3)
Global longitudinal strain,%	-21.2 (+/-3.0)	-22.6 (+/-2.9)	-21.9 (+/-2.8)	-21.0 (+/-2.9)	-19.2 (+/-2.6)
Abnormal GLS	16 (33)	1 (10)	3 (21)	5 (36)	7 (64)
E/A	0.98 (+/-0.3)	1.04 (+/-0.2)	0.89 (+/-0.2)	0.95 (+/-0.4)	1.05 (+/-0.3)
E wave deceleration time, ms	253.9 (+/-74.2)	224 (+/-54)	255.4 (+/-60.0)	282 (+/-90.1)	246 (+/- 80.3)
E', cm/s	7.7 (+/-1.8)	8.2 (+/-1.0)	7.8 (+/-2.2)	7.3 (+/-2.0)	7.9 (+/-1.6)
E/e'	9.5 (+/-1.9)	9.4 (+/-0.9)	8.6 (+/-2.1)	9.9 (+/-1.9)	10.2 (+/-2.3)
Diastolic dysfunction	30 (60)	4 (36)	10(71)	10 (71)	6 (55)
Carotid ultrasound					
Common carotid IMT, mm	0.72 (+/-0.13)	0.64 (+/-0.10)	0.71 (+/-0.14)	0.76 (+/-0.14)	0.76 (+/-0.12)
Common carotid IMT > 75^{th} percentile	12 (24)	1 (9)	3 (21)	4 (29)	4 (36)
Plaques	33 (66)	5 (45)	8 (57)	12 (86)	8 (73)

GLS analysis not possible in 1 study due to poor image quality

Table 6.3. Univariable linear and logistic regression results

	GLS		CIMT		Plaques	
	Beta Coef (95% CI)	p-value	Beta Coef (95% CI)	p-value	OR (95% CI)	p-value
Sex (male v female)	2.70 (1.15 – 4.24)	0.001	0.09 (0.02 – 0.16)	0.02	6.5 (1.7 – 24.7)	0.006
Age	0.05 (-0.11 – 0.21)	0.5	0.009 (0.002 – 0.015)	0.009	1.2 (1.0 – 1.3)	0.03
Antihypertensives (yes v no)	-0.91 (-2.65 – 0.84)	0.3	-0.03 (-0.11 – 0.05)	0.4	0.3 (0.1 – 1.1)	0.06
BMI	0.20 (0.03 – 0.37)	0.02	-0.004 (-001 – 0.004)	0.3	1.1 (0.96 – 1.2)	0.2
Smoking status (current v non/ex)	-0.18 (-3.05 – 2.69)	0.9	0.18 (0.06 – 0.29)	0.004	2.2 (0.2 – 21.4)	0.5
Diabetes mellitus (yes v no)	3.16 (0.43 – 5.88)	0.02	0.02 (-0.11 – 0.15)	0.7	2.1 (0.2 – 20.9)	0.5
Total cholesterol	0.05 (-0.89 – 0.99)	0.9	-0.02 (-0.06 – 0.03)	0.4	0.67 (0.34 – 1.3)	0.2
Night–time SBP	0.85 (0.3 – 1.4)	0.003	0.02 (-0.002 – 0.05)	0.08	1.9 (1.1 – 3.2)	0.03
Daytime SBP	0.47 (-0.24 – 1.17)	0.2	0.02 (-0.01 – 0.05)	0.3	1.2 (0.7 – 2.0)	0.4
Study SBP	0.53 (0.01 – 1.06)	0.05	0.01 (-0.01 – 0.03)	0.4	1.16 (0.8 – 1.7)	0.4

Beta coefficients and odds ratios for night-time SBP, daytime SBP and study SBP represent per 10 mmHg rise

Table 6.4. Sex and age adjusted linear and logistic regression results

	GLS Model 1		**GLS Model 2**		**GLS Model 3**	
	Beta Coef (95% CI)	p-value	Beta Coef (95% CI)	p-value	Beta Coef (95% CI)	p-value
Sex (male v female)	2.21 (0.64 – 3.77)	0.007	2.61 (0.89 – 4.33)	0.004	2.44 (0.64 – 4.23)	0.009
Age	-0..5 (-0.20 – 0.10)	0.5	0.01 (-0.14 – 0.16)	0.9	0.002 (-0.15 – 0.15)	1.0
Night-time SBP	0.68 (0.11 – 1.25)	0.02	-	-	-	-
Daytime SBP	-	-	0.08 (-0.61 – 0.78)	0.8	-	-
Study SBP	-	-			0.17 (-0.40 – 0.74)	0.6
	CIMT Model 1		**CIMT Model 2**		**CIMT Model 3**	
	Beta Coef (95% CI)	p-value	Beta Coef (95% CI)	p-value	Beta Coef (95% CI)	p-value
Sex (male v female)	0.07 (-0.01 – 0.14)	0.07	0.07 (-0.01 – 0.14)	0.09	0.08 (-0.0003 – 0.16)	0.05
Age	0.01 (0.0001 – 0.01)	0.05	0.01 (0.001 – 0.01)	0.02	0.01 (0.001 – 0.01)	0.02
Night-time SBP	0.01 (-0.02 – 0.03)	0.6	-	-	-	-
Daytime SBP	-	-	0.01 (-0.02 – 0.04)	0.6	-	-
Study SBP	-	-	-	-	-0.005 (-0.03 – 0.02)	0.7
	Plaques Model 1		**Plaques Model 2**		**Plaques Model 3**	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Sex (male v female)	4.8 (1.16 – 19.86)	0.03	6.11 (1.39 – 26.75)	0.02	8.4 (1.64 – 43.01)	0.01
Age	1.11 (0.97 – 1.28)	0.1	1.14 (0.99 – 1.31)	0.06	1.15 (1.00 – 1.32)	0.05
Night-time SBP	1.47 (0.80 – 2.69)	0.2	-	-	-	-
Daytime SBP	-	-	0.95 (0.55 – 1.65)	0.9	-	-
Study SBP	-	-	-	-	0.80 (0.49 – 1.30)	0.4

Model 1 Night-time SBP adjusted for sex and age
Model 2 Daytime SBP adjusted for sex and age
Model 3 Study SBP adjusted for sex and age
Beta coefficients and odds ratios for night-time SBP, daytime SBP and study SBP represent per 10 mmHg rise

Table 6.5. Multivariable adjusted linear and logistic regression results

	GLS Model 1 Beta Coef (95% CI)	p-value	**GLS Model 2** Beta Coef (95% CI)	p-value	**GLS Model 3** Beta Coef (95% CI)	p-value
Sex (male v female)	1.79 (-0.03 – 3.6)	0.05	1.97 (0.03 – 3.9)	0.05	2.02 (0.03 – 4.01)	0.05
Age	0.002 (-0.17 – 0.17)	1.0	0.06 (-0.10 – 0.21)	0.5	0.06 (-0.10 – 0.22)	0.5
BMI	0.06 (-0.13 – 0.26)	0.5	0.11 (-0.08 – 0.30)	0.2	0.11 (-0.08 – 0.30)	0.2
Smoking (current v non/ex)	-0.01 (-2.82 – 2.80)	1.0	0.27 (-2.61 – 3.15)	0.9	0.28 (-2.60 – 3.16)	0.8
Diabetes mellitus (yes v no)	1.91 (-0.75 – 4.56)	0.2	2.16 (-0.57 – 4.89)	0.1	2.16 (-0.61 – 4.93)	0.1
Total cholesterol	0.28 (-0.62 – 1.17)	0.5	0.38 (-0.54 – 1.29)	0.4	0.38 (-0.54 – 1.31)	0.4
Night-time SBP	0.52 (-0.13 – 1.16)	0.1	-	-	-	-
Daytime SBP	-	-	0.04 (-0.66 – 0.75)	0.9	-	-
Study SBP	-	-	-	-	-0.01 (-0.61 – 0.58)	1.0
	CIMT Model 1 Beta Coef (95% CI)	p-value	**CIMT Model 2** Beta Coef (95% CI)	p-value	**CIMT Model 3** Beta Coef (95% CI)	p-value
Sex (male v female)	0.07 (-0.01 – 0.15)	0.07	0.07 (-0.01 – 0.15)	0.1	0.07 (-0.01 – 0.16)	0.08
Age	0.01 (-0.001 – 0.01)	0.08	0.01 (0.004 – 0.01)	0.04	0.01 (0.0003 – 0.1)	0.04
BMI	-0.003 (-0.01 – 0.004)	0.4	-0.003 (-0.01 – 0.004)	0.4	-0..003 (-0.01 – 0.004)	0.5
Smoking (current v non/ex)	0.15 (0.03 – 0.27)	0.02	0.16 (0.04 – 0.28)	0.01	0.16 (0.04 – 0.28)	0.01
Diabetes mellitus (yes v no)	0.02 (-0.10 – 0.13)	0.8	0.02 (-0.09 – 0.14)	0.7	0.02 (-0.10 – 0.14)	0.7
Total cholesterol	-0.01 (-0.05 – 0.03)	0.5	-0.01 (-0.05 – 0.03)	0.6	-0.01 (-0.05 – 0.03)	0.6
Night-time SBP	0.01 (-0.02 – 0.03)	0.5	-	-	-	-
Daytime SBP	-	-	0.01 (-0.02 – 0.04)	0.5	-	-
Study SBP	-	-	-	-	0.001 (-0.02 – 0.95)	0.2

Continued…

Table 6.5. Continued

	Plaques Model 1 OR (95% CI)	p-value	**Plaques Model 2** OR (95% CI)	p-value	**Plaques Model 3** OR (95% CI)	p-value
Sex (male v female)	4.66 (0.78 – 27.80)	0.09	5.70 (0.84 – 38.50)	0.07	6.57 (0.93 – 46.49)	0.06
Age	1.17 (0.99 – 1.38)	0.07	1.19 (1.01 – 1.40)	0.03	1.21 (1.02 – 1.42)	0.03
BMI	1.10 (0.93 – 1.30)	0.3	1.13 (0.95 – 1.33)	0.2	1.13 (0.96 – 1.34)	0.1
Smoking (current v non/ex)	6.81 (0.30 – 157.32)	0.2	10.28 (0.38 – 280.48)	0.2	9.16 (0.39 – 217.16)	0.2
Diabetes mellitus (yes v no)	0.61 (0.04 – 10.57)	0.7	0.74 (0.04 – 12.38)	0.8	0.93 (0.05 – 16.23)	1.0
Total cholesterol	0.63 (0.25 – 1.56)	0.3	0.69 (0.29 – 1.64)	0.4	0.70 (0.29 – 1.70)	0.4
Night-time SBP	1.31 (0.65 – 2.66)	0.5	-	-	-	-
Daytime SBP	-	-	0.86 (0.46 – 1.62)	0.6	-	-
Study SBP	-	-	-	-	0.78 (0.45 – 1.37)	0.4

Model 1 Night-time SBP adjusted for sex, age, BMI, smoking, diabetes mellitus and total cholesterol
Model 2 Daytime SBP adjusted for sex, age , BMI, smoking, diabetes mellitus and total cholesterol
Model 3 Study SBP adjusted for sex, age , BMI, smoking, diabetes mellitus and total cholesterol
Beta coefficients and odds ratios for night-time SBP, daytime SBP and study SBP represent per 10 mmHg rise

6.5. Discussion

We have demonstrated an association of night-time systolic blood pressure with 2 measures of subclinical cardiovascular disease, GLS and carotid plaques, in a community based middle-aged population sample. These associations were attenuated in multivariable models. No such associations were seen for daytime or study systolic blood pressures and subclinical cardiovascular disease.

Cumulative blood pressure exposure over a 25 year period is associated with subclinical systolic and diastolic dysfunction assessed by speckle tracking echocardiography in middle age. (39) Uncontrolled 24 hour blood pressure has also been shown to be associated with abnormal GLS, while uncontrolled office blood pressure was not, in treated hypertensive patients. (40) Few studies have specifically addressed the association of night-time blood pressure and GLS. Kalaycioglu et al found a significant reduction in GLS in non-dippers compared to dippers in a sample of 86 treated hypertensive diabetic patients with mean age 57.8 years. They also reported night-time systolic blood pressure to be independently associated with GLS and global longitudinal strain rate (GLSR) in linear regression models adjusted for age, sex and left ventricular mass index. (22) In untreated hypertensive patients Tadic et al found reduced 2D and 3D left ventricular GLS and reduced atrial longitudinal strain in non-dippers compared to dippers. (23) Açar et al also examined left atrial strain in dippers and non-dippers and found reduced atrial function in non-dippers. (41) Others have examined right heart mechanics and found reduced function in non-dippers. (42) Our results suggest an association between increased night-time systolic blood pressure and subclinical left ventricular systolic dysfunction. We also found night-time systolic blood pressure to have a stronger association than daytime systolic blood pressure and study blood pressure with other echocardiographic markers of subclinical cardiac damage such as LA volume and LV mass. (Data not shown)

CIMT does improve cardiovascular risk prediction models but the overall impact is small. (43) There are concerns regarding measurement methods. (44) Moreover, increasing IMT is recognised as a normal ageing phenomenon which further complicates interpretation of CIMT measurements. (45-47) The use of CIMT is

therefore not without controversy and while the European cardiovascular prevention guidelines continue to give it a IIa level of recommendation for risk assessment in those at moderate overall risk, (48) American guidelines no longer recommend routine measurement of CIMT in clinical practice for the assessment of cardiovascular risk. (49) The addition of plaques has been shown to improve the predictive performance of CIMT. (28, 50) Findings on the association of night-time blood pressure and CIMT are conflicting. Cuspidi et al reported no difference in CIMT or plaques between those with nocturnal normotension and nocturnal hypertension. (10) On the other hand, Wang et al reported an association between nocturnal hypertension and CIMT in patients with chronic kidney disease. (51) Cuspidi and colleagues have recently reported the results of a meta-analysis that examined the association of non-dipping with carotid atherosclerosis and found higher CIMT and greater prevalence of plaques in non-dippers. (52) While we found no association between night-time systolic blood pressure and CIMT we did find an association with carotid plaques in univariable analysis. We measured CIMT at the distal 1 cm of the common carotid artery as guidelines recommend, while we assessed all of the extracranial carotid vessels for plaques. (36) This may have contributed to the differential findings for CIMT and plaques as they likely reflect different stages of atherosclerosis and plaques are more likely to develop in areas of turbulent flow such as the bifurcation. (53) In addition we may not have had sufficient power to detect an association between night-time blood pressure and CIMT.

The evidence for the prognostic importance of night-time blood pressure is compelling. (7) However the potential underlying mechanisms are unclear and include altered sympathetic nervous system activity, disturbed baroreflex sensitivity, increased sodium sensitivity and obstructive sleep apnoea. (7) It may be that night-time blood pressure is subject to less variability and more accurately represents true blood pressure. (54) Reverse causality is also possible and elevated night-time blood pressure may merely be a marker of more severe end organ damage. Cuspidi and colleagues have recently carried out a systematic review and meta-analysis on the association of nocturnal hypertension with subclinical cardiac

and carotid disease documented by ultrasound and found increased left ventricular mass index and CIMT in those with nocturnal hypertension compared to those with nocturnal normotension. (55) They acknowledge the cross-sectional nature of existing data and that the causal relationship between nocturnal hypertension and subclinical cardiovascular disease remains unproven. Our study provides some prospective data on subclinical target organ damage and our results suggest that elevated night-time blood pressure may contribute more than daytime or office blood pressure to cardiac and vascular end organ damage. However large prospective randomised trials with interventions aimed at normalising night-time blood pressure are required to resolve the questions that remain regarding the importance of night-time blood pressure as a therapeutic target. The methods of a large prospective open-label blinded randomised controlled trial have recently been published which will answer this question. The TIME (Treatment In Morning versus Evening) trial aims to randomise 10,269 hypertensive patients to either morning or evening dosing of anti-hypertensive medications. The primary end-point is vascular death or hospitalisation for the composite of non-fatal myocardial infarction or non-fatal stroke. (56)

Limitations:

This is a small study and the sample size may have provided insufficient power to detect true associations between night-time systolic blood pressure and target organ damage in multivariable models and for CIMT in particular. The ultrasound machines used were in fulltime clinical use and could only be used for research scans at the end of the working day therefore collection of imaging data was limited by access to the ultrasound machines. This resulted in a prolonged data collection period. Given these feasibility issues a decision was taken after 50 participants had been recruited to proceed with data analysis. Based on our results we had 86% power to detect a true association between night-time blood pressure and GLS. However for CIMT we had just 33% power and would have required a sample size of 162 to avoid a type II error. (57)

Selection bias is another limitation as those who took part in this study were more likely to self-report a history of hypertension therefore the sample is not

representative of the full Mitchelstown Cohort (40% v 29% previous doctor diagnosis of hypertension). Similarly they were more likely to report being on anti-hypertensive medication at baseline (42% versus 29%). In addition the use of antihypertensive medications in the sample increased between 2010 and 2014 from 42% (n = 21) to 61% (n = 30) which may have impacted results although one would expect that increased use of anti-hypertensive medications would be more likely to influence results towards the null hypothesis. While our study provides some prospective imaging data in a community based sample the lack of ultrasound data at baseline recruitment means it is not possible to draw inference on the temporal relationship for the observed associations of night-time systolic blood pressure with GLS and carotid plaques.

In addition night-time blood pressure profiles are not fully reproducible. (58, 59) We were able to assess the reproducibility of blood pressure profiles in 47 of those who took part in this study. There were no significant differences in mean blood pressure levels between 2010 and 2014. However the reproducibility of dipping status was poor with just 24% maintaining the same profile after 4 years. The reproducibility of blood pressure profiles defined by the absolute blood pressure level was better but still just 40% (Appendix 6). These findings highlight the limitations of applying thresholds and categories to continuously distributed risk factors but also the need to be cautious when interpreting results of studies examining nocturnal blood pressure profiles based on a single ABPM recording.

The strength of this study lies in the novel question addressed as limited studies have assessed the association of night-time blood pressure and GLS. (22, 23) In addition these participants will continue to be followed up for the Mitchelstown Cohort Study so further prospective data will be available over time.

Conclusion:

This study supports an association of night-time systolic blood pressure with markers of subclinical cardiac and vascular disease. We didn't find a significant association between these markers and daytime systolic blood pressure. When assessing ABPM results the absolute night-time systolic blood pressure seems to be

the most important prognostic parameter. However whether normalising night-time blood pressure improves prognosis remains unanswered and only a large randomised controlled trial involving chronotherapy can address this.

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7. Discussion

The overall aim of this thesis was to investigate how ambulatory blood pressure monitoring (ABPM) refines blood pressure measurement and to explore the association of night-time blood pressure with subclinical target organ damage. This was achieved through primary and secondary data analysis and a systematic review.

7.1. Summary of findings

Using ABPM to assess blood pressure clarifies diagnosis and management decisions for hypertension. In addition it allows examination of the night-time blood pressure window, and, as we have shown elevated night-time systolic blood pressure is better associated with subclinical target organ damage than daytime systolic blood pressure or dipping status. Therefore when interpreting ABPM results the night-time systolic blood pressure mean seems to be the most important prognostic marker.

The first objective of this thesis was to examine how ABPM refines office blood pressure measurement. We demonstrated that overall hypertension prevalence was similar when blood pressure was measured in a standardised fashion in the office or by ABPM, however at an individual level ABPM resulted in the reclassification of approximately a quarter of patients, with prevalence rates of white coat and masked hypertension in untreated individuals of 11% and 13% respectively (Chapter 2).

Having demonstrated the utility of ABPM in the assessment of blood pressure we then sought to explore the nocturnal blood pressure window and its association with target organ damage. The second objective was to determine whether dipping status or the absolute night-time blood pressure level is more important. We found absolute night-time blood pressure to be better associated with ECG LVH and microalbuminuria than dipping status (Chapter 3). The third objective was to explore the association of isolated nocturnal hypertension, a classification based on the absolute blood pressure level, and target organ damage. A systematic review of

the literature demonstrated the evidence for the association to be inconclusive as did analysis of data from the Mitchelstown Cohort Study (Chapter 4).

The final objective was to build on the findings of chapter 3 and investigate the association of night-time systolic blood pressure with ultrasound markers of cardiac and vascular damage. We first outlined the image acquisition protocols and quality control methods used to acquire the ultrasound data (Chapter 5). We then examined the association of night-time blood pressure with global longitudinal strain (GLS) measured by speckle tracking echocardiography, carotid intima media thickness (CIMT) and carotid plaques (Chapter 6). The results demonstrated an association for night-time systolic blood pressure with GLS and carotid plaques in unadjusted analysis. The findings persisted for GLS in sex and age adjusted analysis but were attenuated in fully adjusted models.

7.2. Where findings fit in the literature

Few population studies have used ABPM to quantify the burden of hypertension at a population level. In a random sample of adults aged 60 years or older in Spain Banegas et al found hypertension prevalence was lower when the 24 hour ABPM threshold was compared to casual blood pressure measured in the home (62.1% versus 68.8%) while control rates were higher (54.1% versus 37.4%). (1) When they used the daytime threshold they had similar results (60.6% versus 68.8% prevalence and 59.7% versus 37.4% control). We found the prevalence rates using the daytime ABPM threshold compared to the study blood pressure were similar to one another (61% versus 60%) although control rates were higher (54% versus 46%). Similar to Banegas et al we found the 24 hour ABPM threshold resulted in lower prevalence of hypertension (50% versus 60%) and higher control rates (68% versus 46%) compared to study blood pressure (chapter 2). Like us Banegas et al found over a quarter of people had their hypertensive status reclassified by ABPM and conclude that using ABPM would facilitate more appropriate management decisions.

Some have advocated for the routine use of ABPM in research settings. (2, 3) The recent controversy surrounding renal artery denervation supports the use of 24 hour ABPM in clinical trials particularly when new procedures are being tested. (4)

However for population prevalence studies particularly in developing countries the routine use of ABPM is unlikely to be feasible. In addition the results of chapter 2 suggest that overall prevalence rates may not be dramatically impacted on by using ABPM depending on the threshold chosen although this does require further study. However it is clear that at the individual level a large proportion of people are reclassified by ABPM and it should be routinely used to guide management decisions in clinical practice. It should also be noted that chosen thresholds do have an impact on white coat and masked hypertension prevalence rates as the IDACO investigators have also shown with ranges from 6.3% to 12.5% and 9.7% to 19.6% respectively. (5)

A cost-effective analysis of using ABPM to diagnose hypertension found that additional costs related to using ABPM are offset by savings on antihypertensive therapy. (6) The National Institute for Health and Care Excellence (NICE) in the United Kingdom recommend ABPM to confirm the diagnosis of hypertension. (7) A recent statement from the United States Preventive Services Task Force makes a similar recommendation. (8) The European Society of Cardiology hypertension guidelines recommend office blood pressure as the gold standard for screening, diagnosis and management of hypertension but acknowledge the important role of out of office blood pressure in hypertension management. (9) A position paper from the European Society of Hypertension outline a list of clinical indications for the use of ABPM including identifying white coat and masked phenomena. (10) The routine use of ABPM will guide appropriate management and may help address therapeutic inertia as demonstrated by one Irish study. (11) However despite the recommendations of a number of guideline authorities some have urged caution prior to the routine adoption of ABPM for the diagnosis of hypertension citing lack of evidence and that cost savings should not be the primary motivating factor. (12)

The prognostic importance of night-time blood pressure is well recognised. (13, 14) The night-time blood pressure dipping phenomenon has been the subject of much investigation and comment, (15-19) but 28 years after it was first described, (20) it is still not clear if non-dipping should be a therapeutic target. Some investigators have concluded that the absolute night-time blood pressure is better associated

with clinical outcomes than non-dipping. (21, 22) Perez-Lloret et al addressed the comparative role of nocturnal hypertension and non-dipping and their association with target organ damage in 2008 and concluded that nocturnal hypertension was better associated with LVH. More recently there has been increasing interest in the comparative roles of nocturnal hypertension and non-dipping and others have similarly concluded that nocturnal hypertension rather than non-dipping is better associated with target organ damage. (23-27) We explored night-time blood pressure and its association with ECG LVH and microalbuminuria and found the association for the absolute night-time blood pressure level was greater than that for dipping status in multivariable models (Chapter 3). We concluded that review of the absolute night-time blood pressure prior to considering dipping status may be the optimal approach when assessing night-time blood pressure. Others have also proposed that the absolute nocturnal blood pressure is better related to risk and that the circadian variability or dipping status can refine risk evaluation in hypertension. (28)

There are a number of issues that require consideration in relation to this. Firstly blood pressure is a continuous variable and categorising it in any way including dipping is not ideal. However this is true for every blood pressure definition and as already discussed physicians require diagnostic thresholds that define normal and abnormal when managing patients. The analysis in chapter 3 was repeated using dipping as a continuous variable with similar findings (Appendix 4). Secondly night-time blood pressure profiles are not fully reproducible. (16) However definitions that use absolute blood pressure levels rather than dipping status seem to be more reproducible (Appendix 7). (29) Thirdly when non-dipping and nocturnal hypertension co-exist the cardiovascular risk profile of an individual seems to be worse when compared to those who have either profile alone. (23) The presence of both profiles together may therefore represent more advanced hypertensive disease. On the other hand these phenomena frequently exist independently of eachother and may actually represent different underlying processes. (28) It has also been suggested that trying to separate their underlying significance may be difficult. (22, 28) What we need are further intervention trials of chronotherapy to

elucidate if normalising night-time blood pressure profiles improves prognosis. Our work and that of others would suggest that the absolute night-time blood pressure mean should be the primary therapeutic target of such trials. The methods of the TIME (Treatment In Morning versus Evening) study, have recently been published. (30) This is a large prospective randomised open label trial which will address whether evening or morning dosing of antihypertensive medications improves cardiovascular outcome. However the trial design doesn't allow for ABPM data collection so even if the trial has a positive outcome questions will still remain on mechanisms.

A systematic review was undertaken in chapter 4 to explore the association of isolated nocturnal hypertension with target organ damage. Isolated nocturnal hypertension is a very interesting phenomenon and has been shown to be associated with increased risk of mortality and cardiovascular events. (31) It may offer some insight into the pathophysiological basis of the prognostic importance of night-time blood pressure. Just 4 studies addressed the association with target organ damage and different markers were used in each of these so a narrative synthesis was carried out from which no definitive conclusions could be drawn. An updated search carried out in February 2016 revealed no new studies that satisfied the inclusion criteria (Appendix 5). We also carried out an analysis on the association of isolated nocturnal hypertension and its association with microalbuminuria and ECG Cornell Product Voltage in the baseline data from the Mitchelstown Cohort Study. There was no statistically significant increase in either marker of target organ damage in those with isolated nocturnal hypertension compared to those who are normotensive. However the sample size was small with just 29 individuals with isolated nocturnal hypertension so the results may represent a type II error. We focused our analysis on untreated individuals in order to avoid the confounding effect of anti-hypertensive medication.

Some interesting observations can be made on isolated nocturnal hypertension. If night-time blood pressure carries greater prognostic significance as it seems to, one could expect more target organ damage in those with isolated nocturnal hypertension compared to normotensives. We were unable to draw a definite

conclusion on this but examining this profile in more detail in future research studies may help provide some explanation on the greater prognostic importance of night-time blood pressure. On the other hand the reproducibility of isolated nocturnal hypertension has been questioned in a recent study. (32) We examined reproducibility of blood pressure profiles categorised by absolute blood pressure in 47 of the participants who took part in the ultrasound study in chapter 6. We found only modest reproducibility although this was better than that of dipping status (Appendix 6).

The prevalence of isolated nocturnal hypertension varies according to ethnicity and seems to be lowest in Caucasian populations and higher in those of Asian and African ethnicity. (33) If isolated nocturnal hypertension is to be further developed as a research topic, focusing the research on these geographical regions is likely to provide the most impactful results for clinical practice. In addition these areas have different relative contributions of stroke and coronary heart disease to mortality rates with a higher contribution from stroke in China, Africa, and South America. (34) China also has high levels of dietary salt intake and salt sensitivity has been postulated as a potential mechanism for elevated night-time blood pressure. (35, 36) These are interesting research topics to further explore in those with isolated nocturnal hypertension.

Measurement is a key element of medical research and clinical practice. What we measure needs to be a valid and reliable reflection of the true measurement. Chapter 5 focused on the imaging protocols and quality control processes applied to the acquisition and reading of GLS and CIMT. We demonstrated good reproducibility of results which compare favourably with the work of other investigators. (37-44) We were therefore able to apply these methods in chapter 6 which built on chapter 3 and focused on the association of night-time systolic blood pressure with GLS measured by speckle tracking echocardiography, CIMT and carotid plaques.

In chapter 6 we demonstrated an association of night-time systolic blood pressure with subclinical left ventricular systolic dysfunction documented by GLS and carotid

plaques in unadjusted models. Findings for GLS persisted in sex and age adjusted models but were attenuated in fully adjusted models. No such associations were seen for daytime systolic blood pressure. To the best of our knowledge Kalaycioglu et al are the only other investigators to specifically address the association of absolute night-time blood pressure and left ventricular GLS measured by speckle tracking echocardiography. They focused on dipping status but also found night-time systolic blood pressure to be associated with GLS in linear regression models adjusted for age, sex and left ventricular mass index. (45) Their total sample size was 86 and included patients treated for hypertension and type II diabetes mellitus. Similarly in 147 recently diagnosed untreated hypertensive patients Tadic et al demonstrated reduced GLS in non-dippers compared to dippers. They found the mean twenty four blood pressure level to be a significant predictor of GLS. (46) Our study is the first study to specifically address the association of night-time blood pressure level and GLS in a community based sample using speckle tracking echocardiography and supports the findings of others but requires corroboration in larger prospective studies.

Many of the studies that have examined the association of night-time blood pressure with target organ damage are cross-sectional in nature which limits interpretation. (47-50) Chapter 6 provides some follow-up data on target organ damage but the lack of baseline ultrasound data is a limitation. However these patients will continue to be followed up through the Mitchelstown Cohort Study which strengthens the work as there is potential for follow-up imaging studies.

7.3. Implications for research

Some of the research implications of this work have already been discussed such as the use of ABPM in research studies, targeting the absolute night-time blood pressure mean in therapeutic trials, focusing research on isolated nocturnal hypertension studies in geographical areas where it is most prevalent and the need for further adequately powered prospective studies examining the association of night-time blood pressure and subclinical cardiac dysfunction documented by speckle tracking echocardiography. In particular such studies should focus on

untreated individuals in order to avoid the significant confounding effect of anti-hypertensive medications on night-time blood pressure.

The potential mechanisms behind the importance of night-time blood pressure are not well understood but include altered sympathetic nervous system activity, disturbed baroreflex sensitivity, increased sodium sensitivity and sleep quality. (13, 51, 52) In shift workers it has been shown that the average night-time blood pressure during the day shift is similar to the average daytime blood pressure during the night shift. The mean sleep blood pressure was similar during both shift periods. (53) The diurnal variations in blood pressure therefore seem to be determined by activity/sleep cycles rather than any inbuilt rhythm. There is epidemiological evidence supporting an association between obstructive sleep apnoea and hypertension and blunted night-time dip. (54)

Few researchers have addressed the issue of sleep quality and its association with night-time blood pressure. Manning et al examined sleep quality by questionnaire in 79 untreated hypertensive patients. Those who reported good sleep quality had lower mean systolic blood pressure during sleep and were more likely to be dippers. (16) Verdecchia et al again used a questionnaire to assess sleep deprivation in 2934 untreated individuals with hypertension and followed patients up for a median of 7 years. They found night-time systolic blood pressure to be a significant predictor of prognosis when reported sleep deprivation while wearing the ABPM device was less than 2 hours but it lost significance when more than 2 hours sleep deprivation was reported. (55) Similarly increased sleep disturbance assessed subjectively resulted in higher night-time blood pressure and attenuated the association with subclinical cardiac disease documented by echocardiography. (56)

Others have found differences between sleep assessed subjectively and objectively. When measured objectively by wrist actigraphy there was no difference in sleep quality while wearing an ABPM device while subjectively good sleepers reported an adverse impact on sleep quality when wearing the device. (57) Evolving technology such as low stress devices may help reduce any impact of ABPM on sleep quality and make wearing the monitors more amenable to individuals but any new devices

will require formal validation prior to being adopted into clinical practice. (58) The whole area of sleep quality and its impact on the prognostic importance of night-time blood pressure warrants further investigation.

Precision medicine is gaining steady momentum. This is a concept for disease treatment and prevention that takes into account individual variability in molecular, genomic, cellular, clinical, behavioural, physiological, and environmental parameters for each person. (59) The USA have committed to building a national cohort with the aim of carrying out research to improve health outcomes through precision medicine. (60) A recent editorial in the Journal of the American Medical Association discussed how precision medicine might be applied to hypertension. (59) We propose that ABPM combined with markers of target organ damage, along with existing cardiovascular risk prediction tools, already offer the opportunity to profile patients and apply precision medicine to hypertension. Despite this and the inclusion of these tools in clinical guidelines, treatment and control rates of hypertension remain inadequate worldwide. (61) Therefore work aimed to investigate how existing knowledge in the hypertension field should be adequately implemented may be prudent in the first instance. The World Heart Federation's Roadmap for raised blood pressure takes such a practical approach to applying existing knowledge into strategies for improved cardiovascular outcomes. (62) Roadmaps go beyond the evidence to the real world where patients live and healthcare professionals practise in different resource environments.

7.4. Implications for practice

It seems clear that ABPM should be used routinely in the management of hypertension. The routine use of ABPM in clinical practice has been recommended by some experts for many years. (63-65) Without it over a quarter of individuals receive suboptimal care with medications being unnecessarily commenced or titrated in the case of white coat hypertension, or the opposite for masked hypertension. Not only that but it is cost-effective. In addition the prognostic information that night-time blood pressure offers is only available through ABPM. The benefit of normalising night-time blood pressure profiles through therapeutic intervention remains to be fully proven but the initial studies have been promising.

(66-69) However the concept of chronotherapy has yet to be universally adopted into clinical practice guidelines although the American Diabetes Association did give the administration of one or more anti-hypertensives at bedtime a level A recommendation in 2013. (70) The TIME study may change guideline recommendations when its results are available in the future. (30)

Searching for asymptomatic organ damage is recommended in guidelines as part of the work-up of patients with hypertension. Routine evaluation should include a urine sample and ECG. (7, 9) Echocardiography and carotid ultrasound are recommended in the European Society of Cardiology guidelines as additional tests based on history, physical examination and routine laboratory tests. (9) While not yet mainstream, speckle tracking echocardiography, and GLS in particular, is increasingly being adopted into routine clinical use and offers additional prognostic information that can help further guide treatment decisions.

In Ireland the feasibility of using pharmacists to make ABPM more accessible in the community has been shown. (71) Involving community pharmacists in hypertension management has also been shown to improve adherence and control rates. (72) This seems a sensible approach but would require careful planning with engagement of all stakeholders given recent controversies in both Ireland and the UK when plans for pharmacists to administer the flu vaccination were introduced. (73-75) The Pharmaceutical Society of Ireland has engaged in such a consultation process regarding the wider role of pharmacists in the care of patients in the Irish healthcare setting through the Future Pharmacy Practice Project. They are due to publish a report shortly which may offer a position on the future potential input of pharmacists into hypertension management in Ireland. (76)

7.5. Implications for policy

Up until now GPs in Ireland have not been reimbursed to provide ABPM in their general medical services (GMS) contract. Therefore the only way for patients who have a medical card, and are therefore entitled to free healthcare, to access ABPM is through referral to secondary care or out of their own pocket. For the approximately 60% of the population who don't have a medical card this is also

how the system operates. The National Cardiovascular Health Policy 2010-2019 document published in 2010 states that the "overall contribution of ambulatory blood pressure monitoring to primary care detection and management of high blood pressure has yet to be fully ascertained" and suggests that practices be encouraged to invest in the technology. (77) This is outdated given the clinical and cost-effectiveness evidence that now exists. (6, 78) Policy makers have responded, and as of May 1st 2016 GPs will be reimbursed €60 to provide ABPM to patients on the GMS contract. It must be acknowledged that this is a big step forward in the care of those with hypertension in this country. However those without a medical card will continue to face access and financial barriers to ABPM. This is likely to have consequences given results from the Irish Longitudinal Study on Ageing which demonstrated these people are less likely to be on anti-hypertensive medication compared to those with a medical card. (79)

Other policy implications were discussed in chapter 2 such as the importance of investment in health information technology and incentives for data coding. Chronic disease registries are increasingly important in surveillance and measuring healthcare quality. The Spanish have successfully implemented a national ABPM registry. (80) An ABPM database exists in Ireland but has limited information outside of the raw ABPM data. Nonetheless it has been a source of important and fruitful research. (71, 81, 82) There are difficulties that would need to be overcome in order to establish a national ABPM registry in Ireland. Funding is the first obvious difficulty but even if funding were available the establishment of a national registry requires special legislation to be passed. (83) Competing interests from other clinical fields for their own registries will add to the difficulties. Therefore the establishment of a formal national ABPM clinical registry will require visionary and innovative leadership to drive it from a policy and clinical perspective.

7.6. Limitations

The limitations of each of the individual studies included in this thesis have already been discussed and will not be repeated. We have demonstrated an association between night-time blood pressure and a number of markers of target organ damage but we have not resolved the issue of reverse causality. I consider this to

be the main limitation of this work. Elevated night-time blood pressure may merely be a marker of more severe target organ damage rather than a cause of it. This is an inherent problem with cross-sectional data. While chapter 6 provides some prospective data the lack of ultrasound data at baseline recruitment means it is not possible to draw inference on the temporal relationship for the observed associations of night-time systolic blood pressure with GLS and carotid plaques. These may also have been evident at baseline had that data been available.

7.7. Conclusion

I believe hypertension cannot be effectively managed at the individual level without using ABPM. In particular night-time blood pressure offers vital prognostic information that can only be gleaned by using ABPM. The absolute night-time blood pressure level seems to be better associated with target organ damage than dipping and may be a better therapeutic target in future chronotherapy studies. Using ABPM to examine the full twenty four hour blood pressure profile is the way forward in guiding hypertension treatment decisions. However the results of large prospective studies are necessary before chronotherapy can be adopted into guidelines and routine clinical practice.

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Appendix 1: Research training

Modules for credit University College Cork

- Advanced Epidemiology (EH6031) (10 credits)
- Advanced Biostatistics (ST6011) (5 credits)
- Survival Analysis (ST6012) (5 credits)
- Systematic Reviews for the Health Sciences (PG7016) (5 credits)
- The PhD II: From Development to Completion (PG7003) (5 credits)

Other relevant training

- Good Clinical Practice
  University College Cork, Ireland 2013, updated 2015

- The International Society for Cardiovascular Disease Epidemiology and Prevention 46th 10 day international teaching seminar on cardiovascular disease epidemiology and prevention
  Mysore, India 2014

- Fundamentals of Clinical Trials
  Online course from Harvard School of Public Health and Harvard Medical School 2013 – 2014

- An Introduction to Cochrane Systematic Reviews
  University College Galway, Ireland 2013

- Workshop on Scientific Writing
  University College Cork, Ireland 2013

- Health in Numbers: Quantitative Methods in Clinical and Public Health Research
  Online course from Harvard School of Public Health 2012 – 2013

- "Speckle tracking imaging and analysis" Meet the experts - Advanced Training Course
  Leiden University Medical Centre, Leiden, The Netherlands 2013

- Speckle Tracking Echocardiography training
  Leiden University Medical Centre, Leiden, The Netherlands 2012

- Hands-on CIMT Training
  Amsterdam Medical Centre, The Netherlands 2012

- Basic Statistics for Researchers
  University of Limerick 2012

- Hypertension Summer School
  European Society of Hypertension, Dublin, Ireland 2012

- Carotid IMT Clinical Training Course
  University of Wisconsin Atherosclerosis Imaging Research Program Lab, USA 2011

Appendix 2: Research output and dissemination

Thesis publications

- **O'Flynn AM,** Curtin RJ, Perry IJ, Kearney PM. Hypertension Prevalence, Awareness, Treatment and Control. Should 24 hour Ambulatory Blood Pressure Monitoring be the Tool of Choice? Journal of Clinical Hypertension. 2016;18(7):697-702

- **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. Journal of Hypertension. 2015;33(11):2257-64.

- **O'Flynn AM,** Madden JM, Russell AJ, Curtin RJ, Kearney PM. Isolated nocturnal hypertension and subclinical target organ damage: a systematic review of the literature. Hypertension Research. 2015;38(8):570-5

Other original manuscript publications

- **O'Flynn AM**, McHugh SM, Madden JM, Harrington JM, Perry IJ, Kearney PM. Applying the ideal cardiovascular health metrics to couples: a cross-sectional study in primary care. Clinical Cardiology. 2015;38(1):32-8.

- Madden JM, **O'Flynn AM**, Fitzgerald, AP, Kearney PM. Correlation between Short-Term Blood Pressure Variability and Left Ventricular Mass Index: A Meta-Analysis. Hypertension Research. 2016;39(3):171-7

- Madden JM, **O'Flynn AM**, Dolan E, Fitzgerald AP, Kearney PM. Short-term blood pressure variability over 24 h and target organ damage in middle-aged men and women. Journal of Human Hypertension. 2015;29(12):719-25

Abstract publications

- **O'Flynn AM**, Curtin RJ, Perry IJ, Kearney PM. Hypertension Prevalence, Awareness, Treatment and Control. Should 24 Hour Ambulatory Blood Pressure be the Tool of Choice? National Institute of Health Sciences Research Bulletin. Volume 7, Issue 3, page 19, February 2016

- **O'Flynn AM,** Madden JM, Russell AJ, Curtin RJ, Kearney PM. Isolated nocturnal hypertension and subclinical target organ damage: a systematic review of the literature. National Institute of Health Sciences Research Bulletin. Volume 7, Issue 3, page 20, February 2016

- **O'Flynn AM,** McHugh SM, Madden JM, Harrington JM, Perry IJ, Kearney PM. Applying the ideal cardiovascular health metrics to couples: a cross-sectional study in primary care. National Institute of Health Sciences Research Bulletin. Volume 7, Issue 3, page 21, February 2016

- **O'Flynn AM**, Curtin RJ, Perry IJ, Kearney PM. Hypertension prevalence, awareness, treatment and control: the impact of ambulatory blood pressure monitoring. Irish Journal of Medical Science. Volume 183 Supplement 8: 389-435

- **O'Flynn AM**, McHugh SM, Madden JM, Harrington JM, Perry IJ, Kearney PM. Spousal concordance for cardiovascular health in a primary care based sample. Irish Journal of Medical Science. Volume 183 Supplement 8: 389-435

- **O'Flynn AM**, Madden JM, Russell AJ, Curtin RJ, Kearney PM. Isolated nocturnal hypertension and subclinical target organ damage: a systematic review of the literature. Journal of Hypertension. 2014 Volume 32 e-Supplement 1: e556, PP.34.03

- **O'Flynn AM**, Curtin RJ, Perry IJ, Kearney PM. Hypertension prevalence, awareness, treatment and control: the impact of ambulatory blood pressure monitoring. Journal of Hypertension. 2014 Volume 32 e-Supplement 1: e249, PP.10.35

- **O'Flynn AM**, McHugh SM, Madden JM, Harrington JM, Perry IJ, Kearney PM. Spousal concordance for cardiovascular health in a primary care based sample. European Heart Journal. 2014 Volume 35 Supplement 1: P1305

- **O'Flynn AM**, Curtin RJ, Perry, IJ, Kearney, PM. Night-Time Blood Pressure - Does Dipping Tell the Full Story? National Institute of Health Sciences Research Bulletin. Volume 7, Issue 1, page 8, January 2014

- **O'Flynn AM**, Curtin RJ, Perry IJ, Kearney PM. Night-time Blood Pressure and Subclinical Target Organ Damage: Findings from a Primary Care Based Population Sample. Journal of Human Hypertension. 2013 Volume 27 Supplement 1: S17.

- **O'Flynn AM**, Curtin RJ, Perry IJ, Kearney PM. Night-time Blood Pressure and Subclinical Target Organ Damage: Findings from a Primary Care Based Population Sample. Irish Journal of Medical Science 2013 182 SUPPL. 8 (S390).

Oral presentations

- Applying the ideal cardiovascular health metrics to couples: a cross-sectional study in primary care.
  Jacqueline Horgan Bronze Medal Prize meeting, Royal College of Physicians of Ireland, Dublin, 2015.

- Night-time Blood Pressure and Subclinical Target Organ Damage: Findings from an Irish Primary Care Based Population Sample.
  Annual Scientific Meeting of the Association of Departments of General Practice in Ireland, University College Cork, 2014

- Hypertension Prevalence, Awareness, Treatment and Control: The Impact of Ambulatory Blood Pressure Monitoring.
  Annual Scientific Meeting of the Association of Departments of General Practice in Ireland, University College Cork, 2014

Poster presentations

- The Association of Night-time Systolic Blood Pressure with Ultrasound Markers of Subclinical Cardiac and Vascular Damage. The British Cardiovascular Society Annual Conference, Manchester, UK, 2016.

- The Association of Night-time Systolic Blood Pressure with Ultrasound Markers of Subclinical Cardiac and Vascular Damage. New Horizons – Translational Research Conference, School of Medicine, University College Cork. 2015.

- Spousal concordance for cardiovascular health in a primary care based sample. National Institute for Preventive Cardiology Conference, Galway, 2015.

- The Association of Night-time Systolic Blood Pressure with Ultrasound Markers of Subclinical Cardiac and Vascular Damage. National Institute for Preventive Cardiology Conference, Galway, 2015.

- Cardiovascular Health and Spousal Concordance in a Primary Care Based Sample. The Irish Cardiac Society, Athlone, 2014.

- Hypertension Prevalence, Awareness, Treatment and Control: The Impact of Ambulatory Blood Pressure Monitoring. The Irish Cardiac Society, Athlone, 2014.

- Cardiovascular Health and Spousal Concordance in a Primary Care Based Sample. The European Society of Cardiology, Barcelona, Spain, 2014.

- Isolated Nocturnal Hypertension and Subclinical Target Organ Damage: A Systematic Review. The joint meeting of the European Society of Hypertension and International Society of Hypertension, Athens, Greece, 2014.

- Hypertension Prevalence, Awareness, Treatment and Control: The Impact of Ambulatory Blood Pressure Monitoring. The joint meeting of the European Society of Hypertension and International Society of Hypertension, Athens, Greece, 2014.

- Cardiovascular Health and Spousal Concordance in a Primary Care Based Sample. The Annual Scientific Meeting of the Association of the Departments of General Practice in Ireland, University College Cork, 2014.

- Night-time Blood Pressure and Subclinical Target Organ Damage: Findings from an Irish Primary Care Based Population Sample. The Faculty of Public Health Medicine Winter Scientific Meeting in the Royal College of Physicians of Ireland, Dublin, 2013.

- Night-time Blood Pressure and Subclinical Target Organ Damage: Findings from an Irish Primary Care Based Population Sample. The Health Research Board Centre for Health and Diet Research Conference, University College Cork, 2013.

- Night-time Blood Pressure and Subclinical Target Organ Damage: Findings from an Irish Primary Care Based Population Sample. The Irish Cardiac Society, Killarney, 2013.

- Night-time Blood Pressure and Subclinical Target Organ Damage: Findings from an Irish Primary Care Based Population Sample. The British Hypertension Society, University of Greenwich, London, UK, 2013.

- Night-time Blood Pressure and Subclinical Target Organ Damage: Findings from an Irish Primary Care Based Population Sample. The College of Medicine and Health and Health Research Board Clinical Research Facility Conference, University College Cork, 2013.

Awards

- Best poster presentation: Applying the ideal cardiovascular health metrics to couples: a cross-sectional study in primary care.
  National Institute for Preventive Cardiology Conference, Galway, 2015.

- Michael C Berndt Gold Medal for Research Innovation: Night-time Blood Pressure and Subclinical Target Organ Damage: Findings from a Primary Care Based Population Sample
  College of Medicine and Health and Health Research Board Clinical Research Facility Conference, University College Cork, 2013.

Other collaborative work

Poster presentations

- Hanrahan MT, O'Flynn AM, Kearney P, Kearney PM. Appropriate Use of Elective Coronary Angiography in Patients attending Cork University Hospital with suspected Coronary Artery Disease. New Horizons – Translational Research Conference, School of Medicine, University College Cork. 2015.

- Madden JM, O'Flynn AM, Dolan E, Fitzgerald A, Kearney PM. Short-term Blood Pressure Variability over 24 hours and Target Organ Damage in Middle-Aged Men and Women. SPHeRE Network 1st Annual Conference, RCSI, Dublin, 2015.

- Madden JM, O'Flynn AM, Dolan E, Fitzgerald A, Kearney PM. Short-term Blood Pressure Variability over 24 hours and Target Organ Damage in Middle-Aged Men and Women. Conference on Applied Statistics in Ireland, University College Cork, 2015.

- Clarke Ú, Keane E, O'Flynn AM, Kearney PM. Hypertension prevalence in Irish school children: findings from the Cork Children's Lifestyle Study (CCLaS). College of Medicine and Health research day, Universtiy College Cork, 2014.

- Hurley C, Sinnott C, O Connor J, O' Flynn AM, McCarthy V, Kearney P. Engaging GPs in clinical trials: Barriers and facilitators encountered in the Thyroid Hormone Replacement for Subclinical Hypothyroidism (TRUST) study. The Annual Scientific Meeting of the Association of the Departments of General Practice in Ireland, University College Cork, 2014.

- Hanrahan M, McCarthy V, O'Connor J, Russell A, O'Flynn AM, Kearney P. Normalisation of Subclinical Hypothyroidism to Euthyroidism during the TRUST Trial. The Annual Scientific Meeting of the Association of the Departments of General Practice in Ireland, University College Cork, 2014.

- Hurley C, Sinnott C, O Connor J, O' Flynn AM, McCarthy V, Kearney P. Engaging GPs in clinical trials: Barriers and facilitators encountered in the Thyroid Hormone Replacement for Subclinical Hypothyroidism (TRUST) study. The Irish Research Nurses Network (IRNN) 7th Annual Conference, Dublin, 2014.

- Hanrahan M, McCarthy V, O'Connor J, Russell A, O'Flynn AM, Kearney P. Normalisation of Subclinical Hypothyroidism to Euthyroidism during the TRUST Trial. The Health Research Board Centre for Health and Diet Research Conference, University College Cork, 2013.

Appendix 3: Supplemental data for chapter 3

Supplemental table 3.5 Logistic regression results for night to day ratio and target organ damage

	ACR ≥ 1.1 mg/mmol		ECG LVH	
	Odds Ratio (95%CI)	P-value	Odds Ratio (95%CI)	P-value
Night to day ratio (+0.1)	1.6 (1.3 – 2.2)	0.000*	1.6 (1.2 – 2.3)	0.003*
Partially adjusted	1.6 (1.2 – 2.1)	0.001*	1.4 (1.0 – 2.0)	0.03*
Fully adjusted	1.0 (0.7 – 1.5)	0.8	1.1 (0.8 – 1.7)	0.6

ACR = Albumin:creatinine ratio; LVH = Left ventricular hypertrophy; CI = Confidence interval;
SBP = systolic blood pressure; DBP = diastolic blood pressure
Adjusted = sex, age, diabetes, anti-hypertensives, smoking, BMI
Fully adjusted = sex, age, diabetes, anti-hypertensives, smoking, BMI plus adjusted for absolute night-time systolic blood pressure
* Statistically significant

Supplemental table 3.6 Linear regression results for night to day ratio and target organ damage

	Log ACR		Cornell product	
	Beta coefficient (95% CI)	P-value	Beta coefficient (95%CI)	P-value
Night to day ratio (+0.1)	0.2 (0.1 – 0.2)	0.000*	120 (67 – 174)	0.000*
Partially adjusted	0.1 (0.1 – 0.2)	0.000*	85 (30 – 140)	0.002*
Fully adjusted	- 0.03 (-0.1 – 0.05)	0.5	1 (-61 – 64)	1.0

ACR = Albumin:creatinine ratio; CI = Confidence interval;
ACR log transformed due to skewed data
Adjusted = sex, age, diabetes, anti-hypertensives, smoking, BMI
Fully adjusted = sex, age, diabetes, anti-hypertensives, smoking, BMI plus adjusted for absolute night-time systolic blood pressure
* Statistically significant
Variance inflation factors were calculated for the adjusted models and all values were under 1.7 indicating multi-collinearity did not arise

Supplemental table 3.7 Logistic regression results for absolute blood pressure and target organ damage in treated participants

n=350	ACR ≥ 1.1 mg/mmol		ECG LVH	
	Odds Ratio (95%CI)	P-value	Odds Ratio (95%CI)	P-value
Night-time SBP (+10 mmHg)	1.4 (1.2 – 1.8)	<0.001*	1.3 (1.1 – 1.7)	0.01*
Partially adjusted	1.4 (1.1 – 1.8)	0.002*	1.3 (1.0 – 1.7)	0.02*
Fully adjusted	1.5 (1.1 – 2.0)	0.01*	1.6 (1.1 – 2.2)	0.007*
Night-time DBP (+5 mmHg)	1.2 (1.0 – 1.5)	0.02*	1.0 (0.8 – 1.2)	0.8
Partially adjusted	1.2 (1.0 – 1.5)	0.02*	1.0 (0.8 – 1.2)	1.0
Fully adjusted	1.3 (1.0 – 1.7)	0.03*	1.2 (0.9 – 1.5)	0.3
Daytime SBP (+10 mmHg)	1.3 (1.0 – 1.6)	0.02*	1.1 (0.8 – 1.4)	0.6
Adjusted	1.3 (1.0 – 1.6)	0.06	1.0 (0.8 – 1.4)	0.7
Fully adjusted	0.9 (0.7 – 1.3)	0.7	0.7 (0.5 – 1.1)	0.1
Daytime DBP (+5mmHg)	1.1 (0.9 – 1.3)	0.2	0.9 (0.7 – 1.1)	0.2
Adjusted	1.1 (0.9 – 1.3)	0.3	0.9 (0.7 – 1.1)	0.3
Fully adjusted	0.9 (0.7 – 1.2)	0.5	0.8 (0.6 – 1.1)	0.1
Twentyfour hour SBP (+10 mmHg)	1.5 (1.1 – 1.8)	0.002*	1.2 (0.9 – 1.6)	0.1
Adjusted	1.4 (1.1 – 1.8)	0.008*	1.2 (0.9 – 1.6)	0.2
Twentyfour hour DBP (+5 mmHg)	1.2 (1.0 – 1.4)	0.08	0.9 (0.8 – 1.2)	0.5
Adjusted	1.2 (1.0 – 1.4)	0.1	0.9 (0.7 – 1.2)	0.6

ACR = Albumin:creatinine ratio; LVH = Left ventricular hypertrophy; CI = Confidence interval; SBP = systolic blood pressure; DBP = diastolic blood pressure

Adjusted = sex, age, diabetes, smoking, BMI

Fully adjusted = sex, age, diabetes, smoking, BMI plus daytime blood pressure further adjusted for night-time blood pressure and vice versa

* Statistically significant

Supplemental table 3.8. Logistic regression results for absolute blood pressure and target organ damage in untreated participants

n=670	ACR ≥ 1.1 mg/mmol		ECG LVH	
	Odds Ratio (95%CI)	P-value	Odds Ratio (95%CI)	P-value
Night-time SBP (+10 mmHg)	1.7 (1.4 – 2.0)	<0.001*	1.3 (1.1 – 1.6)	0.01*
Partially adjusted	1.6 (1.3 – 1.9)	<0.001*	1.3 (1.0 – 1.6)	0.04*
Fully adjusted	1.6 (1.2 – 2.1)	0.002*	1.2 (0.8 – 1.7)	0.5
Night-time DBP (+5 mmHg)	1.4 (1.2 – 1.6)	<0.001*	1.1 (0.9 – 1.3)	0.6
Partially adjusted	1.4 (1.2 – 1.6)	<0.001*	1.1 (0.9 – 1.4)	0.5
Fully adjusted	1.3 (1.0 – 1.7)	0.009*	1.0 (0.8 – 1.4)	0.8
Daytime SBP (+10 mmHg)	1.5 (1.3 – 1.7)	<0.001*	1.3 (1.0 – 1.6)	0.02*
Adjusted	1.4 (1.2 – 1.7)	<0.001*	1.3 (1.0 – 1.6)	0.04*
Fully adjusted	1.0 (0.7 – 1.3)	0.9	1.2 (0.8 – 1.7)	0.5
Daytime DBP (+5mmHg)	1.3 (1.2 – 1.5)	<0.001*	1.1 (0.9 – 1.3)	0.5
Adjusted	1.3 (1.1 – 1.5)	0.001*	1.1 (0.9 – 1.4)	0.4
Fully adjusted	1.1 (0.9 – 1.3)	0.6	1.1 (0.8 – 1.5)	0.6
Twentyfour hour SBP (+10 mmHg)	1.6 (1.3 – 1.9)	<0.001*	1.3 (1.0 – 1.6)	0.02*
Adjusted	1.5 (1.2 – 1.8)	<0.001*	1.3 (1.0 – 1.7)	0.04*
Twentyfour hour DBP (+5 mmHg)	1.4 (1.2 – 1.6)	<0.001*	1.1 (0.9 – 1.3)	0.5
Adjusted	1.4 (1.2 – 1.6)	<0.001*	1.1 (0.9 – 1.4)	0.4

ACR = Albumin:creatinine ratio; LVH = Left ventricular hypertrophy; CI = Confidence interval; SBP = systolic blood pressure; DBP = diastolic blood pressure

Adjusted = sex, age, diabetes, anti-hypertensives, smoking, BMI

Fully adjusted = sex, age, diabetes, anti-hypertensives, smoking, BMI plus daytime blood pressure further adjusted for night-time blood pressure and vice versa

* Statistically significant

Supplemental table 3.9. Logistic regression results for dipping status and target organ damage in treated participants

n=350	ACR ≥ 1.1 mg/mmol	ECG LVH	ACR ≥ 1.1 mg/mmol		ECG LVH	
	n = 50	n = 38	OR (95%CI)	P-value	OR (95%CI)	P-value
	n	n				
Dippers	22	17	1		1	
Non-dippers	18	12	1.7 (0.9 – 3.3)	0.1	1.4 (0.6 – 3.0)	0.4
Extreme dippers	7	4	0.9 (0.4 - 2.3)	0.9	0.7 (0.2 – 2.1)	0.5
Reverse dippers	3	5	2.7 (0.7 – 11.1)	0.2	8.1 (2.2 – 29.3)	0.001*
Partially adjusted						
Dippers			1		1	
Non-dippers			1.6 (0.8 – 3.3)	0.2	1.3 (0.6 – 2.9)	0.6
Extreme dippers			0.9 (0.4 – 2.2)	0.8	0.7 (0.2 – 2.2)	0.5
Reverse dippers			2.6 (0.6 – 11.1)	0.2	7.0 (1.8 – 26.8)	0.005*
Fully adjusted						
Dippers			1		1	
Non-dippers			1.2 (0.6 – 2.5)	0.6	1.1 (0.5 – 2.7)	0.8
Extreme dippers			1.3 (0.5 – 3.3)	0.6	0.8 (0.2 – 2.6)	0.7
Reverse dippers			1.0 (0.2 – 5.2)	1.0	4.9 (1.0 – 23.3)	0.046*

ACR = Albumin:creatinine ratio; LVH = Left ventricular hypertrophy; OR = Odds ratio; CI = Confidence interval
Partially adjusted = sex, age, diabetes, smoking, BMI
Fully adjusted = sex, age, diabetes, smoking, BMI plus further adjusted for night-time systolic blood pressure
* Statistically significant

Supplemental table 3.10. Logistic regression results for dipping status and target organ damage in untreated participants

n=670	ACR ≥ 1.1 mg/mmol	ECG LVH	ACR ≥ 1.1 mg/mmol		ECG LVH	
	n = 67	n = 32	OR (95%CI)	P-value	OR (95%CI)	P-value
	n	n				
Dippers	42	17	1		1	
Non-dippers	16	6	1.2 (0.6 – 2.1)	0.6	1.1 (0.4 – 2.7)	0.9
Extreme dippers	7	8	0.4 (0.2 – 0.9)	0.02*	1.2 (0.5 – 2.8)	0.7
Reverse dippers	2	1	1.6 (0.3 – 7.6)	0.6	1.9 (0.2 – 15.9)	0.5
Partially adjusted						
Dippers			1		1	
Non-dippers			1.0 (0.5 – 1.9)	1.0	0.8 (0.3 – 2.3)	0.7
Extreme dippers			0.4 (0.2 – 0.8)	0.02*	1.1 (0.4 – 2.7)	0.9
Reverse dippers			1.4 (0.3 – 6.8)	0.7	1.5 (0.2 – 13.5)	0.7
Fully adjusted						
Dippers			1		1	
Non-dippers			0.8 (0.4 – 1.5)	0.4	0.6 (0.2 – 1.8)	0.4
Extreme dippers			0.5 (0.2 – 1.1)	0.1	1.4 (0.5 – 3.5)	0.5
Reverse dippers			0.5 (0.1 – 2.9)	0.4	0.7 (0.1 – 7.1)	0.8

ACR = Albumin:creatinine ratio; LVH = Left ventricular hypertrophy; OR = Odds ratio; CI = Confidence interval
Partially adjusted = sex, age, diabetes, smoking, BMI
Fully adjusted = sex, age, diabetes, smoking, BMI plus further adjusted for night-time systolic blood pressure
* Statistically significant

Supplemental table 3.11. Logistic regression results for pulse pressure and target organ damage				
n=1046	ACR ≥ 1.1 mg/mmol Odds Ratio (95%CI)	P-value	ECG LVH Odds Ratio (95%CI)	P-value
Night-time Pulse Pressure (+10 mmHg)	1.7 (1.4 – 2.0)	<0.001*	1.7 (1.4 – 2.1)	<0.001*
Adjusted	1.6 (1.3 – 1.9)	<0.001*	1.6 (1.3 – 2.1)	<0.001*
Daytime Pulse Pressure (+10 mmHg)	1.4 (1.2 – 1.7)	<0.001*	1.5 (1.2 – 1.8)	<0.001*
Adjusted	1.3 (1.1 – 1.6)	0.006*	1.3 (1.0 – 1.7)	0.02*

ACR = Albumin:creatinine ratio; LVH = Left ventricular hypertrophy; CI = Confidence interval; SBP = systolic blood pressure; DBP = diastolic blood pressure
Adjusted = sex, age, diabetes, anti-hypertensives, smoking, BMI
* Statistically significant

Appendix 4: Systematic review search strategy

MOOSE checklist for search strategy

Qualifications of searchers

Dr. AnneMarie O'Flynn and Mr. Jamie Madden have both received training in systematic review methods. They both completed module PG7016 "Systematic Reviews for the Health Sciences" in University College Cork. Dr. O'Flynn has also completed the Health Research Board Cochrane course "An introduction to systematic reviews, the Cochrane Collaboration and the Cochrane Library". Search methodology was discussed with Mr. Cathal Kerrigan, Therapies & Basic Sciences for Medicine Librarian, Boston Scientific Health Sciences Library, University College Cork.

Search strategy

Three medical literature databases were searched in March 2014. No filter was applied to the publication dates. The following search terms, combined using 'AND' or 'OR' according to the principles of Boolean logic, were used as text words and/or MESH terms:

Circadian Rhythm [MeSH Major Topic]
Blood Pressure Monitoring, Ambulatory [MeSH Major Topic]
hypertension
(isolated OR masked) AND (nocturnal OR 'night-time' OR nighttime OR 'night time') AND hypertension
(end OR target) AND organ AND (damage OR disease)
microalbuminuria
left AND ventricular AND hypertrophy
left AND ventricular AND mass
electrocardio*
echocardio*
arterial AND stiffness
augmentation AND index

pulse AND wave AND velocity

carotid AND ultrasound

carotid AND intima AND media AND thickness

cimt

asymptomatic AND carotid AND stenosis

ankle AND brachial AND index

flow AND mediated AND dilat*

endothelial AND dysfunction

magnetic AND resonance AND imaging

computed AND tomography

mri

ct

white AND matter AND hyperintensities

white AND matter AND lesions

retinopathy

retinal AND photography

coronary AND calcium AND score

These terms were further combined as follows:
(((((isolated OR masked) AND (nocturnal OR night-time OR nighttime OR night time) AND hypertension)) OR (((Hypertension) AND "Blood Pressure Monitoring, Ambulatory") AND "Circadian Rhythm"))) AND ((((((((((((((((((((microalbuminuria) OR (Left AND ventricular AND hypertrophy)) OR (Left AND ventricular AND mass)) OR electrocardio*) OR echocardio*) OR (arterial AND stiffness)) OR (augmentation AND index)) OR (Pulse AND wave AND velocity)) OR (carotid AND ultrasound)) OR (carotid AND intima AND media AND thickness)) OR CIMT) OR (asymptomatic AND carotid AND stenosis)) OR (ankle AND brachial AND index)) OR (flow AND mediated AND dila*)) OR (endothelial AND dysfunction)) OR (((((((magnetic AND resonance AND imaging)) OR (computed AND tomography)) OR MRI) OR CT)) AND (((white AND matter AND hyperintensities)) OR (white AND matter AND lesions)))) OR retinopathy) OR (retinal AND photography)) OR (Coronary AND calcium AND score))) OR ((end OR target) AND organ AND (damage OR disease)))

We developed the search strategy for PubMed and adapted it for use in the other databases.

Effort to include all available studies

Studies in all languages were included

Databases searched

PubMed →109 titles identified (10 potentially relevant)

EMBASE → 813 titles identified (8 potentially relevant)

Cochrane Library → 32 identified (0 relevant)

Search engine and reference manager

Google Chrome was the web browser used to search the databases and potentially relevant studies were imported into the Endnote reference management software package.

Use of hand searching

The references of the included studies and those of reviews on the subject were examined for further potentially relevant studies.

List of citations included and excluded

Included:

1. Li Y, Staessen JA, Lu L, Li L-H, Wang G-L, Wang J-G. Is Isolated Nocturnal Hypertension a Novel Clinical Entity?: Findings From a Chinese Population Study. Hypertension. 2007 August 1, 2007;50(2):333-9.

2. Lu L, Li Y, Huang QF. [The relationship between isolated nocturnal hypertension and left ventricular hypertrophy]. Zhonghua nei ke za zhi [Chinese journal of internal medicine]. 2008 Oct;47(10):819-22.

3. Wijkman M, Länne T, Engvall J, Lindström T, Östgren CJ, Nystrom FH. Masked nocturnal hypertension—a novel marker of risk in type 2 diabetes. Diabetologia. 2009 2009/07/01;52(7):1258-64.

4. Ogedegbe G, Spruill TM, Sarpong DF, Agyemang C, Chaplin W, Pastva A, et al. Correlates of Isolated Nocturnal Hypertension and Target Organ Damage in a Population-Based Cohort of African Americans: The Jackson Heart Study. Am J Hypertens. 2013 May 15. Epub 2013/05/17.

Excluded:

1. Endothelial-dependent flow-mediated dilation in African Americans with masked-hypertension. Veerabhadrappa P, Diaz KM, Feairheller DL, Sturgeon KM, Williamson ST, Crabbe DL, Kashem AM, Brown MD. Am J Hypertens. 2011 Oct;24(10):1102-7

Reason excluded:

Didn't assess isolated nocturnal hypertension (day and night masked hypertension assessed together)

2. Fan HQ, Li Y, Thijs L, Hansen TW, Boggia J, Kikuya M, et al. Prognostic value of isolated nocturnal hypertension on ambulatory measurement in 8711 individuals from 10 populations. Journal of hypertension. 2010 Oct;28(10):2036-45.

Reason excluded:

Examined hard cardiovascular endpoints

3. Epidemiology, pathophysiology, and prognosis of isolated night - time hypertension. Wang J.-G. Journal of Hypertension 2012 30 SUPPL. 1 (e17)

Reason excluded:

Conference abstract including duplicate analysis of Chinese population

4. The effect of isolated masked nocturnal hypertension on arterial stiffness. Bakalakou E, Kyfnidis K, Kallistratos E, Tsoukas A, Hamondraka E, Zacharopoulou I, Kouremenos N, Chiotelis I, Koukouzeli A, Manolis A. European Heart Journal 2013 34 SUPPL. 1 (1050)

Reason excluded:

Conference abstract didn't assess isolated nocturnal hypertension (Defined masked nocturnal hypertension)

5. Night - time hypertension and target organ damage in never treated patients. Kyvelou S., Vyssouli G., Karpanou E., Gialernios T., Tzamou V., Lampropoulos K., Adamopoulos D. Stefanadis C. Journal of Hypertension 2010 28 SUPPL. A (e81)

Reason excluded:

Conference abstract without a normotensive comparison group

6. Li LH, Li Y, Huang QF, Sheng CS, Staessen JA, Wang JG.Isolated nocturnal hypertension and arterial stiffness in a Chinese population. Blood Press Monit. 2008 Jun;13(3):157-9.

Reason excluded:

Duplicate study

7. Masked hypertension, nocturnal blood pressure and retinopathy in normotensive patients with type 1 diabetes. Rodrigues TC, Canani LH, Viatroski RS, Hoffmann LH, Esteves JF, Gross JL. Diabetes Res Clin Pract. 2010 Feb;87(2):240-5.

Reason excluded:

Didn't assess isolated nocturnal hypertension (Defined masked nocturnal hypertension)

8. Masked nocturnal hypertension and target organ damage in hypertensives with well-controlled self-measured home blood pressure. Hoshide S, Ishikawa J, Eguchi K, Ojima T, Shimada K, Kario K. Hypertens Res. 2007 Feb;30(2):143-9.

Reason excluded:

Didn't assess isolated nocturnal hypertension (Defined masked nocturnal hypertension)

9. Kawano Y, Horio T, Matayoshi T, Kamide K. Masked hypertension: subtypes and target organ damage. Clin Exp Hypertens. 2008 Apr;30(3):289-96.

Reason excluded:

Review article

Articles published in languages other than English

The authors of the included non-English article were contacted for an English version. This was not available. The article was translated with an online translation programme and this was checked with a native Chinese speaker.

Abstracts and unpublished studies

Proceedings papers were considered for inclusion but none met the inclusion criteria for the final narrative review.

Contact with authors

The authors of the Lu et al article were contacted for an English version. This was not available. We also contacted the authors of the Wijkman et al study for further descriptive information on the isolated nocturnal hypertension group but this was also unavailable.

Updated search February 2016

An updated search was carried out on the 22nd of February 2016. Four new potential titles were identified. The abstracts of these were reviewed and compared to the inclusion criteria. One was excluded as it was a review article. The other 3 abstracts were proceedings papers. These were also excluded. One assessed isolated nocturnal hypertension in children attending paediatric nephrology units and was therefore not population based. One assessed nocturnal hypertension not isolated nocturnal hypertension. The source population for the final study wasn't evident from the abstract. An attempt to contact the author to clarify this was unsuccessful. The study was therefore also excluded.

List of citations excluded February 2016

Excluded

1. Isolated nocturnal hypertension is associated with increased pulse wave velocity and carotid intima-media thickness in children with chronic kidney disease (CKD): Results from the 4C study. Duzova A., Doyon A., Kirchner M., Kracht D., Zeller R., Bayazit A.K., Sozeri B., Canpolat N., Karagoz T., Deveci M., Niemirska A., Erdem S., Kassai B., Candan C., Simonetti G., Melk A., Querfeld U., Schaefer F., Wühl E. Pediatric Nephrology 2015 30:9 (1552-1553)

Reason excluded:

Assessed isolated nocturnal hypertension in children attending paediatric nephrology units and was therefore not population based.

2. Serum cystatin-C as a marker for left ventricular hypertrophy in isolated nocturnal hypertension. Androulakis E., Papageorgiou N., Chatzistamatiou E., Latsios G., Tsioufis C., Papaioannou S., Brili S., Antoniades C., Kallikazaros I., Tousoulis D. European Heart Journal 2015 36 SUPPL. 1 (675-676)

Reason excluded:

Source population not clear.

3. Correlates of isolated nocturnal hypertension and target organ damage in untreated hypertension. Androulakis E., Tousoulis D., Chatzistamatiou E., Papageorgiou N., Moustakas G., Hatzis G., Toutouzas K., Synetos A., Kallikazaros I., Stefanadis C. European Heart Journal 2014 35 SUPPL. 1 (31)

Reason excluded:

Assessed nocturnal hypertension not isolated nocturnal hypertension

4. Isolated nocturnal hypertension - a new clinical entity identified from ambulatory blood pressure monitoring. Dukát A., Mistríková L., Baláž D., Sabaka P., Čelovská D., Gavorník P., Gašpar L. Interni Medicina pro Praxi 2014 16:4 (141-144)

Reason excluded:

Review article

Appendix 5: Participant information leaflet and consent form

CONSENT BY SUBJECT FOR PARTICIPATION IN RESEARCH PROTOCOL

Section A

Protocol Number:_____ Patient Name:_____

Title of Protocol: Hypertension to Cardiovascular Disease, Can We Map the Course and Prevent the End-points?

Doctor(s) Directing Research: Dr. AnneMarie O'Flynn Phone: (021 4205537)

You are being asked to participate in a research study. The doctors at University College Cork study the nature of disease and attempt to develop improved methods of diagnosis and treatment. In order to decide whether or not you want to be a part of this research study, you should understand enough about its risks and benefits to make an informed judgment. This process is known as informed consent. This consent form gives detailed information about the research study, which will be discussed with you. Once you understand the study, you will be asked to sign this form if you wish to participate.

Section B

I. NATURE AND DURATION OF PROCEDURE(S):

As part of this study you will have an ultrasound scan of your carotid arteries. You have one carotid artery on each side of your neck. This is a painless, non-invasive diagnostic test that uses low-power, high-frequency sound waves which come from an ultrasound probe through the neck and are then reflected back to form an image of the blood vessels. The images will be used to measure the thickness of the vessel wall and to check for the presence of any significant narrowing of the blood vessels. For the scan you will be asked to lie on a couch and you will have to move your head from left to right depending on which side is being imaged. Cold gel will be applied to the skin and the ultrasound probe will be moved up and down over the neck. The scan will take approximately 40 minutes to complete.

As part of this study you will also have an echocardiogram. This is similar to a carotid ultrasound scan except the sound waves are transmitted to the heart through the chest wall and are then reflected back to form an image of the heart. The images will be used to analyse the function of the heart muscle. For the scan you will have to lie at an angle on your side and your chest area will be exposed. Cold gel will be applied to the skin and the ultrasound probe will be moved up and down over the chest. The scan will take approximately 40 minutes to complete.

We may also ask you to have a 24 hour blood pressure monitor. You will already have had one of these when you were first seen for the Cork and Kerry Phase II Study (now known as the Mitchelstown Study). Similar to the last time a cuff will be placed on your arm which will be connected to a small box. You will be

asked to wear this for 24 hours. The cuff will blow up at regular intervals throughout the day and night to measure your blood pressure. You will also be asked to complete a questionnaire on your usual sleep quality and to keep a record of activities and sleep times while you wear the monitor.

II. POTENTIAL RISKS AND BENEFITS:

There is little risk involved in an ultrasound scan. You will have to lie as instructed for the scan. There is a possibility that a significant abnormality may be detected. If this were to happen an appointment with a specialist will be arranged for you. The purpose of the scans is to check for early changes in your blood vessels and heart. Your results will be looked at with many others for an association with certain blood pressure patterns. If an association is identified it may allow doctors to identify people who may be at higher risk of developing heart disease and strokes in the future and treat them to prevent these events. You may find that the blood pressure cuff is uncomfortable and may cause you to have difficulty sleeping as it will blow up at intervals during the night also.

III. POSSIBLE ALTERNATIVES:

You may choose not to participate.

Section C AGREEMENT TO CONSENT

The research project and the treatment procedures associated with it have been fully explained to me. All experimental procedures have been identified and no guarantee has been given about the possible results. I have had the opportunity to ask questions concerning any and all aspects of the project and any procedures involved. I am aware that participation is voluntary and that I may withdraw my consent at any time. I am aware that my decision not to participate or to withdraw will not restrict my access to health care services normally available to me. Confidentiality of records concerning my involvement in this project will be maintained in an appropriate manner. When required by law, the records of this research may be reviewed by government agencies and sponsors of the research.

I understand that the sponsors and investigators have such insurance as is required by law in the event of injury resulting from this research.

I, the undersigned, hereby consent to participate as a subject in the above described project conducted at the Cork Teaching Hospitals. I have received a copy of this consent form for my records. I understand that if I have any questions concerning this research, I can contact the doctor(s) listed above. If I have further queries concerning my rights in connection with the research, I can contact the Clinical Research Ethics Committee of the Cork Teaching Hospitals, Lancaster Hall, 6 Little Hanover Street, Cork.

After reading the entire consent form, if you have no further questions about giving consent, please sign where indicated.

Signature of Doctor: _____

Signature of Subject: _____

Date: _____ Time: _____

Appendix 6: Short report on the reproducibility of nocturnal blood pressure profiles

Background:

The limited reproducibility of night-time blood pressure patterns is recognised (1) and it has been suggested that using absolute blood pressure categories rather than dipping status may be more reproducible. (2) However, this approach is also limited with just one third of those with isolated nocturnal hypertension retaining this pattern after 2 to 4 years in one small study. (3) This was again examined more recently with similar findings. (4) We therefore sought to establish the reproducibility of nocturnal blood pressure profiles in participants of the Mitchelstown Cohort Study.

Methods:

Baseline ABPM measurements were performed using the MEDITECH ABPM-05 in 2010 and data was stored using the dabl ABPM system. The monitors were programmed to record the blood pressure every 30 minutes throughout the 24 hour period. Participants kept a diary of the times they went to bed and got up. Diary times were used to calculate mean daytime and night-time blood pressures. Mean 24 hour blood pressure was calculated as the mean of all the readings throughout the 24 four hour period.

Follow-up ABPM measurements were performed in 2014 using the Spacelabs 90217 monitor. Measurements were performed every 30 minutes throughout the day and night. Data was stored using the Spacelabs 92506 Ambulatory Blood Pressure Report Management System software. Participants kept a diary of the times they went to bed and got up. Diary times were used to calculate mean daytime and night-time blood pressures. Mean 24 hour blood pressure was calculated as the mean of all the readings throughout the 24 four hour period.

Night-time ambulatory blood pressure was categorised by dipping status as follows:

(1) Dipping pattern: 10 to 20% fall in night-time systolic blood pressure

(2) Non-dipping pattern: < 10% fall in night-time systolic blood pressure

(3) Extreme dipping pattern: > 20% fall in night-time systolic blood pressure

(4) Reverse dipping pattern: Rise in night-time systolic blood pressure

Ambulatory blood pressure was also categorised based on the absolute blood pressure levels into 4 groups:

(1) Normotension: Daytime blood pressure < 135/85 mmHg and night-time blood pressure < 120/70 mmHg

(2) Isolated daytime hypertension: Daytime blood pressure ≥ 135/85 mmHg and night-time blood pressure < 120/70 mmHg

(3) Isolated nocturnal hypertension: Daytime blood pressure < 135/85 mmHg and night-time blood pressure ≥ 120/70 mmHg

(4) Sustained day-night hypertension: Daytime blood pressure ≥ 135/85 mmHg and night-time blood pressure ≥ 120/70 mmHg

Mean blood pressures for 2010 and 2014 were compared using a paired t-test. The reproducibility of night-time dipping status and absolute blood pressure patterns were assessed using Cohen's kappa statistic. (5)

Results:

Fifty individuals took part in this study. We excluded 3 studies from the analysis due to incomplete follow-up ABPM data. Mean daytime blood pressure was 129/77 mmHg and mean night-time blood pressure was 114/66 mmHg on follow-up ABPM. Overall mean blood pressures were similar in 2010 and 2014. Table 1. The reproducibility of blood pressure profiles categorised by dipping status was low at 24% with a kappa statistic of -0.11 ($p = 0.89$) while reproducibility based on categorisation by absolute blood pressure was fair at 40% with a kappa statistic of 0.21 ($p < 0.005$). Tables 2 and 3.

Table 1. Blood pressure levels 2010 v 2014			
N =47	2010 Mean+/-SD	2014 Mean+/-SD	p-value
Daytime systolic, mmHg	133+/-12	129+/-14	0.05
Daytime diastolic, mmHg	79+/-9	77+/-8	0.2
Night-time systolic, mmHg	117+/-15	114+/-17	0.1
Night-time diastolic, mmHg	66+/-9	66+/-9	0.9
Twenty four systolic, mmHg	127+/-11	123+/-14	0.05
Twenty four diastolic, mmHg	74+/-8	73+/-8	0.3
3 follow-up ABPM results excluded due to incomplete data			

Table 2. Dipping status 2010 v 2014					
N = 47	2014				
2010	Dippers	Non-dippers	Extreme dippers	Reverse dippers	Total
Dippers	5	11	5	1	22
Non-dippers	8	3	2	2	15
Extreme dippers	2	3	1	0	6
Reverse dippers	1	1	0	2	4
Total	15	18	8	5	47
kappa statistic = -0.11 (p = 0. 89)					

Table 3. Blood pressure categories 2010 v 2014					
2010	Normotension	Isolated daytime hypertension	Isolated nocturnal hypertension	Day/night hypertension	Total
Normotension	9	0	1	0	10
Isolated daytime hypertension	4	3	1	6	14
Isolated nocturnal hypertension	7	0	4	1	12
Day/night hypertension	4	2	2	3	11
Total	24	5	8	10	47
kappa statistic = 0.21 (p < 0.005)					

Discussion:

Our findings demonstrates the limited reproducibility of night-time blood pressure profiles with poor reproducibility of dipping status and only fair reproducibility of absolute blood pressure categories despite overall similar mean blood pressures. The use of antihypertensive medications increased between 2010 and 2014 from 42% (n = 21) to 61% (n = 30) which may have impacted these results. However when those not on medication were analysed separately the kappa statistics were -0.2 (p = 0.9) for dipping status and 0.43 (p < 0.001) for absolute blood pressure

categories. Blood pressure is a continuous risk factor. (6) Thresholds define the levels where investigation and treatment have more benefit than harm, (7) and for this reason are important but clinicians and public health professionals need to recognise the limitations of thresholds and that significant numbers of events occur in those below definitions of normal. (8)

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Appendix 7: Portable document format (PDF) of publications