AN EVALUATION OF A COMMUNITY PHARMACY BASED, PHARMACIST-LED INTERVENTION PACKAGE TARGETED TO THE PATIENTS' ADHERENCE STATUS, TO ACHIEVE AND MAINTAIN TARGET BLOOD PRESSURE (BP) CONTROL BY OPTIMISING ANTIHYPERTENSIVE MEDICINE ADHERENCE

BY

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ABSTRACT

Antihypertensive pharmacotherapy is associated with poor adherence. No validated method exists to establish patients' likely adherence level. A systematic review and a single, Swedish community pharmacy practice-based pilot study were undertaken investigating blood pressure (BP) optimization from pharmacist-led, community pharmacy-based antihypertensive adherence interventions titrated to individual patients.

The systematic review showed generic interventions are often used for optimizing BP. Different intervention outcomes vary: positive, negative and no effect has been demonstrated.

Pilot study participants (n=153) were categorised into adherence subgroups (A=Adherent, IR=Intentionally non-adherent rational, II=Intentionally non-adherent irrational, U=Unintentionally non-adherent) based on responses to questionnaire format adherence screens. Interventions were designed intuitively to optimize adherence for each subgroup: changes in blood pressure and adherence attitudes were assessed.

A significant reduction in mean systolic BP (SBP) (3 mmHg, $P<0.05$), with no change in mean diastolic BP (DBP) was seen overall. However, outcomes varied with subgroup: adherence was enhanced in the U subgroup (decreased SBP: 3 mmHg; DBP: no change), but indications of a detrimental effect were observed in the II subgroup (SBP: no change; increased DBP: 3 mmHg).

It is feasible to assign patients to different adherence subgroups in community pharmacy, which may optimize medicines adherence through personalization of interventions.

DEDICATION

To my loving parents

"A merry heart doeth good like a medicine"

Proverbs 17:22, King James Version

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Uppsala, Sweden 11th January 2017 Amirthan Amirthalingam

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LIST OF DEFINITIONS AND/OR ABBREVIATIONS

(xy)*	Add-on drug after visit 0
8-item MMAS	8-item Morisky Medication Adherence Scale
A	Adherent
AC	Allocation concealment (selection bias)
ACEinh	Angiotensin Converting Enzyme (ACE) inhibitor
ACEinhHCT	Angiotensin Converting Enzyme (ACE) inhibitor and hydrochlorothiazide
AD	Adherence
ADR	Adverse drug reaction
ADSG	Adherence subgroup
AH	Antihypertensive
AHMG	Antihypertensive medication group
Alpha	Alpha blocker
ARB	Angiotensin-II receptor blocker
ARBHCT	Angiotensin-II receptor blocker and hydrochlorothiazide
BA	Before and After
BAS	Before and After Study
BB	Beta-blocker
BBCCB	Beta-blocker and calcium channel blocker
BI	Baseline imbalance
BMI	Body Mass Index
BMQ	Belief about Medicines Questionnaire

BMQC	Beliefs about Medicines Questionnaire Specific Concerns score
BMQH	Beliefs about Medicines Questionnaire Harm score
BMQN	Beliefs about Medicines Questionnaire Specific Necessity score
BMQO	Beliefs about Medicines Questionnaire General Overuse score
BOA	Blinding of outcome assessment (detection bias)
BP	Blood pressure
BPP	Blinding of participants and personnel (performance bias)
C	counselling
CCB	Calcium-channel blocker
CG	Control Group
ChDBP	Change in diastolic blood pressure
ChPulse	Change in pulse
ChSBP	Change in systolic blood pressure
CKD	Chronic kidney disease
COPD	chronic obstructive pulmonary disease
CPV	Community pharmacy visits
CV	cardiovascular
CWIRT	Comparability with individually randomized trials
DAA	Dose administration aid
DBP	Diastolic Blood Pressure
DRP	Drug-related problem
DTP	drug therapy-problem
EAP	Employee Assistance Program for disease management
ED	Educational

EPOC	Effective Practice and Organisation of Care
ESC	European Society of Cardiology
ESH	European Society of Hypertension
fin	final BP reading
FQ	Frequency
GP	General Practitioner
HBPM	home blood pressure monitoring
HCG	Hidden Control Group
HI	High-intensity
HLOC	health specific locus of control
HMR	Home medicines review
HR	High risk
IA	Incorrect analysis
I	medication explanation leaflet
IG	Intervention Group
IG ED	Intervention Group Education
IG MI	Intervention Group Medication Synchronization
II	Intentional non-adherent irrational
ini	initial BP reading
INT	Intervention
IODA	Incomplete outcome data addressed (attrition bias)
IR	Intentional non-adherent rational
ISH	International Society of Hypertension

ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LD	Loop diuretic
LI	Low-intensity
LOC	Loss of clusters
LR	Low risk
LS	Lifestyle
MANCOVA	Multivariate analysis of covariance
MANOVA	Multivariate analysis of variance
MARS adj	Medication Adherence Report Scale adjusted mean score
MARS score	Medication Adherence Report Scale score
MARS	Medication Adherence Report Scale
MESH	Medical Subject Headings
MHLOC	Multidimensional health locus of control
MMAS	Morisky Medication Adherence Scale
MNCHP	Model Neighborhood Comprehensive Health Program, Inc.
MPR	Medication Possession Ratio
MTM	Medication Therapy Management
MUR	Medication use review
NMS	New Medicines Service
NRCT	Non-randomised controlled trial
OB	Other bias
OC	Patients serve as their own control
OR	Odds ratio

PC	Pharmaceutical Care
PCG	Pharmacist Care Group
PCS	Prospective cohort study
PE	Physical Exercise
PHCU	primary health care unit
PICOS	participants, interventions, comparators, outcomes, study design
PMP	Patient medication profile
PN	Participant number
PRISMA	preferred reporting items for systematic reviews and meta-analyses
PSD	Potassium-sparing diuretic
QoL	Quality of Life
QUORUM	quality of reporting of meta-analysis
R	reminder sheet
RB	Recruitment bias
RCT	Randomised controlled trial
RMS	Repeated measures study
RR	Refill reminder
RSG	Random sequence generation (selection bias)
S-A	Self-administer
SBP	Systolic Blood Pressure
SCS	Smoking cessation program
SD	Standard deviation
SE	Standard error
SG	Study group

SGr	Subgroup
SR	Selective reporting (reporting bias)
SRRS	Social Readjustment Rating Scale
StDev	Standard deviation
StDu	Study duration
TABS	Tool for Adherence Behaviour Screening
TD	Thiazide diuretic
TEAM	Team Education and Adherence Monitoring
TG	Test group
TPSD	Thiazide and potassium-sparing diuretic
U	Unintentional non-adherent
UCG	Usual Care Group
UR	Unclear risk
VA	Veterans Affairs
WB	Witness batch
WHO	World Health Organization
WSU	Wayne State University employees participating in employer wellness plan

1 General introduction

1.1 Pharmaceutical care and the community pharmacist role in hypertension management

Pharmacists have a competence which is useful in medicines optimisation – to ensure safe and effective medicines use (West and Isom, 2014; WHO, 2003). This makes up a portion of the philosophy of "pharmaceutical care". The concept of pharmaceutical care is a relatively new philosophy, with the pharmacist as a health care provider in cooperation with other health care professions and resources to work on the aim of achieving improved health and quality of life in patients and the public (WHO, 1994; WHO, 2003). Pharmaceutical care is largely defined as "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life" (Hepler and Strand, 1990; Wiedenmayer *et al*., 2006; Wiffen *et al*., 2012).

There is a possibility that pharmacists could have extended roles in healthcare than what is established today (West and Isom, 2014). Community pharmacists being one of the largest healthcare professions in the world is more available to the patient compared to any other member of the healthcare staff (Mossialos *et al*., 2013). The profession could take on a role of having a larger clinical responsibility for patient care, such as in one of the most globally prevalent diseases – hypertension. Management of hypertensive patients with poor adherence could be done at a community pharmacy. The patient care would be done in collaboration with primary care. Those patients who exhibit physiological problems which cannot be dealt with at the community pharmacy would be undergoing treatment at a general practitioner or a specialist hypertension clinic. However, there are many challenges and obstacles along the

way to ensure an effective working system. Guidelines need to be developed to obtain a simple flow of the working roles involved (West and Isom, 2014). There is no overlap between developing the role of the community pharmacist and the evidence-base for practice and policy. Mossialos and co-workers in 2013 performed an umbrella review to identify published systematic reviews on the effectiveness of community pharmacist interventions. Thirty-three systematic reviews were identified since the year 2000. The systematic reviews explored the evidence for the increasing role of the community pharmacist. Results from the umbrella review point to a vague evidence base. However, many countries have already started to apply policies to provide the community pharmacist with increased patient-centred duties. Despite this, there is a requirement to perform research to examine policy changes within countries (Mossialos *et al*., 2013).

1.2 Medicines management, a patient-centred approach and medicines optimisation

Medicines management encompasses the therapeutic, economical and risk aspects of medicines (Wiffen *et al*., 2012). By providing consultation to resolve issues and concerns patients may be experiencing relating to medication-taking and whether these are justified will influence their medication-taking. A patient-centred approach is when the clinician and patient work together from the perspective of same opportunity and a mutual decision-making approach. This relates to bringing out the patient's beliefs and provide information based on evidence. The patient-centred approach is inter-linked with the foundation of medicines optimisation (Grimes and Barnett, 2014). As the Royal Pharmaceutical Society in the United Kingdom states: "Medicines optimisation is about ensuring that the right patients get the right

choice of medicine, at the right time. By focusing on patients and their experiences, the goal is to help patients to: improve their outcomes; take their medicines correctly; avoid taking unnecessary medicines; reduce wastage of medicines; and improve medicines safety" (Royal Pharmaceutical Society, 2013). A patient-centred approach with the determinants of blood pressure and adherence/non-adherence is presented in Figure 1.1.

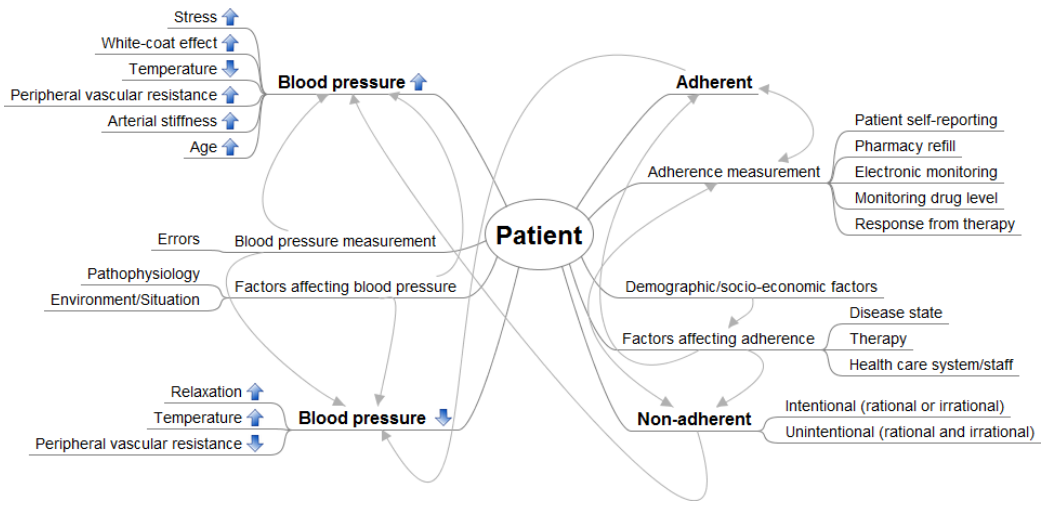


Figure 1.1 A patient-centred approach: determinants of blood pressure control (left) and adherence/non-adherence (right). The long arrows indicate relationships, whereas the small arrows preceding the determinants of blood pressure control indicate an increase (↑) or a decrease (↓) (Source: Personal collection).

1.3 History of blood pressure (BP) measurement

Considering history, in ancient Greece, both Hippocrates and Galen possessed the knowledge of arteries and veins. For more than 1000 years Galen's theory was accepted. The theory being no connection between veins and arteries. This coupled with a forward and backward blood flow originating from the heart. It was until the Renaissance period, during the Middle Ages, when Galen's theory was rejected. New experiments confirmed the modern

understanding of the heart and circulation. In 1616, a man named William Harvey described the circulatory system as a one-way system including capillaries (Nadar and Lip, 2009).

Stephen Hales being an English clergyman measured blood pressure for the first time in a horse in 1733. A blood pressure machine was invented about 100-150 years later, which by a non-invasive manner measured blood pressure in humans (Kotchen, 2011; Nadar and Lip, 2009).

This was the basis for the instrument by Riva-Rocci in 1896, setting the stage for the modern devices. René Laennec invented the stethoscope which then assisted the Russian scientist NS Korotkoff in 1905 to check the pulse with an inflated blood pressure cuff, hence the term "Korotkoff sounds". High blood pressure was noted as "hypertension". "Benign essential hypertension" was distinct from "Malignant hypertension". The condition of "Benign essential hypertension" was seen in conditions where it was thought to be somewhat of a positive outcome to maintain an elevated blood pressure. However, "Malignant hypertension" was categorized as a hypertensive state being harmful (Nadar and Lip, 2009).

Not much change was seen in the way blood pressure was measured during the first 50 years of the 1900s. During the end of the 20th century, sophisticated blood pressure instruments were developed as a controversy surrounding health-related concerns to mercury. Electronic and aneroid devices have largely substituted the blood pressure instrument containing mercury. Despite this, mercury-containing instruments are still being used for calibration purposes with standardized protocols to ensure accuracy (Kotchen, 2011).

1.4 Hypertension guidelines

During the 1970s and 1980s, larger studies as the Framingham study portrayed the relationship between hypertension and cardiovascular risk (Nadar and Lip, 2009). About the same time, the World Health Organization (WHO) and International Society of Hypertension (ISH) initiated a publication of hypertension guidelines. Recommendations for clinical decisions were described in these guidelines. Regional guidelines with subsequent updates were also developed in accordance with variations in healthcare and economic resources between countries. In the United States, The National Heart, Lung and Blood Institute issued "Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure". Starting in 2003, the European Society of Hypertension (ESH) and European Society of Cardiology (ESC) launched their hypertension guideline (Kotchen, 2014).

1.5 Hypertension

Hypertension is described as an increased blood pressure which persists over time (Wilkins *et al*., 2011). Oxford Handbook of Nephrology and Hypertension defines hypertension as: "a level of blood pressure which places an individual at increased risk of cardiovascular events and, when treated, results in more benefit than harm" (Steddon *et al.,* 2014). As seen by this definition, the hypertensive state itself presents a risk factor for various other cardiovascular conditions (Wilkins *et al*., 2011). There is a lengthy list of causes to hypertension. The disease can be attributed to either pathophysiological and/or environmental factors (Kaplan *et al*., 2015). The cause of hypertension is unknown in about 90-95% of the cases. This type of hypertensive state is referred to as primary or "essential hypertension". The remaining

proportion where hypertension can be attributed to a certain cause is termed "secondary hypertension" (Kaplan *et al*., 2015; Wilkins *et al*., 2011).

The prevalence of hypertension in adults around the world reached 25% in the year 2000 estimation, equating to approximately 972 million people worldwide suffering from hypertension. This number is thought to increase to about 1,6 billion by the year 2025 (Warrell *et al*., 2010). Blood pressure which is uncontrolled in the longer perspective sets the likelihood for cardio- and cerebrovascular morbidity and mortality among people (Gwadry-Sridhar *et al*., 2013). As the life-span for people in developed countries increases, the prevalence of hypertension continues to rise (Kaplan *et al*., 2015).

In developing countries, the rise of hypertension is connected to the increasing amount of people suffering from diseases such as diabetes and obesity. However, as there are only a small number of studies on the incidence of hypertension in the general adult population, not much is known about the incidence (Kaplan *et al*., 2015; Lacruz *et al*., 2015). Within the next 20 years, the World Health Organisation (WHO) predicts that hypertension will continue to be a preventable cause of early mortality. It is considered that hypertension will almost cause 7.1 million deaths a year around the world (Warrell *et al*., 2010).

1.6 Blood pressure (BP)

The contraction phase of the heart is termed systole. During the systolic phase, the pressure in the left ventricle will reach about 120 mmHg which causes the blood to be released to the aorta. In turn, the pressure rise in the ventricle causes the aorta to stretch, due to the walls of the large arteries being elastic. This process also makes a forward flow of blood. The systolic

pressure reaches a maximum level of about 110 mmHg as arterial pressure (Ward and Linden, 2013).

Between two systolic phases is diastole, when the heart is filled with blood. The minimum arterial pressure before the next systolic phase is termed diastolic pressure, with a value of around 80 mmHg. Blood pressure is indicated as the systolic arterial pressure over diastolic arterial pressure. These values cannot be transformed into mean values as the heart is found to be around 60% in a diastolic state. Rather, it is feasible to calculate the mean arterial pressure as diastolic pressure+1/3 pulse pressure. The difference between systolic and diastolic pressure is termed pulse pressure. A pressure gradient is created when the heart pumps the blood into the arteries. This means that the pressure in the arteries and veins is not the same. It enables a flow of blood throughout the vasculature (Stanfield, 2013; Ward and Linden, 2013).

The mean arterial pressure is also the product of cardiac output and total peripheral resistance. Cardiac output is the product of the heart rate and stroke volume, with heart rate being the number of contractions per minute. During each heartbeat, both the left and right ventricle contract together. Hence, the heart rate is same for both the ventricles. A cardiac output at rest is about 5 L/minute. The stroke volume is the blood volume being pumped out from each ventricle per beat. During rest, the stroke volume is about 70 mL. This increases to about 20 L during exercise. To maintain the balance in cardiac output to venous return, the stroke volume is regulated accordingly. In response, the heart size is changed. In certain pathological conditions, there is a chronic heart enlargement. The walls of the ventricles stretch creating more muscle tension. The task to keep the blood pressure tuned in the ventricle becomes

arduous, as an enlarged ventricle needs to create sufficient pressure to respond to the cardiac output (Stanfield, 2013; Ward and Linden, 2013, Warrell *et al*., 2010).

The occurrence of blood pressure varies with age with isolated diastolic blood pressure being the common feature in younger age groups. This can be explained by the presence of peripheral vascular resistance in younger people. As the aorta is being elastic in young people, it dampens the systolic pressure. The phenomenon is present until about age 50, whereby the peripheral vascular resistance is reduced. Hence, with an increase in age, the aorta becomes stiff. However, the systolic pressure will already increase from around age 40. For long it has been thought that diastolic blood pressure determined hypertension definition and goal blood pressure. Most cases of hypertension are found in the age groups over 50 years, meaning that systolic blood pressure is of most importance when considering cardiovascular risk (Warrell *et al*., 2010). However, it is also shown that an elevated SBP has a stronger impact on angina, myocardial infarction and peripheral arterial disease when compared to an elevated DBP which has a larger effect on abdominal aortic aneurysm (Rapsomaniki *et al*., 2014).

The blood pressure classification set by the European Cardiology Society/European Hypertension Society is shown in Figure 1.2.

Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

[a]The blood pressure (BP) category is defined by the highest level of BP, whether systolic or diastolic. Isolated systolic hypertension should be graded 1, 2, or 3 according to systolic BP values in the ranges indicated.

Figure 1.2. Definitions and classification of office blood pressure levels in mmHg (Source: Mancia, *et al*. (2013) 2013 ESH/ESC Guidelines for the management of arterial hypertension, European Heart Journal, 34 (28): 2159-2219 by permission of Oxford University Press).

1.7 Adherence and non-adherence

In the literature, the concepts 'adherence', 'compliance' and 'concordance' are being used in a synonymous manner in relation to medication-taking behaviour. However, these concepts do not have a similar meaning (Hugtenburg *et al*., 2013; Snowden and Marland, 2013).

The adherence project which started in year 2001 by the WHO, with the objective of generating an improvement in adherence to treatments of chronic conditions defined adherence as: "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (WHO, 2003). The National Institute for Health and Care Excellence (NICE) in the UK defines adherence as "the extent to which the patient's action matches the agreed recommendations (National Institute for Health and Care Excellence, 2009). A clinician takes patient-related factors such as beliefs and knowledge into account when referring to the term

"adherence" and the patient may not have a choice of the medication included in the treatment (WHO 2003; Wiffen *et al*., 2012). In this thesis when it is referenced to the level to which a patient takes their medication, the concept of adherence is being used. The term is used in the context of the explicit definition as stated by WHO in the year 2003 (WHO, 2003).

Compliance refers to if a medicine has been administered or not, i.e. how far the patient has followed the clinical practitioner's instructions on following the pharmacotherapy. It does not include an agreement between the patient and prescriber to follow the therapy (Osterberg and Blaschke, 2005; Snowden and Marland, 2013; Wiffen *et al*., 2012).

The concept of concordance was introduced by a working group gathered by the Royal Pharmaceutical Society of Great Britain in 1995. Concordance is the approach to build an agreement between the prescriber and the patient to undertake the treatment (Snowden and Marland, 2013; Vrijens *et al*., 2012).

Adherence rates to prescribed medicines are about 50 per cent, leading to reduced treatment benefits with the larger possibility of morbidity and mortality among patients (Nieuwlaat *et al*., 2014; WHO, 2003). Medication wastage is also a consequence of non-adherence to pharmacotherapy (Jackson *et al*., 2014). The societal cost becomes high when there is a cost of medicines waste due to non-adherence (Wiffen *et al*., 2012). Non-adherence also contributes to a negative economic impact on healthcare (Garfield *et al*., 2011; Osterberg and Blaschke, 2005).

A definition of non-adherence is patients administering <80% of what has been instructed by the prescriber (Krousel-Wood *et al*., 2004; Nieuwlaat *et al*., 2014). However, this 80% cut-off point has been debated (WHO, 2003). Moreover, non-adherence can also take the form of

administering more than what has been instructed (Nieuwlaat *et al*., 2014; Osterberg and Blaschke, 2005). Despite this, it is more common with missed doses (Osterberg and Blaschke, 2005). Factors which affect adherence can be grouped into social and psychological dimensions (Lehane and McCarthy, 2007a). The World Health Organization in 2003 set out five categories of factors influencing adherence: a) Socio-economic – in general, a less developed society leads to poor adherence; b) Health care team/health system – an inadequate health care system negatively affects adherence. However, the relationship between the clinician and the patient could improve adherence; (c) Condition - the requirements of the disease which the patient encounters influences adherence e.g. disability and disease severity; (d) Therapy - factors associated with the therapy e.g. a complex drug regimen, side-effects arising from treatment and the duration of treatment; (e) Patient – there will be a negative impact on adherence if the patient possesses poor knowledge and skills to manage symptoms arising from the illness and the treatment. Patient-related factors also include attitudes, beliefs and perceptions about the disease and treatment as well as expectations of treatment. The patient could lack an understanding of the cost/benefit of treatment (WHO, 2003).

Both intentional and unintentional forms of non-adherence should be considered when examining non-adherence to medications. There is the possibility of these categories corresponding to each other, meaning there is no absolute mutual exclusiveness (Clifford *et al*., 2008). Intentional non-adherence relates to when patients take on an active role including a reasoning process leading up to a decision of complying or not complying with instructions (Lehane and McCarthy, 2007b). The motivation of the patient and beliefs about administering medication influences intentional non-adherence. Unintentional non-adherence is connected to the capability of the patient to administer the medicine (Clifford *et al*., 2008). Patients who

are unintentional non-adherent are “passive” for reasons such as for example age, forgetfulness, cost and medication side-effects (Lehane and McCarthy, 2007b). In addition, there is the role of rational and irrational behaviour when considering non-adherence (Lehane and McCarthy, 2007b). It is important to establish the type of non-adherence to reach the best choice of intervention to optimize adherence (Lowry *et al*., 2005).

1.8 Irrational non-adherence

An irrational thought is defined as an unconscious mental process or irrational internal logic. Theories of health and adherence behaviour such as the Health Belief Model and Theory of Reasoned Action are thought to be formed on the basis that behaviour is rational (Horne *et al*., 1999; Lehane and McCarthy, 2007b). However, there are some researchers who reason human decision-making and behaviour suffer from cognitive inconsistencies and biases. This leads to the processes of behavioural change in some instances not being objective or rational. The social cognitive theory lacks inclusion of unconscious mental processes and ”irrational” internal logic in health-behaviour reasoning. Therefore, behaviour due to irrational decision-making could hold a partial explanation for the existence and upholding of non-adherence. Irrationality relating to non-adherence stems from a non-evidence based manoeuvre. It can be regarded as a failure to follow the prescribed regime without some definitive reasons not to e.g. side-effects and forgetfulness. There exist a few psychological theories which explain the occurrence of irrational behaviour (Lehane and McCarthy, 2007b).

Psychological defence mechanisms are unconscious self-protective instincts/dispositions from a potential threat. They keep psychological health at balance but also serve to protect against illness. However, this leads to minimal or no motivation for taking in new information or

change a health behaviour such as medication adherence. Psychological reactance is a theory which describes irrational decision-making. The patient may not pay attention to treatment advice to protect and uphold their freedom even though there may be health risks involved. However, in psychological reactance, there is no strong connection to adherence behaviour. Another theory is cognitive heuristics leading to biases and not being able to think logically. An over- or underestimation of risk is seen in heuristics. Social cognition models reason that a risk/benefit analysis is done before an adherence decision is made. The way risk is interpreted could be influenced by a failing evaluation. The reasons for failure include ”rules of thumb” or mental shortcuts. Hence, tasks or the availability of information could trouble the concentration of the patient on the illness and necessity of medication (Lehane and McCarthy, 2007b).

1.9 Theories of adherence

Explanations and models of medication adherence and non-adherence have changed over the time course. In the beginning, there was a focus on the role of physician-patient communication on patient satisfaction, understanding and forgetting as factors determining adherence. However, health behaviour research soon showed that it was not successful with information alone to modify the behaviour. Therefore, the patient’s beliefs, motivation and planning activity were factors for further examination. Social cognition and self-regulatory models displayed the importance of beliefs about the illness and treatment as well as the individuals’ own ability to follow treatment/advice (Jackson *et al*., 2014).

To understand the factors behind intentional non-adherence, researchers focused on social cognitive theory. The theory considers the flows of thought which affect social behaviour. The existing psychological theories explain health beliefs in adherence (Horne *et al*., 1999).

There are so many factors of adherence appearing to be associated with adherence that there is no universal theory for adherence management. In the pilot study in Chapter 3, the intentional/unintentional sides of non-adherence are considered because they appear to be intuitively one area in community pharmacy that will be met. For example, some patients may be forgetful, another group of patients could be concerned about their medication. In the case of the therapy causing the patient to feel worse, the likelihood to recognize treatment benefits reduces (Kaplan *et al*., 2015).

1.9.1 The Health Belief Model

The Health Belief Model was constructed to provide an explanation to when an individual dismisses health-promoting behaviour or going for a screening. The model addresses that health-related behaviour, i.e. to adhere is weighed up with the observed awareness of the disease and positive effects of the behaviour. It also consists of the concept of barriers to performing the behaviour and which ideas could initiate the behaviour. The initiation of the health behaviour is dependent on stimuli. There is a connection between the health behaviour and an individual's beliefs about the threat a disease poses - the health behaviour is connected to the risks/benefits of performing the behaviour (Horne *et al*., 2005; Ross *et al*., 2004).

1.9.2 The Necessity-Concerns framework

Patient-related factors form a strong role with regards to beliefs/perceptions about treatment, the illness and healthcare system (Foot *et al*., 2016). Research into long-term conditions shows that key beliefs are connected to common-sense examinations of prescribed medications: the perceptions of the personal need for treatment (necessity beliefs) and concerns for potential adverse consequences (Horne *et al*., 2013). Beliefs about medications and concerns determine medication adherence (Kjeldsen *et al*., 2011). Medication beliefs are influenced by factors such as symptoms, decisions on dose alteration to reduce side effects and financial reasons. There is an increased likelihood of medication beliefs determining medication adherence when non-adherence is not random, meaning non-adherence at this instance is a consequence of the patient deciding to go about to take the medicine in a different way (Foot *et al*., 2016). Belief about medications can consider intentional non-adherence than when non-adherence is unintentional (Clifford *et al*., 2008).

Beliefs about medicines form the *necessity-concerns framework* which has foreseen adherence in many illness categories (Foot *et al*., 2016). The necessity-concerns framework addresses key beliefs on patients' attitudes and decisions about treatment (Horne *et al*., 2013). The Belief about Medicines Framework is built on the Health Belief Model: when a behaviour is chosen, a cost-benefit analysis is done where the observed benefits are weighed against the observed costs (Foot *et al*., 2016). A validated questionnaire called Belief about Medicines Questionnaire quantifies necessity beliefs and concerns which makes it possible to explore beliefs connected to adherence (Horne *et al*., 2013).

1.9.3 Meichenbaum and Turk's adherence theory

In the WHO report "Adherence to long-term therapies: evidence for action" it is mentioned an adherence model formed by authors Meichenbaum and Turk. Four different factors influence adherence: knowledge and skills, beliefs, motivation and action. A weakness in any of these factors will lead to non-adherence (WHO, 2003).

1.9.4 Theory of reasoned action/Theory of planned behaviour

The Theory of reasoned action suggests that knowledge and ability of a patient to get hold of knowledge influences the development of beliefs. In a task, such as self-administering medicine the beliefs about the necessity of the medicine versus concerns of side-effects form the basis of adherence or non-adherence (Gatti *et al*., 2009). The theory of reasoned actioned transformed into the Theory of planned behaviour indicating activity is secondary to intention. The health-behaviour is determined by intentions. The source of intention is attitude, subjective rules and the observed control over behaviour (Horne *et al*., 2005; Ross *et al*., 2004). Attitude relating to the behaviour is a product of the beliefs about the likely outcome and the recognized value of the outcome. The view of others regarding the behaviour and motivation to uphold these views are included in the subjective rule. Behavioural control is the dimension to which the individual recognizes to keep the behaviour under control. It is influenced by beliefs linked with control which is related to internal and external factors. Internal factors are skills and information, whereas external factors would e.g. be recognized barriers. Attitudes and subjective rules determine behaviour through intention. By contrast, observed control of behaviour has an impact on both intention and behaviour. Nonetheless, in

different circumstances, there could be variations in attitude, subjective rules and observed control over behaviour (Horne *et al*., 2005).

1.9.5 Attribution theory

Attribution theory describes the thinking processes surrounding the cause of situations (Horne *et al*., 2005). People's perspective of social reality can be foreseen and controlled (Bowling, 2009). When negative situations arise, there is an exploration of cause and outcome. This is based on past experiences and influences the upcoming answer and the adjustment to the illness. The causal theory can influence beliefs about cure, which then determines the behaviour and adjusting to disease. There exist internal and external causes as well as additional areas: stability – the time-line of the cause of disease, globality – overall or specific cause, universality – personal or generic factors and controllability – factors which could be controlled or uncontrolled (Horne *et al*., 2005).

1.9.6 Locus of control beliefs

The theory of controlling health was put into a measure which is referred to as health specific locus of control (HLOC). Health control is dependent on internal and external factors. Examples of internal factors are information or ability, whereas an example of an external factor would be opportunity (Bowling, 2009). A revision to HLOC was made which transformed into the multidimensional health locus of control (MHLOC). This was done due to research showing that control beliefs could be grouped into separate scales. Beliefs relating to HLOC could foresee certain health behaviours. However, the measures of locus of control cannot appraise specific health behaviours. There is not a robust evidence base for locus of

control beliefs relating to adherence. A different perspective on this is that locus of control beliefs which are specific for the circumstance is strongly related to adherence compared to locus of control beliefs about overall health (Horne *et al*., 2005).

1.9.7 Outcome efficacy and self-efficacy

Beliefs surrounding the control and performance of behaviours as well as the efficacy of beliefs were described by Bandura in 1986. There are two forms of efficacies relating to these beliefs: a) outcome efficacy which transforms into an effective outcome b) self-efficacy which determines if the individual will/will not perform the behaviour. Self-efficacy is influenced by the individual's own behaviour and others' behaviour. The individual's own behaviour is further affected by their partner. There is possibly more weight to self-efficacy when considering complex behaviours. An evidence base exists which shows a connection between self-efficacy and medication adherence. Moreover, beliefs about health control, outcome- and self-efficacy are influenced by the past and other thinking processes (Horne *et al*., 2005).

1.9.8 Stages of change model/transtheoretical model

In the stages of change model, also referred to as the transtheoretical model, a behavioural change process consists of five stages: a) Precontemplation - not thinking of behavioural change, b) Contemplation – thinking of behavioural change c) Preparation (getting ready for behavioural change) d) Action (undergoing behavioural change) e) Maintenance (behavioural change which is continued for a period). The five stages do not always run in a chronological order. Behavioural change is formed upon the present behaviour and the intention to change,

which therefore provides a foundation to comprehend the intentional behavioural aspect. For each stage, the model enables grouping of health behaviours and allows identification of interventions (Karupaiah *et al*., 2015, WHO, 2003).

Another stages of change model termed as the Health Action Process Approach is built on Health Behaviour Model, Theory of Planned Behaviour and efficacy beliefs. The model was introduced by Schwarzer in 1992. It consists of two phases with the first phase seeking to decide the power of the intention. This phase is motivational and consists of attitudes to risk, self-efficacy and the likelihood of outcomes. The second phase referred to as volitional is when intention goes into a performance. Self-efficacy beliefs again influence this stage together with a plan and control of the performance (Horne *et al*., 2005).

1.9.9 Self-regulatory model

Leventhal's self-regulatory model built on the basis that information provided as a threat was needed to increase motivation to execute a health behaviour. Despite this, it is required a plan to execute the behaviour (Horne *et al*., 2005). In the self-regulatory model, the health-related behaviour is determined by ideas forming themes of illness representations: identity/nature, time-line, cause, consequences and cure/control of the illness. Beliefs which surround these themes give rise to coping strategies (Ross *et al*., 2004). These influence adherence as this is a problem focused coping strategy with the patient as the problem-solver (Horne *et al*., 2005; Ross *et al*., 2004). Relating to adherence, the patients will weigh the proposed treatment with beliefs about the illness. This evaluation is a dynamic process and informs the patient on whether to adhere or not. The way the treatment is being portrayed is a determining factor in the self-regulatory model, together with the plan of executing the health behaviour as well as

the assessment of the plan (Horne *et al*., 1999, Horne *et al*., 2005). The success of the treatment is also a determining factor. If the treatment is not successful, the patient will not continue, may change to another coping strategy or have an altered perception of the illness (Horne *et al*., 2005; Ross *et al*., 2004). The necessity of treatment and concerns have a larger impact on adherence than illness beliefs (Horne *et al*., 2005). Therefore, there is a strengthening explanation of the self-regulatory model on adherence by adding an assessment of beliefs about medication (Horne *et al*., 1999).

1.9.10 Information-motivation-behavioural skills model (IMB model)

The IMB model is a model that has been used to gain an understanding of health behaviour activity (Gleason-Comstock *et al*., 2015). It proposes that action of a behaviour seeking to improve health is determined by information, motivation and skills (Osborn and Egede, 2010; WHO, 2003). Information relates to factors as knowledge and management of the disease. It also includes knowing the risk and the behaviour to deal with the risk. The patients' beliefs, attitudes as well as social rules and support systems influence motivation. Acquisition of the required skills to put the behaviour into action forms the skills factor in the IMB model (Gleason-Comstock *et al*., 2015; WHO, 2003). Both information and motivation can directly influence behaviour. However, there is no strong connection between information and motivation. Thus, if both information and motivation are present, it will increase the possibility for adherence (WHO, 2003).

1.9.11 Medication error theory

The Medication error theory was formed by Barber in 2002 and built upon Reason's human error theory in organizations. Manoeuvres which are not safe can be divided into two categories: intended and unintended, which is like intentional and unintentional non-adherence. Thus, intentional non-adherence is grouped in a violation which is a conscious diversion from the action the patient is supposed to execute in practice. These diversions can be positive (e.g. not taking a diuretic before going on a long journey or negative (e.g. choosing not to get the medication dispensed) (Barber, 2002; Horne *et al*., 2005).

Intentional non-adherence can also be a knowledge-based or rule-based mistake. With a mistake, a patient executes an action in which it is intended to be the correct way to go about, though the patient is not aware of the wrong action. An example of a rule-based mistake is a concern of a side-effect making the patient stop administering the medication though the patient is not experiencing the side-effect. A knowledge-based mistake could be in a situation in which the patient has no medication supply at home. The reason for this is not to be blamed at the patient. There is a decision by the patient to delay the clinic visit to get a new prescription instead of going to the pharmacy getting an emergency refill (Barber, 2002; Horne *et al*., 2005).

Unintentional non-adherence is categorized in slips or lapses. Slips could be for example accidentally taking the wrong pill. Slips occur due to the patient having inadequate concentration. Lapses occur due to poor memory, e.g. forgetfulness causing the patient to miss a dose (Barber, 2002; Horne *et al*., 2005).

1.9.12 Medication Adherence Model

A theoretical medication adherence framework named the Medication Adherence Model which was published in 2002 looked at the processes relating to medication adherence in patients with hypertension. The model was built on previous cognitive theories. It describes the two categories of non-adherence: intentional decision were patients miss doses and unintentional interruption where medications are not taken. The key concepts in the framework are: 1) purposeful action: starting and keeping up an adherence decision is based on need, effectiveness and safety 2) patterned behaviour: medication-taking patterns are determined by access, routine and remembering 3) feedback where information, prompts and events are used by the patient to value and evaluate the health treatment. The feedback, in turn, influences purposeful action and patterned behaviour (Johnson, 2002).

1.9.13 COM-B

According to Jackson and co-workers, (2014) existing adherence models and frameworks are not sufficient. Firstly, they do not pay attention to automatic processes (e.g. habit). Secondly, there is no description of behaviours being dynamic such as the experience of adherence/non-adherence leading to change in factors (e.g. beliefs about medications). Thirdly, the factors at a holistic level are neglected, i.e. the relationship between factors determining adherence and adherence itself. In addition, there is the overlap between intentional and unintentional non-adherence. Finally, the current adherence theories do not provide information on how to go about to establish change (Jackson *et al*., 2014).

There are behaviour change techniques which develop and refine interventions. The methods which change health-related behaviours have been described in a taxonomy with 93 techniques. It is possible in this taxonomy to categorize factors which explain health-related behaviours. This has resulted in a dynamic psychological model with mechanisms of behavioural change which is referred to as ”COM-B”. It builds on a US consensus meeting and existing theories of behaviour. Factors which influence medication adherence found in three studies have been added to COM-B creating a framework for choosing interventions which suggest the possible intervention and specific interventions for each component. The three components Capability, Opportunity, Motivation are interlinked which in turn affect the performance of behaviour (Jackson *et al*., 2014).

1.10 Antihypertensive medicines adherence

In the late 1950s, there was the advent of safe and tolerated antihypertensive drugs e.g. thiazide diuretics. Almost a decade later, the first randomized controlled trial was conducted on blood pressure lowering agents for hypertension leading to positive cardiovascular effects. It did not take long until the importance of adherence to antihypertensive pharmacotherapy was identified (Gosmanova and Kovesdy, 2015).

Large studies show the positive effects of BP control on reduced cardiovascular morbidity and mortality (Burnier, 2006). Besides, antihypertensive drugs have clearly shown positive outcomes: 20-25% reduction in acute coronary syndrome, 30-35% reduction in stroke and 50% reduction in heart failure (Gosmanova and Kovesdy, 2015). According to WHO, identification and treatment of hypertension have shown vital health and economic benefits. Hypertension will increasingly be treated with antihypertensive medicines (Kaplan *et al*.,

2015). Despite this, hypertension is everywhere still inadequately managed. The lack of adherence to blood pressure lowering medicines plays a major role (Morgado *et al*., 2011; WHO, 2013).

The adherence rate to blood pressure lowering medicines depends on the population being studied but is in the range between 50-70 percent (WHO, 2003; Morgado *et al*., 2011). Rates could be higher for specific antihypertensive drug classes and in patients on monotherapy with a low number of doses (Gosmanova and Kovesdy, 2015). It is important to bear in mind that there is a difference between adherence in clinical trials and in the community. In clinical trials, there are highly motivated patients who are aware that adherence is being monitored (Burnier, 2006).

It is vital to understand the barriers which inhibit the process of reaching BP targets (Gosmanova and Kovesdy, 2015). Reasons for non-adherence to antihypertensive medications can, for example, relate to the asymptomatic nature of hypertension, the chronic requirement for treatment, complex drug regimens, costs and beliefs about medications (Kaplan *et al*., 2015; Lee *et al*., 2006; Morgado *et al*., 2011; Wiffen *et al*., 2012). Evidence shows that about 50% of patients discontinue treatment within a year, even though treatment is being offered (Kaplan, 2015; WHO, 2003).

A study conducted in England by Quine and co-workers, 2012 suggested and examined a framework for the psychological elements which determine antihypertensive medication adherence. Three groups of factors were included in the framework: a) demography, health status and medication regimen b) cognitions and motivation c) intention to adhere. Questionnaires were distributed by post to patients with hypertension from primary care centres. The first set of questionnaires examined the proposed framework and assessed

antihypertensive medication adherence using the 4-item Morisky Medication Adherence Scale (MMAS-4). After 8 weeks, antihypertensive medication was assessed with MMAS-4. The results indicate that cognitions and motivation form a major part of the framework. The authors suggest that motivational-type of interventions must especially be useful to target intentional non-adherence (Quine *et al*., 2012).

Most hypertension patients have the goal blood pressure of <140/90 mmHg, a target which is a surrogate of adherence. There is a signal of non-adherence if the patient does not have controlled office blood pressure, even though the patient is on polypharmacy with antihypertensive drugs. Despite this, the signal of non-adherence can be skewed during office BP measurement by the patient experiencing a ”white-coat”-effect: a higher office BP in comparison to ambulatory measurement. There could also be the effect of ”white-coat”-improved adherence surrounding the clinic visits: the patient will improve the adherence momentarily for the clinic visit. Therefore, BP should not be considered alone when assessing adherence to antihypertensive pharmacotherapy. It should be a marker used in conjunction with adherence screening tools (Gosmanova and Kovesdy, 2015).

1.11 Interventions to optimize antihypertensive medication adherence

The WHO in the year 2003 mentioned there is no specific approach or intervention to improve antihypertensive medication adherence. Further research is needed to which interventions are likely to improve antihypertensive medication adherence. However, it is required a behavioural change to reach optimized adherence to long-term medication therapy (WHO, 2003). This involves learning, adopting and upholding medication-taking behaviour using methods such as rewards and reminders. Interventions which are tailored are more

likely to be effective in reaching behavioural change compared to non-tailored interventions. Therefore, there is a need for comprehensive interventions which include cognitive, behavioural and affective methods which are customised. These interventions should be based on an objective assessment of the behaviour of administering medicines. In addition, clinicians should have an awareness of the prevalence of adherence in the hypertensive population (Burnier, 2006; WHO, 2003).

Patel and Taylor in 2002 conducted a study where the relationship between illness attribution, perceived control and adherence to antihypertensive medications was investigated. The study was performed in 122 patients (18 years and above) with a goal to reduce BP. Patients underwent written and follow-up telephone questions on patients' illness attributions, awareness of control and medication adherence. This study showed that acceptance of medical advice and information was dependent on beliefs about health condition. In turn, this shows that when patients' beliefs about the disease are revealed and considered, better outcomes are reached (Patel and Taylor, 2002).

Burnier, 2006 suggests that a comfortable drug regimen which is quite free of side-effects and a positive/supportive approach to treatment is the best way forward to improve adherence to antihypertensive pharmacotherapy (Burnier, 2006).

It needs to be ensured that medicines do not have a negative impact on the quality of life of the patient. Therapy-related factors such as dosage regimen can be adjusted to less frequent administrations during the day, which is shown to increase adherence. Side-effects can be a therapy-related factor, where the patient reaches a decision that side-effects outweigh the future benefits of the medication therapy. In the presence of dose-dependent side-effects, the physician may alter the dose to a lower dose. This is to increase the adherence to the

medication therapy, although with the risk of not reaching optimal BP control. Consequently, the tolerability of the medication and dosing frequency influence the medication-taking behaviour. Adherence is improved with a good patient-clinician communication as well as regular treatment follow-up. A shared-decision making approach between the patient and physician should be sought, with the selection and adjustment of the pharmacotherapy being a joint decision. Patients should be given instruction on how to use their medications in a reasonable manner - emphasizing the necessity of medication and keeping BP control. The patients' management relating to missed doses, recognizing and taking care of side-effects is crucial in obtaining optimized adherence. Training of healthcare staff is required for a non-judgemental counselling and in the proper selection of antihypertensive medications (Burnier, 2006; Osterberg and Blaschke, 2005: WHO, 2003).

Moreover, self-monitoring of BP where patients are taught to measure and monitor their own BP will be useful in achieving improved rates of antihypertensive medication adherence. This in combination with patients learning to assess their own adherence (Osterberg and Blaschke, 2005; WHO, 2003).

1.12 Methods of measuring medication adherence

Historically, adherence screening has been noted all the way back dating to the time of Hippocrates. There is no optimal way to measure adherence as each adherence screening tool present their own pros and cons (Osterberg and Blaschke, 2005). Rather, a triangulated approach of methods of measuring medication adherence provides a better picture and is used in research (Garfield *et al*., 2011; Osterberg and Blaschke, 2005).

There exist direct methods or indirect methods of measuring adherence. Therapeutic drug monitoring is a direct method where the drug concentration is for example measured in blood or urine. However, these methods are costly. Indirect measures include self-report questionnaires, pill counts, assessment of treatment response, electronic monitors and assessment of refill rates using pharmacy records. Self-report questionnaires are simple in practice, though patients may not be accurate about their adherence providing a good picture to the practitioner (Osterberg and Blaschke, 2005; Wiffen *et al*., 2012).

1.12.1 Self-reported medicines adherence screening questionnaires

Before initiating the pilot study described in Chapter 3, it was not known if the Belief about Medicines Questionnaire (BMQ) would have been sufficient alone. At the same time, the 8-item Morisky Medication Adherence Scale (8-item MMAS) or Medication Adherence Report Scale (MARS) could have been used alone. However, the limitation is that these questionnaires are not being precise enough. Indeed, there is no universal method to screen adherence. The intention of triangulation is to add precision to the adherence screening and to determine the robustness of the questionnaires. Thus, the triangulative approach combines the pros and cons of different adherence models which provides for a more precise adherence screening.

Sections 1.12.1.1 to 1.12.1.3 provide the theory for the self-reported medicines adherence screening questionnaires employed in the community pharmacy-based pilot study (Chapter 3).

1.12.1.1 8-item Morisky Medication Adherence Scale

The 8-item Morisky Medication Adherence Scale (8-item MMAS) is a self-reported measure of medication taking. It was developed from an earlier validated 4-item scale. From the 4-item to the 8-item scale there have been added items including circumstances which surround adherence behavior. Each item in the scale measures specific medication-taking behavior. (Morisky *et al*., 2008). The reason for choosing this measurement instrument is that compared to other self-reported medication adherence scales, the 8-item Morisky scale has already been used in a study for medication adherence of patients with hypertension and thus naturally will serve as an optimal medication adherence measurement tool for this study.

Morisky and co-workers conducted a study in the year 2008 where the primary objective was to examine the psychometric properties and test the concurrent and predictive validity of an 8-item structured, self-reported medication adherence measure in primarily low income, minority patients with hypertension. The study included 1367 patients. According to the authors of the study, the 8-item medication adherence scale was reliable and significantly associated with blood pressure control. Furthermore, it is stated in this study that the medication adherence scale is relatively simple and practical to use in clinical settings. In addition, the authors state that this instrument can be used initially to identify patients with adherence problems, and can also be used to monitor adherence over the course of the treatment (Morisky *et al.*, 2008).

An evaluation of the association and concordance of a new 8-item self-report Morisky Medication Adherence Scale (MMAS) with prescriptions claims in a managed care population consisting of older adults with hypertension was done by Krousel-Wood and co-

workers, 2009. This was a cross-sectional study were pharmacy records were taken for managed care adult hypertensive patients aged 65 years and above. A total of 87 study participants completed a survey including the 8-item MMAS. Medication Possession Ratio (MPR) was also one of the approaches used to assess adherence. This was calculated using the pharmacy data. The authors of the study conclude that the MMAS is significantly associated with antihypertensive pharmacy refill adherence. Furthermore, they state that although further validation of the MMAS is needed, it may be useful in identifying potential low medication adherers in clinical settings (Krousel-Wood *et al*., 2009).

Holt and co-workers in 2012 conducted a cross-sectional analysis by using data from 1817 participants in the Cohort Study of Medication Adherence among Older Adults. The authors examined the association between life events, antihypertensive medication adherence and the role of coping. MMAS-8 was used to assess antihypertensive medicines adherence. Life events among the study participants that occurred 12 months before the study interview was assessed by the Holmes Rahe Social Readjustment Rating Scale (SRRS). Coping levels were assessed using an adapted version of the John Henry Active Coping Scale. The analysis showed that older adults with low coping skills and more life events had lower adherence to prescribed antihypertensive medications (Holt *et al*., 2012).

Elliott and co-workers (2014) in a randomised controlled study evaluated the effectiveness of the New Medicines Service (NMS) in community pharmacies in England using the 8-item MMAS to assess medication adherence in patients (Elliott *et al*., 2014).

1.12.1.2 Medication Adherence Report Scale

Another questionnaire for measuring self-reported medicines adherence is the Medication Adherence Report Scale which was developed in England. This questionnaire contains five statements surrounding self-reported adherence. The statements include: forgetfulness, altering the dosage, stopping to take the medication, missing a dose and taking less than instructed. Response categories for the statements are made of a 5-point Likert scale: 1=always, 2=often, 3=sometimes, 4=rarely, and 5=never. This questionnaire is chosen as a method in the proposed study since it has been translated into Swedish with the back-translation approved by the original author and has previously been used in a study performed in a pharmacy setting in Sweden (Mårdby *et al*., 2007).

An examination of the intentional and unintentional aspects of medication non-adherence in patients diagnosed with hypertension was performed by Lehane and McCarthy in the year 2007. A study population consisting of 73 participants with hypertension were recruited. These patients attended outpatients' clinics of two university hospitals. MARS was included in a researcher administered questionnaire containing 3 other questionnaires (Lehane and McCarthy, 2007a).

A German translation of MARS named MARS-D was used in a study aimed at assessing whether MARS-D was an appropriate instrument for measuring patient adherence. MARS-D was sent to 1488 patients with chronic diseases and patients with risk factors for cardiovascular disease. This study concludes that preliminary psychometric evaluation of MARS-D is encouraging. The authors state that MARS-D is an appropriate measure to detect patients at risk of non-adherence (Mahler *et al*., 2010)

The Medication Adherence Report Scale (MARS) was used in a study by Ramanath and co-workers in 2012. The objective of this study was to know the impact of clinical pharmacist interventions on medication adherence and quality of life. Their study was a prospective, randomized, interventional study with 52 patients completing the study. The authors conclude that the impact of clinical pharmacist provided patient counselling had a positive impact on medication adherence and quality of life (Ramanath *et al*., 2012).

1.12.1.3 Beliefs about Medicines Questionnaire

The Beliefs about Medicines Questionnaire is a method to assess cognitive representations of medication. It is built up of two sections: BMQ-Specific and BMQ-General. These two sections can be used either together or independently. BMQ-Specific consists of two 5-item factors. It assesses beliefs about the necessity of prescribed medication, concerns about the prescribed medication based on beliefs about the danger of dependence and long-term toxicity and the disruptive effects of medication. BMQ-General contains 2 four-item factors: it assesses the beliefs surrounding that medicines are harmful, addictive, poisons which should not be taken continuously and that medicines are overused by doctors (Horne *et al*., 1999). The reason for choosing this questionnaire in the pilot study described in Chapter 3 is that it covers a wide range of patient perceptions on medicines use and therefore can capture the issues which patients face with their antihypertensive medicines usage with special reference to barriers to antihypertensive medicines adherence.

Both the BMQ and MARS were used in a study performed in Sweden by Mårdby and co-workers in 2007. The objective of this study was to analyze any association between general beliefs about medicines and self-reported adherence among pharmacy clients and to examine

general beliefs about medicines by background variables. The questionnaire data were collected by one of the researchers who approached pharmacy clients at 7 different community pharmacies in Gothenburg, Sweden. The study population consisted of 324 pharmacy clients. 54% of these participants were considered non-adherent. In conclusion, General-Harm was associated with adherence to medication among Swedish pharmacy clients. Country of birth, education and medicine use influenced beliefs about medicines (Mårdby *et al*., 2007).

1.12.2 Pill count

Pill count involves comparing the remaining number of pills in the medicines package with the number of pills which would be remaining if the patient was adherent. Apart from being a straightforward method, there exist practical issues which are detrimental for its reliability; such as dumping pills, it may not be clear if the medicine was really administered, lack of instruction that tablet counting will be performed during research, patients bringing the pills etc. (Krousel-Wood *et al*., 2004; Smith, 2002).

The validity of patient report, pharmacy dispensing records, and pill counts as measures of antihypertensive adherence using electronic monitoring as the validation standard was evaluated in a study by Choo and co-workers in 1999. This study included 286 members of a managed care organization who were at least 18 years of age, had prescription drug coverage and underwent monotherapy with antihypertensive medicine. Based on automated pharmacy dispensing records, prescription refill adherence was determined 12 months prior to enrollment in the study. A pill count was done during the study were pharmacists counted the

remaining number of tablets in the returned medication vials when the participants did a prescription refill during the study (Choo *et al*., 1999).

De Souza and co-workers evaluated whether adherence to a drug regimen helped to identify patients with resistant hypertension. In this study, a study population of 44 hypertensive patients was prospectively studied. These patients were resistant to a 3-drug regimen and were followed for 12 months. The pill count method and a Morisky questionnaire were used to assess adherence (de Souza *et al*., 2009).

A pill count was used as a method in a study done by Martin and co-workers in 2011. The purpose of this study was to examine the effectiveness of a community-based, multimedia intervention on medication adherence among hypertensive adults. This study was a randomized controlled trial in rural south Alabama, United States. Study participants were 434 low-income adults receiving medication free of charge from a public health department or Federally Qualified Health Center. Registered nurses and a community health advisor assessed adherence by pill count when the study participant made a visit to the clinic to make a medication refill. The participants had to bring in their medicine bottles. Any remaining pills had to also be brought the clinic. This would enable the participant to receive a full 90-day medicine supply. Data recorded regarding the returned pills consisted of the medication name, strength, dosing, the number of pills returned and the number of pills dispensed (Martin *et al*., 2011).

1.12.3 Pharmacy refills

Medication Possession Ratio (MPR) is a method used to assess medicine adherence by using pharmacy refill data. MPR is the ratio of the total days of medication supplied to the total

days between medication refills. The value of MPR is always >0 because the numerator will be >0. An MPR=1 corresponds to 100% compliance. To patients who get different antihypertensive medicines simultaneously (polypharmacy), a separate MPR should be calculated for each medication. An average MPR can then be calculated. Attention should be given when calculating an average MPR value, due to that compliance can vary between different medicines. In fixed-dose combinations (single medication containing two or more active ingredients) only one MPR should be calculated (Halpern *et al*., 2006).

In an observational study conducted in the United States by Schmitt and co-workers, 2007 a Veterans Affairs (VA) cohort of patients with chronic kidney disease (CKD), patterns of medication adherence for all antihypertensive classes of prescriptions during a 2-year period were examined. The primary objective of this study was to examine the independent relationship between the level of adherence observed in clinical practice, and the achieved level of blood pressure control during the entire study period. A secondary objective was to describe the patient characteristics that may be associated with the level of adherence to antihypertensive medications in a CKD cohort. The study consisted of 7227 chronic kidney disease patients receiving at least one antihypertensive prescription between 2006 and 2007. Prescription information was taken from a database containing electronic records of outpatient prescriptions/refills information and other patient data. Medication Possession Ratio was used to assess antihypertensive medicines adherence. The authors of this study state that 33% of the CKD patients had poor medication adherence and that medication adherence worsened with declining renal function. In addition, the authors state that poor medication adherence is associated with a 23% greater risk of uncontrolled hypertension. In CKD practice, monitoring and improving adherence could contribute to better outcomes (Schmitt *et al*., 2007).

Mabotuwana and co-workers, 2009 performed a study in New Zealand in which they developed a computational framework to identify patient cohorts with poor adherence to long-term medication through analysis of electronic prescribing patterns. This was illustrated using the electronic medical records of a New Zealand general practice among patients with hypertension and diabetes. The focus was on adherence to Angiotensin Converting Enzyme inhibitors (ACEinh) and/or angiotensin-II receptor blockers (ARB). Analysis of medication supply was based on the concept of MPR (Mabotuwana *et al*., 2009).

MPR was included in a cohort study in China which evaluated the factors associated with adherence with ACE inhibitors. This study included all adult patients who were prescribed an ACE inhibitor and did at least 2 consecutive visits to any primary care clinics of one large territory of Hong Kong from January 2004 to June 2007. Data was obtained from a computer system adopted in the year 2000 were health care professionals were provided direct entry to the electronic clinical management system. Prescriptions at every clinical visit, the demographic details of patients and other clinical data were logged into this database. The study showed that 88% were adherent of 6408 eligible patients (Wong *et al*., 2010).

There is the effect of noise at the beginning and/or end of the MPR data collection period, i.e. the patient already could have initiated a medicine's package when the MPR data was collected. Toward the end of the MPR data collection, the patient may yet not have completed the bottle before next medicine refill (an example shown in Figure 1.3).

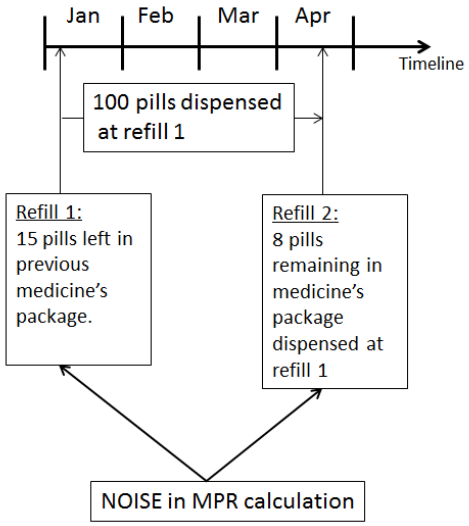


Figure 1.3. Example of noise in MPR during a 3-month time frame (Source: Personal collection).

To reduce the noise, it is important to allow for an MPR data collection spanning over a long period, e.g. 6-9 months (see example in Figure 1.4)

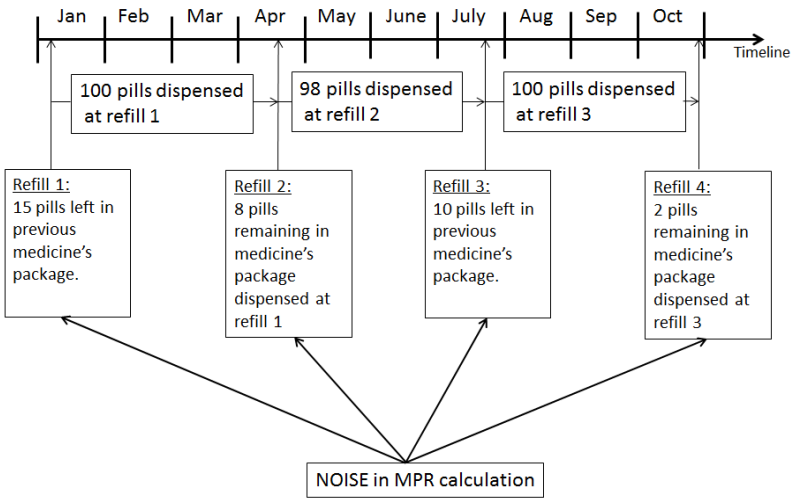


Figure 1.4. Example of noise in MPR during a 9-month time frame (Source: Personal collection).

1.13 Prescribing guidelines for antihypertensive medications in Sweden and United Kingdom (UK) respectively

In Uppsala County, Sweden, the prescribing guideline recommends an ACE inhibitor (ACEinh) or generic losartan/candesartan and/or a low-dose thiazide diuretic (TD) or a calcium-channel blocker (CCB) as first-in-line antihypertensive pharmacotherapy. Beta-blockers (BB) are recommended in the case of co-morbidity, e.g. when having congestive heart failure or a migraine. An ACE inhibitor can be substituted with an ARB if the patient experiences side-effects such as a cough (Landstinget i Uppsala län, 2016; The Swedish Medical Products Agency, 2016). The prescribing guideline within Uppsala County largely complies with the national prescribing recommendations in Sweden:

1st choice: a) ACEinh or ARB, dihydropyridine CCB or TD b) If optimal effect not achieved with monotherapy including one antihypertensive drug class: ACEinh or ARB + CCB or TD. c) If optimal effect not achieved including two antihypertensive drug classes: combine all three drug classes (ACEinh or ARB + CCB + TD) in full-dose

2nd choice: a) BB b) Alpha blocker (Alpha) or spironolactone if first-in-line therapy is not an adequate.

In comparison to the Swedish guidelines, NICE in the UK have categorized the choice of antihypertensive treatment into four steps:

Step 1) Patients aged <55 years: An ACEinh or a low-cost ARB. If the patient does not tolerate an ACEinh, the medication can be substituted with a low-cost ARB. Patients aged >55 years and black people (African or Caribbean origin) of all ages: CCB. In those situations where a CCB is inappropriate or not tolerated: TD. Chlortalidone or indapamide is

recommended when starting or changing diuretics. However, in those patients with BP control who already are undergoing treatment with bendroflumethiazide or hydrochlorothiazide, the pharmacotherapy can remain unchanged.

Although BB not being first-in-line antihypertensive pharmacotherapy, this drug class can be taken into account for young patients especially in the following situations: patients not tolerating or where there is a contraindication to ACEinh and ARB; female with potential to become pregnant; patients where there confirmation of increased activity in the sympathetic nervous system. If monotherapy with BB is not sufficient, a CCB should be added as dual therapy instead of a TD. The reason is to decrease the risk of the patient developing diabetes.

Step 2) If BP remains uncontrolled after step 1: CCB + ACEinh or ARB. If a CCB is inappropriate or not tolerated: TD. Black people (African or Caribbean origin): ARB + CCB instead of ACEinh + CCB.

Step 3) If BP remains uncontrolled after step 2: triple therapy with ACEinh or ARB + CCB + TD.

Step 4) If the clinic BP is >140 mmHg/90 mmHg it should be treated as resistant hypertension after following triple therapy in optimal doses with ACEinh or ARB + CCB + diuretic. Four antihypertensive drugs can be considered or consulting a specialist for advice. Depending on the potassium level in blood, the patient can be prescribed either low-dose spironolactone or higher-dose TD. It is important to monitor sodium and potassium levels in the blood as well as the renal function when adding a diuretic for patients with resistant hypertension. Alpha or BB can be prescribed if diuretic pharmacotherapy is not tolerated by the patient or if contraindicated. A specialist should be consulted if BP control is not achieved with treatment

including four antihypertensive drugs (National Institute for Health and Care Excellence, 2016).

Both the Swedish and NICE guidelines state that ACEinh and ARB should not be combined (National Institute for Health and Care Excellence, 2016; The Swedish Medical Products Agency, 2016). This is due to increased risk of side-effects and the absence of a combined drug effect (The Swedish Medical Products Agency, 2016).

1.14 Previous studies

There have been earlier studies which have examined the potential to improve adherence to antihypertensive medications in community pharmacy, but these have limitations because they do not attempt to evaluate the adherence status of the patients and generally do not target an intervention to that status.

Dating back to 1973, an American randomised controlled trial was performed by McKinney and co-workers on a small patient population with essential hypertension at a community pharmacy with an intervention and control group (McKenney *et al*., 1973). During almost 30 years after this study was published, there was a research gap until the year 2000. In England, Blenkinsopp and co-workers (2000) conducted a randomised controlled trial in 20 community pharmacies with 180 patients completing the study. The objective of their study was to determine the effect of a community pharmacist-led intervention on adherence to antihypertensive pharmacotherapy. Outcome measures were blood pressure control, self-reported adherence and patient satisfaction with pharmaceutical services. Pharmacists in the intervention group interviewed patients in relation to their hypertension treatment plan by using a structured protocol with questions. The authors conclude that simple intervention (oral

or written information, contact with/referral to the physician) had positive effects on blood pressure control, self-reported adherence and patient satisfaction with pharmaceutical services (Blenkinsopp *et al*., 2000).

Among studies conducted in the beginning of the 2000s, it is observed an approach to adopting different study designs (Chabot *et al*., 2003; Garção and Cabrita, 2002; Hughes *et al.*, 2002; Taylor et al., 2003). Even though the studies being relatively small-scale, there was a build-up of outcome measures such as quality of life on patients and the economic perspective of community pharmacist interventions on healthcare (Hughes *et al.*, 2002; Zillich *et al*., 2005). Exploring the effects of high-intensity or low-intensity interventions in subgroups were of interest in studies performed in years 2002 and 2005 (Hughes *et al.*, 2002; Zillich *et al*., 2005).

The impact of ethnicity or socioeconomic status to blood pressure control was explored. Eight African-American patients with hypertension participated in a very small study by Taylor and co-workers in 2003 (Taylor *et al*., 2003). Another example of focusing on an ethnic group is seen in the study by Lai and co-workers (2007) including Latino/Hispanic patients (Lai, 2007). Svarstad and co-workers (2013) conducted a study in the US with almost 500 African-American patients (Svarstad *et al*., 2013). Chabot and co-workers (2003) reported blood pressure changes in high-income patients and low-income patients (Chabot *et al*., 2003).

Evaluation of lifestyle factors on blood pressure control, e.g. BMI, physical activity, smoking cessation, alcohol consumption and salt restriction is seen especially among the modern studies (Aguiar *et al*., 2012; Aguwa *et al*., 2008; Chabot *et al*., 2003; Júnior *et al*., 2008; Nemerovski *et al*., 2013; Octavia and Florica, 2011; Pojskic *et al.*, 2014; Sharma *et al*., 2014).

The modern studies are larger though with a more complex set of interventions. The studies will be explored in detail in the systematic review.

1.15 Community pharmacy system and adherence programmes in Sweden

The Swedish pharmacy market changed in the year 2009 following a long period of government-owned pharmacies since the year 1970. Prior to 1970, the pharmacies were privately owned. The re-regulation was done to increase the availability of pharmacies (Sporrong and Nordén-Hägg, 2014). This resulted in an increase of about 40% of pharmacies, meaning it now exists about 1300 pharmacies in Sweden (The Swedish Pharmacy Association, 2016). The achievement was especially seen in well-populated areas. The change of legislation resulted in the ownership of pharmacies to international companies, private entrepreneurs, government-owned pharmacies etc. (Sporrong and Nordén-Hägg, 2014; The Swedish Pharmacy Association, 2016). To ensure that each pharmacy met quality standards, the legislation set a condition of having a specially appointed pharmacist for this function (Sporrong and Nordén-Hägg, 2014).

In Sweden, there are three categories of pharmacy staff, two of these having dispensing rights and can counsel patients. The first one is the pharmacist with a four to five-year long education at university level, the second being the dispensing pharmacist with a two to three-year university education. The dispensing pharmacist is a profession only available in Sweden, Norway, and Finland. The third professional staff type is the pharmacist technician with a two-year upper secondary school education. Pharmacy technicians are not allowed to dispense medicines. However, they can offer patient counselling of over-the-counter products

(Södergård, 2008; Westerlund and Björk, 2006). The Swedish pharmacies have about 300000 customers visits a day (The Swedish Pharmacy Association, 2016).

Södergård conducted a review in 2008 to identify the practice, education, and research of pharmacists in Sweden on adherence to treatment. At the time, no adherence programmes were observed in Swedish pharmacies. However, the conclusion drawn by Södergård was that practice and education on adherence would change with the re-regulation of the Swedish pharmacy market (Södergård, 2008).

In the year 2013, the Swedish government delegated the Swedish Medical Products Agency to perform a feasibility study on structured medicines reviews, to improve adherence to prescribed pharmacotherapy. The study was initiated in the year 2014 in patients on pharmacotherapy for asthma/chronic obstructive pulmonary disease. Despite this, a drawback of this study is that no effect outcome was evaluated (The Swedish Medical Products Agency, 2014).

1.16 Thesis approach

This chapter has provided a general introduction to the underlying theory on adherence and hypertension management in community pharmacy.

An inductive approach has been employed in the present thesis, whereby it was generally looked at the literature (not systematic) to obtain ideas to formulate the thesis approach, upon which the ideas were mind-mapped.

The general view of the literature provided a conceptual framework on how to conduct the pilot study, allowing the first stage of aims and objectives to be developed. It was thought to

perform a systematic review and then conduct a pilot study. Furthermore, the findings from the specific systematic review allowed a second iteration of the aims and objectives of the pilot study. It was clear that the existing ways to establish patients' likely adherence level were inadequate. Consequently, a novel approach to categorise patients according to their adherence status was developed.

1.17 Aims and objectives

1.17.1 Systematic review

- **Aim:**

- to identify and evaluate mixed-method studies including pharmacist-led interventions within a community pharmacy setting aimed at blood pressure optimisation in patients undergoing oral antihypertensive medication therapy.

- **Objectives:**

- assess the outputs from database searches for systematic review inclusion or exclusion
- summarise the included studies from the perspective of populations, interventions, comparators, outcomes and study design (PICOS)
- assess the risk of bias of included studies with The Cochrane Collaboration's tool for assessing risk of bias
- calculate effect measures for the included studies
- critically examine the included studies in the light of populations, interventions, comparators, outcomes and study design (PICOS) by performing a thematic analysis
- assess publication bias by performing a visual inspection of funnel plots and statistical testing of funnel plot asymmetry

1.17.2 Community pharmacy-based *in vivo* adherence project

- **Aims:**

I) to assess the feasibility of screening antihypertensive medicine adherence in community pharmacy hypertensive patients

II) to deliver community pharmacist-led interventions targeting adherence status according to adherence subgroups to optimise blood pressure (BP)

- **Objectives:**

- establish (a) any issues with the adherence screen

  (b) any indications of outcomes from the allocated interventions

  (c) any indication if certain interventions were detrimental

2 A systematic review of pharmacist-led interventions within a community pharmacy setting aimed at optimising blood pressure (BP) in patients undergoing oral antihypertensive medication therapy

The systematic review was developed in order the refine the examination of what had been done within the research domain of pharmacist-led, community pharmacy-based interventions to optimise blood pressure in patients with oral antihypertensive pharmacotherapy.

2.1 Introduction

Pharmacy practice and policy could possibly be transformed by pharmacist interventions being reported in systematic reviews. Appropriate evidence-based interventions may have a major role in developing the role of the pharmacist in healthcare (Charrois *et al*., 2009). The undertaking of systematic review and meta-analysis provides a way of gaining a summary perspective and judgement on the positive or negative effects and risk of interventions within healthcare. However, studies can be of varying quality, raising questions about their impact (Liberati *et al*., 2009). A systematic review employs a scientific approach with a research question and inclusion/exclusion criteria which determine studies to be included, assessment of study quality from the perspective of bias and outlines the results (Higgins and Green, 2011; Khan *et al*., 2011). Quantitative results from individual studies can possibly be combined with statistical methods, known as a meta-analysis. Qualitative analysis when examining health interventions is emerging and becoming common practice in healthcare (Higgins and Green, 2011). Thematic analysis as a qualitative research method examines data by identifying, analysing and describing arrangements of data, i.e. described as themes, which

are ordered in response to the research question (Braun and Clarke, 2006). Mixed-methods approaches apply both qualitative and quantitative analysis in the same study. This latter approach provides more strength to available evidence compared to solely conducting either a qualitative or quantitative analysis (Tariq and Woodman, 2013). The mixed-methods approach has become established in healthcare research (Hadi and Closs, 2015).

There should be transparent reporting of systematic reviews to facilitate judgements about the pros and cons of the studies: this led to the introduction of the quality of reporting of meta-analysis (QUOROM) statement in 1999. The statement was later updated with the preferred reporting items for systematic reviews and meta-analyses (PRISMA). This provides a guidance on an open and thorough dissemination of systematic reviews and meta-analyses. The participants, interventions, comparators, outcomes and study design (PICOS) approach is suggested by PRISMA, which facilitates the reader to obtain major points of significance in the systematic review (Liberati *et al*., 2009).

The Effective Practice and Organisation of Care (EPOC) Group belongs to the Cochrane Review Group. The latter is an international collaboration aiming to make Cochrane Reviews available for practice and policy decisions. As such, the EPOC Group focuses on conducting systematic reviews for promoting healthcare practice and organisation. Thus, the EPOC Group has set requirements and criteria for the undertaking of EPOC systematic reviews (Effective Practice and Organisation of Care, 2015; Effective Practice and Organisation of Care, 2016).

There are tools for assessing quality in studies in systematic reviews. Many of these tools provide a score to different aspects of quality which will then give a summary score. Furthermore, there are tools which are based on checklists with questions. The Cochrane

Collaboration in years 2005 to 2007 developed a risk of bias assessment tool which instead enabled a domain-specific assessment of the risk of bias. It is difficult to validate the quality of assessment tools since the risk of bias assessment includes a subjective measure (Higgins and Green, 2011).

2.2 Research question

What is the scope of pharmacist-led interventions within a community pharmacy setting aimed at optimising blood pressure?

2.3 Rationale

It is thought to be a positive manoeuvre when community pharmacists counsel and intervene in patients undergoing antihypertensive treatment. However, it is not known if these interventions are positive, negative or have no effect. In addition, the research domain on community pharmacist interventions has not been particularly focused on examining the participants, interventions, comparators, outcomes and study design. Hence, the present study is a systematic attempt to examine this data coupled with a meta-analysis to possibly produce recommendations highlighting the type of intervention to be most appropriate under certain circumstances.

2.4 Objectives

A systematic literature review was performed to identify and evaluate mixed-method studies of community pharmacist-led interventions within a community pharmacy setting aimed at blood pressure optimisation in patients undergoing oral antihypertensive medication therapy.

2.5 Methods

2.5.1 Protocol

A protocol was created where the research question, aims and inclusion criteria were pre-specified (Appendix 5.1). The systematic review followed the PRISMA checklist (Liberati *et al*., 2009; Shamseer *et al*., 2015) and EPOC study design inclusion criteria (Effective Practice and Organisation of Care, 2013). As a mixed-methods study design was employed, a pragmatic approach to the EPOC study design criteria was sought, though not accommodating certain study designs. The reason for following the PRISMA protocol and EPOC criteria was that these tools are internationally recognized guidelines for systematic reviews.

2.5.2 Eligibility criteria

Participants: 18 years and above, undergoing treatment with minimum one oral antihypertensive medicine, with or without co-morbidities, within a community pharmacy setting

Interventions: Interventions in a community pharmacy aimed at optimising blood pressure

Outcomes: Blood pressure

Study design: A mixed-methods approach has been employed to include both qualitative and quantitative data.

2.5.3 Information sources

Searches were performed in the electronic databases Cinahl Plus, Cochrane Database, Embase Classic and Embase **(**1947 to 7 February 2014), Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE® (1946 to 9 February 2014; 16 February 2014), Ovid MEDLINE Daily Update (7 February 2014; 14 February 2014 for search term combination number 8), Ovid OLDMEDLINE (1946 to 1965) and PubMed. Grey literature was searched using Google, LexisNexis and Web of Science. There were no language restrictions in the searches. A repeated search was done in the electronic databases and Google during September 2016.

2.5.4 Search

Medical Subject Headings (MESH) search terms were used in accordance to the Medical Subject Headings for each electronic database: hypertension; antihypertensive agents; pharmacists; intervention studies; pharmaceutical care; medication adherence; blood pressure; pharmacies.

2.5.4.1 Electronic databases

The search term combinations used for the electronic databases are stated in sections 2.5.4.1.1 - 2.5.4.1.5.

2.5.4.1.1 Cinahl Plus

1. (MH “hypertension”) AND (MH “antihypertensive agents”) AND (MH “pharmacists”) OR (MH “pharmacy, retail”) AND (MH ”experimental studies”) AND (MH “medication compliance”) AND (MH “blood pressure”)
2. (MH “pharmacists”) AND (MH ”antihypertensive agents”) AND (MH “experimental studies”) AND (MH “medication compliance”) AND (MH “blood pressure”)
3. (MH “pharmacy, retail”) AND (MH “hypertension”) AND (MH “experimental studies”) AND (MH “medication compliance”) AND (MH “blood pressure”)
4. (MH “pharmacy, retail”) AND (MH “antihypertensive agents”) AND (MH “experimental studies”) AND (MH “medication compliance”) AND (MH “blood pressure”)
5. (MH “pharmacists”) AND (MH “hypertension”) AND (MH “medication compliance”) AND (MH “blood pressure”)
6. (MH “pharmacists”) AND (MH “antihypertensive agents”) AND (MH “medication compliance”) AND (MH “blood pressure”)
7. (MH “pharmacy, retail”) AND (MH “hypertension”) AND (MH “medication compliance”) AND (MH “blood pressure”)
8. (MH “pharmacy, retail”) AND (MH “antihypertensive agents”) AND (MH “medication compliance”) AND (MH “blood pressure”)

2.5.4.1.2 Cochrane Database

1. hypertension AND antihypertensive agents AND (pharmacists OR pharmacies) AND (intervention studies OR pharmaceutical care) AND medication adherence AND blood pressure
2. pharmacists AND antihypertensive agents AND (intervention studies OR pharmaceutical care) AND medication adherence AND blood pressure
3. pharmacies AND hypertension AND (intervention studies OR pharmaceutical care) AND medication adherence AND blood pressure
4. pharmacies AND antihypertensive agents AND (intervention studies OR pharmaceutical care) AND medication adherence AND blood pressure
5. pharmacists AND hypertension AND medication adherence AND pharmaceutical care AND blood pressure
6. pharmacists AND antihypertensive agents AND medication adherence AND pharmaceutical care AND blood pressure
7. pharmacies AND hypertension AND medication adherence AND pharmaceutical care AND blood pressure
8. pharmacies AND antihypertensive agents AND medication adherence AND pharmaceutical care AND blood pressure

2.5.4.1.3 Embase

1. hypertension/ and antihypertensive agent/ and pharmacist/ or pharmacy/ and intervention study/ or pharmaceutical care/and medication compliance/ and blood pressure/
2. pharmacist/ and antihypertensive agent/ and intervention study/ or pharmaceutical care/ and medication compliance/ and blood pressure/
3. pharmacy/ and hypertension/ and intervention study/ or pharmaceutical care/ and medication compliance/ and blood pressure/
4. pharmacy/ and antihypertensive agent/ and intervention study/ or pharmaceutical care/ and medication compliance/ and blood pressure/
5. pharmacist/ and hypertension/ and medication compliance/ and pharmaceutical care/ and blood pressure/
6. pharmacist/ and antihypertensive agent/ and medication compliance/ and pharmaceutical care/ and blood pressure/
7. pharmacy/ and hypertension/ and medication compliance/ and pharmaceutical care/ and blood pressure/
8. pharmacy/ and antihypertensive agent/ and medication compliance/ and pharmaceutical care/ and blood pressure/

2.5.4.1.4 Ovid MEDLINE

1. hypertension/ and antihypertensive agents/ and pharmacists/ or pharmacies/ and intervention studies/ or pharmaceutical services/ and medication adherence/ and blood pressure/
2. pharmacists/ and antihypertensive agents/ and intervention studies/ or pharmaceutical services/ and medication adherence/ and blood pressure/
3. pharmacies/ and hypertension/ and intervention studies/ or pharmaceutical services/ and medication adherence/ and blood pressure/
4. pharmacies/ and antihypertensive agents/ and intervention studies/ or pharmaceutical services/ and medication adherence/ and blood pressure/
5. pharmacists/ and hypertension/ and medication adherence/ and pharmaceutical services/ and blood pressure/
6. pharmacists/ and antihypertensive agents/ and medication adherence/ and pharmaceutical services/ and blood pressure/
7. pharmacies/ and hypertension/ and medication adherence/ and pharmaceutical services/ and blood pressure/
8. pharmacies/ and antihypertensive agents/ and medication adherence/ and pharmaceutical services/ and blood pressure/

2.5.4.1.5 PubMed

1. hypertension AND antihypertensive agents AND pharmacists OR pharmacies AND intervention studies OR pharmaceutical care AND medication adherence AND blood pressure
2. pharmacists AND antihypertensive agents AND intervention studies OR pharmaceutical care AND medication adherence AND blood pressure
3. pharmacies AND hypertension AND intervention studies OR pharmaceutical care AND medication adherence AND blood pressure
4. pharmacies AND antihypertensive agents AND intervention studies OR pharmaceutical care AND medication adherence AND blood pressure
5. pharmacists AND hypertension AND medication adherence AND pharmaceutical care AND blood pressure
6. pharmacists AND antihypertensive agents AND medication adherence AND pharmaceutical care AND blood pressure
7. pharmacies AND hypertension AND medication adherence AND pharmaceutical care AND blood pressure
8. pharmacies AND antihypertensive agents AND medication adherence AND pharmaceutical care AND blood pressure

2.5.4.2 Grey literature

2.5.4.2.1 Google

- Search performed on April 30th, 2014 on first 20 outputs with search term combination number 1. Repeated search on May 9th and May 13th, 2014 on first 100 outputs.
- Search performed on May 13th, 2014 with search term combination numbers 2-9 on first 100 outputs.
- Search performed on August 10th, 2014 with search term combination number 10 on first 100 outputs.

Random search performed in Google:

- on February 6th, 2015 with search term combination number 11. Repeated search on June 4th, 2015
- on April 13th, 2015 with search term combination number 12. Repeated search on June 3rd, 2015
- on May 24th, 2015 with search term combination number 13
- on May 3rd, 2015 with search term combination number 14

1. hypertension adherence community pharmacy
2. hypertension AND antihypertensive agents AND pharmacists OR pharmacies AND intervention studies OR pharmaceutical care AND medication adherence AND blood pressure
3. pharmacists AND antihypertensive agents AND intervention studies OR pharmaceutical care AND medication adherence AND blood pressure
4. pharmacies AND hypertension AND intervention studies OR pharmaceutical care AND medication adherence AND blood pressure
5. pharmacies AND antihypertensive agents AND intervention studies OR pharmaceutical care AND medication adherence AND blood pressure
6. pharmacists AND hypertension AND medication adherence AND pharmaceutical care AND blood pressure
7. pharmacists AND antihypertensive agents AND medication adherence AND pharmaceutical care AND blood pressure
8. pharmacies AND hypertension AND medication adherence AND pharmaceutical care AND blood pressure
9. pharmacies AND antihypertensive agents AND medication adherence AND pharmaceutical care AND blood pressure
10. hypertension compliance community pharmacy
11. hypertension community pharmacy
12. pharmaceutical care blood pressure
13. blood pressure control pharmacy
14. hypertension community pharmacy

2.5.4.2.2 LexisNexis

All searches in LexisNexis performed under Sources: All News, All Languages

- Search performed on March 23rd, 2014 with citations 1-8.
- Search performed on April 2nd, 2014 with citation 9.

1. Lau *et al*., 2010
2. George *et al*., 2010
3. Fikri-Benbrahim *et al*., 2012
4. Svarstad *et al*., 2013
5. Svarstad *et al*., 2009
6. Aguiar *et al*., 2012
7. Robinson *et al*., 2010
8. Aguwa *et al*., 2008
9. Planas *et al*., 2009

2.5.4.2.3 Web of Science

- Search performed on March 23rd, 2014 with citations 1-8.
- Search performed on April 2nd, 2014 with citation 9.

1. Lau *et al*., 2010
2. George *et al*., 2010
3. Fikri-Benbrahim *et al*., 2012
4. Svarstad *et al*., 2013

5. Svarstad *et al*., 2009
6. Aguiar *et al*., 2012
7. Robinson *et al*., 2010
8. Aguwa *et al*., 2008
9. Planas *et al*., 2009

2.5.5 Study selection

Studies were selected independently by two reviewers (the author and a Professor of Clinical Pharmacy). Any disagreements in study selection were resolved by discussion between the two reviewers.

2.5.6 Data collection process

Searches were performed in the electronic databases and grey literature. Study authors were contacted to retrieve additional data or obtain clarification relating to a specific study which revolved around whether the full study had been published, the name of authors, study design, bias, blood pressure data, data enabling calculation of odds ratio or mean difference.

2.5.7 Data items

The information which was collected from studies followed the headings Participants, Interventions, Comparators, Outcomes, Study Design (PICOS) from the PRISMA protocol (Liberati *et al*., 2009; Shamseer *et al*., 2015).

2.5.8 Summary measures

The effect measures were calculated as odds ratios (OR) with 95% confidence intervals using random effects model for dichotomous outcomes, i.e. those studies reporting the proportion of patients with controlled and uncontrolled systolic blood pressure (SBP) and diastolic blood pressure (DBP) respectively at the end of the study. In the studies were proportions of patients were not separately reported for SBP and DBP, both these two outcomes were grouped together as a combined outcome and an OR with 95% confidence interval using random effects model was calculated. Blood pressure control was interpreted as defined in the individual study. Among those studies not reporting data supporting the calculation of an OR, the mean difference was calculated using the random effects model based on end study mean SBP and mean DBP values (continuous outcomes). All data were derived from results being reported as intention-to-treat. Forest plots were created in the software Review Manager version 5.3.5 (The Nordic Cochrane Centre, 2014).

2.5.9 Planned methods of analysis

A measure of consistency for the meta-analysis was performed using the I^2 statistic. This followed thresholds as stated in the Cochrane Handbook: 0 % to 40%: not important; 30% to 60%: moderate heterogeneity; 50% to 90%: substantial heterogeneity; 75% to 100%: considerable heterogeneity (Higgins and Green, 2011).

2.5.10 Additional analyses

A narrative, qualitative summary was performed as a thematic analysis according to the methodology proposed by Braun and Clarke (2006) (Braun and Clarke, 2006). The studies were read through initially to note down initial ideas. During a second phase, the studies were re-read with a focus on coding the entire data set. The codes were collated from each study and categorized under the headings of Participants, Interventions, Comparators, Outcomes and Study designs (PICOS) (Braun and Clarke, 2006; Liberati *et al*., 2009; Shamseer *et al*., 2015). Thematic maps for each heading in PICOS were created based on the occurrence of the codes under each heading. The final themes were then created as a summary of the thematic maps.

2.5.11 Risk of bias in individual studies and across studies

The risk of bias was assessed for each included study according to The Cochrane Collaboration's tool for assessing risk of bias. This risk of bias tool was chosen since it was a universal tool applied in systematic reviews. Although the risk of bias tool is used to only assess the risk of bias in randomized controlled trials, the tool was adapted for use in the mixed-methods approach. Where the study design was cluster-randomized, additional risk of bias was assessed including the elements recruitment bias, baseline imbalance, loss of clusters, incorrect analysis, and comparability of individually randomized trials (Higgins and Green, 2011). An overall study risk of bias was evaluated for each paper based on individual risk items.

2.5.12 Publication bias

2.5.12.1 Funnel plots

Publication bias was assessed by the construction of funnel plots using the software Review Manager version 5.3.5 (The Nordic Cochrane Centre, 2014). Funnel plots with and without grey literature were created for a) odds ratio as an effect estimate of SBP and DBP as a combined outcome and b) mean difference as an effect estimate of SBP and DBP respectively. Funnel plots were not created for odds ratio of SBP or DBP alone since the number of studies were too low to perform the analysis.

2.5.12.2 Testing for funnel plot asymmetry

Funnel plot asymmetry was tested statistically by performing the arcsine version of the test suggested by Rücker and co-workers (Higgins and Green, 2011; Rücker *et al*., 2008). The arcsine-Thompson test suggested by Rücker and co-workers was performed using the R statistics meta package on odds ratio as the effect estimate of SBP and DBP as a combined outcome (Appendix 5.2) (Rücker *et al*., 2008; R Core Team, 2016; Schwarzer *et al*., 2015; Schwarzer, 2016). The test was only performed on odds ratio as an effect estimate of SBP and DBP as a combined outcome since the Cochrane Handbook suggests there be a minimum of 10 studies when testing for funnel plot asymmetry (Higgins and Green, 2011).

2.6 Results

2.6.1 Study selection

Identification of 535 records was obtained through searching in the electronic databases. From these 535 records, duplicates were removed narrowing the number to 10 records. An additional 20 records were identified and screened through grey literature searches in Google, LexisNexis and Web of Science resulting in 30 records screened in total. A further 9 records were excluded because a non-pharmacy healthcare profession was mainly involved in the study, the study design was not exclusively a community pharmacy setting, a high-risk cardiovascular population was involved, no blood pressure outcome was recorded, no blood pressure results were reported, only an abstract was available, or press releases relating to study authors were involved. Twenty-one full-text articles were included in the final systematic review. Among these, all 21 studies underwent qualitative synthesis and 13 studies included in the quantitative synthesis. See flow diagram in Figure 2.1 illustrating the identification process of studies for the systematic review.

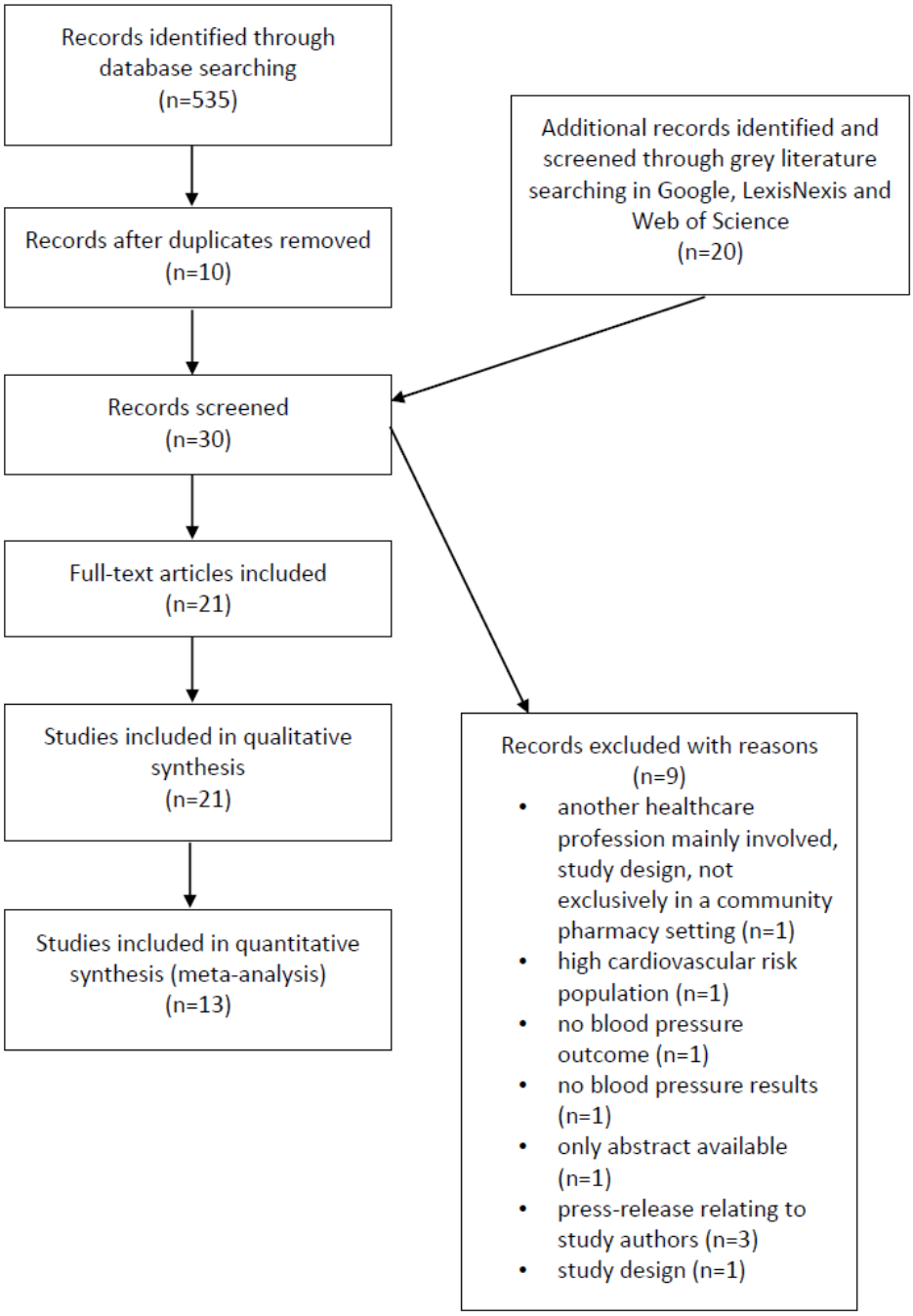


Figure 2.1. A flow chart illustrating the process of identifying studies for the systematic review.

2.6.2 Study characteristics: Participants, Interventions, Comparators, Outcomes, Study Design (PICOS)

The characteristics according to the PICOS classification of the included studies are presented in Table 2.1. Among the included studies there is a mixture of papers from different points across the timeline starting from the year 1973 onward. In total, there were 21 included studies (11 randomized controlled trials (RCTs), 2 before-after studies (BASs), 3 non-randomised controlled trials (NRCTs), 1 repeated measures study (RMS) and 4 prospective cohort studies (PCSs)). Study duration among the studies varied from 3-15 months. Study visits to a community pharmacy ranged from weekly to quarterly intervals. In total, there were 2509 patients who completed the studies. In general, the patients were within the age of 50 to 60 years. The studies included counselling, BP measurement, referral to/contact with a physician, informational materials, reminder aids and diary keeping as interventions. The blood pressure outcome was highly variable across the studies.

Table 2.1. Summary table of included studies in the systematic review displaying authors, year of publication, study design, total number of patients, number of patients completed, outcome measures, participants, interventions, comparisons and outcomes (mean BP change between baseline and final visit). Author, year in italics=study not meeting EPOC study design criteria.

Authors, year	Study design	Total number of patients	Number of patients completed	Outcome measures	Participants	Interventions	Comparisons	Outcomes (Mean BP change between baseline and final visit)
McKenney *et al.*, 1973	• RCT • StDu: 5 months • IG CPV: Monthly visits for 5 months • CG CPV: not reported	50	49	• BP control • study patient knowledge of hypertension and its treatment • AH AD • ADR incidence • patient acceptance • professional time •recommendations to patients and physicians	Patients with hypertension Average age 58 years CG, 62 years SG	• Counselling session • Informational material • Referral to/contact with physician	SG, CG	BP by pharmacist investigator: SG: Before: SBP: 155 mmHg DBP: 98 mmHg After: No data BP by physician: SG: SBP: 8 mmHg ↓ DBP: 2 mmHg ↓ CG: SBP: 5 mmHg ↑ DBP: 10 mmHg ↑
Hughes *et al.*, 2002	• RCT • StDu: 12 months • Low IG CPV: Baseline, 3 months, 6 months, 9 months, 12 months • High IG CPV: Monthly visits for 12 months • CG CPV: Baseline, 12 months	34	21	• AD rates (drug and non-drug interventions) • BP control • ADR incidence • reduced CV complications • QoL • reduction in health care expenditure	Newly commenced on AH drug therapy (Inclusion criteria age stated >18 years and ≥25 years) Mean age 52 years Low IG, 58 years High IG, 53 years CG	• Counselling • BP measurement • Referral to/contact with physician • Informational materials • Reminder aids • Diary	High IG, Low IG, CG	Low IG: SBP: 9 mmHg ↓ DBP: 3 mmHg ↓ High IG: SBP: 5 mmHg ↓ DBP: 9 mmHg ↓ CG: SBP: 26 mmHg ↓ DBP: 12 mmHg ↓

Authors, year	Study design	Total number of patients	Number of patients completed	Outcome measures	Participants	Interventions	Comparisons	Outcomes (Mean BP change between baseline and final visit)
Garção and Cabrita, 2002	• RCT • StDu: 6 months • IG CPV: Monthly visits for 6 months • CG CPV: Baseline and after study completion, medication refill visits	100	82	• BP control • DRPs	Patients with essential hypertension On drug treatment for <6 months Mean age 67 years IG, 64 years CG	• Counselling • BP measurement • Referral to/contact with physician • Informational materials	IG, CG	IG: SBP: 23 mmHg ↓ DBP: 13 mmHg ↓ CG: SBP: 5 mmHg ↓ DBP: 5 mmHg ↓
Taylor et al., 2003	• BAS • StDu: 3 months • CPV: Monthly visits for 3 months	8	8	• AH drug therapy AD • BP control • patient satisfaction	African Americans with hypertension diagnosis Mean age 63 years	• Counselling • BP measurement • Referral to/contact with physician • Informational materials • Reminder aids	BA	SBP: 15 mmHg ↓ DBP: 14 mmHg ↓

Authors, year	Study design	Total number of patients	Number of patients completed	Outcome measures	Participants	Interventions	Comparisons	Outcomes (Mean BP change between baseline and final visit)
Chabot *et al*., 2003	• NRCT • StDu: 9 months • CPV: 3 visits at baseline and 3 visits after INT (home visits with minimum 1 week intervals) Medication refill visits at pharmacy (INT initiated at a medication refill visit)	111	100	• BP levels • drug treatment AD • physical activity • alcohol consumption • BMI • factors affecting AD in hypertensive patients	Patients with hypertension Majority of patients age ≥60 years	• Counselling • BP measurement • Referral to/contact with physician • Informational materials	IG (High income, Low income), CG (High income, Low income)	IG: High-income patients SBP: 8 mmHg ↓ DBP: 7 mmHg ↓ Low-income patients: SBP: 1 mmHg ↑ DBP: 0.4 mmHg ↑ CG: High-income patients: SBP: 1 mmHg ↑ DBP: 4 mmHg ↓ Low-income patients: SBP: 3 mmHg ↓ DBP: 2 mmHg ↓
Zillich et al., 2005	•RCT • StDu: 3 months • LI IG: Baseline, 4 weeks, 10-12 weeks • HI IG: Baseline, 4 weeks, 6-8 weeks, 12 weeks	125	117	• AD • BP difference • Health resource utilization • Pharmacist recommendations	Patients with hypertension diagnosis Mean age 66 years LI IG, 64 years HI IG	• Counselling • BP measurement • Referral to/contact with physician • Information materials • HBPM, HBPM log book	LI IG, HI IG	LI IG: SBP: 9 mmHg ↓ DBP: 6 mmHg ↓ HI IG: SBP: 13 mmHg ↓ DBP: 9 mmHg ↓

Authors, year	Study design	Total number of patients	Number of patients completed	Outcome measures	Participants	Interventions	Comparisons	Outcomes (Mean BP change between baseline and final visit)
Carvalho and Nagavi, 2007	RCT StDu: 3 months CPV: Monthly visits for 3 months	58	47	• AH AD • QoL • BP control • Knowledge, attitude and belief	Patients with hypertension Age not reported (inclusion criteria age >18 years)	• Counselling • BP measurement	TG, CG	TG: SBP: 14 mmHg↓ DBP: 9 mmHg ↓ CG: SBP: 6 mmHg ↓ DBP: 4 mmHg ↓
Lai, 2007	• RMS • StDu: 9 months • CPV: Baseline, 1 month, 3 months, 6 months, 9 months	103	53	• BP control • QoL • AH AD • frequency of BP screenings between baseline and endpoint of INT	Latino/Hispanic patients with hypertension Mean age 55 years	• Counselling • BP measurement • Referral to/contact with physician	BA	SBP: 17 mmHg ↓ DBP: 13 mmHg ↓
Aguwa et al., 2008	• PCS • StDu: 10 months • CPV: Monthly visits for five months during INT period	40	24	• BP • QoL • smoking cessation • AH AD • exercise • salt restriction • alcohol moderation • self BP measurement	Patients with hypertension Mean age 52 years	• Counselling • BP measurement • Referral to/contact with physician • Informational materials	OC, BA	SBP: 14 mmHg ↓ DBP: 11 mmHg ↓

Authors, year	Study design	Total number of patients	Number of patients completed	Outcome measures	Participants	Interventions	Comparisons	Outcomes (Mean BP change between baseline and final visit)
Júnior et al., 2008	• PCS • StDu: 12 months • CPV: Monthly visits for 12 months	30	30	• DTPs • BMI • BP control	Elderly outpatients with hypertension Mean age 66 years	• Counselling • Referral to/contact with physician	BA	SBP: 18 mmHg ↓ DBP: 12 mmHg ↓
Planas *et al.*, 2009	• RCT • StDu: 9 months • IG CPV: Monthly visits for 9 months • CG CPV: Baseline, 3 months, 6 months, 9 months	52	40	• BP control • AH AD	Patients with hypertension and diabetes Mean age 64 years IG, 65 years CG	• Counselling • BP measurement • Referral to/contact with physician	CG, IG	IG: SBP: 17 mmHg ↓ *DBP: 5 mmHg ↓ CG: SBP: 3 mmHg ↑ *DBP: 1 mmHg ↑ *data obtained by e-mail correspondence with study author (Planas, 2015a; Planas 2015b).
Robinson *et al.*, 2010	• NRCT • StDu: 12 months • IG CPV: Monthly visits for 12 months • CG CPV: Monthly visits for 12 months	376	376	• BP control vs. not participating • QoL • better medication-taking practices vs. not participating	Patients with hypertension Age not reported	• Counselling • BP measurement • Informational materials • Referral to/contact with physician	PCG, UCG	PCG: SBP: 10 mmHg ↓ DBP: 3 mmHg ↓ UCG: SBP: 3 mmHg ↓ DBP: 1 mmHg ↓

Authors, year	Study design	Total number of patients	Number of patients completed	Outcome measures	Participants	Interventions	Comparisons	Outcomes (Mean BP change between baseline and final visit)
Octavia and Florica, 2011	• RCT • StDu: 6 months • IG CPV: monthly visits for 6 months • CG CPV: not reported	100	100	• BP control • BMI	Patients with essential hypertension from urban environment Aged 51- 65 years	• Counselling • BP measurement • Referral to/contact with physician	PCG, WB (UCG)	PCG: SBP: 19 mmHg ↓ DBP: 17 mmHg ↓ WB: SBP: 7 mmHg ↓ DBP: 4 mmHg ↓
Skowron *et al.*, 2011	• RCT • StDu: 15 months • IG CPV: 12 visits • CG CPV: 2 visits with minimum 14 months interval	118	84	• Patients' knowledge • QoL • BP control • change in satisfaction and knowledge of pharmacists	Patients with hypertension Undergoing pharmaco-therapy for >6 months Aged ≥31 years	• Counselling • BP measurement	SG, CG	SG: *SBP: 6 mmHg ↓ *DBP: 2 mmHg ↓ CG: *SBP: 5 mmHg ↓ *DBP: 2 mmHg ↓ *BP at final visit measured as arterial BP.
Aguiar et al., 2012	• PCS • StDu: 10 months • CPV: Monthly visits for 10 months	51	35	• BP control • pulse pressure • AH AD • reduction of anthropometric indices	Elderly patients with diagnosed essential hypertension and uncontrolled BP Aged 66-68 years	• Counselling • BP measurement • Informational materials • Referral to/contact with physician	BA	SBP: 27 mmHg ↓ DBP: 10 mmHg ↓

Authors, year	Study design	Total number of patients	Number of patients completed	Outcome measures	Participants	Interventions	Comparisons	Outcomes (Mean BP change between baseline and final visit)
Fikri-Benbrahim *et al.*, 2012	• NRCT • StDu: 31 weeks • IG CPV: Initial phase: 3 visits (1 week between each visit); Intermediate phase: 6 visits (20 week intervention); Final phase: 4 visits (4 weeks between final visit 1 and 2, 1 week between each final visit 2, 3 and 4) • CG CPV: Initial phase: 3 visits (1 week between each visit); Intermediate phase: 1 visit; Final phase: 4 visits (4 weeks between final visit 1 and 2, 1 week between each final visit 2, 3 and 4) (Fikri-Benbrahim, 2014)	180	176	• BP control	Patients with diagnosis of primary hypertension. Mean age 62 years IG, 62 years CG	• Counselling • BP measurement • Informational materials • Referral to/contact with physician	CG, IG, SGr	IG: SBP: 7 mmHg ↓ DBP: 2 mmHg ↓ CG: SBP: 2 mmHg ↓ DBP: 0.1 mmHg ↑

Authors, year	Study design	Total number of patients	Number of patients completed	Outcome measures	Participants	Interventions	Comparisons	Outcomes (Mean BP change between baseline and final visit)
Nemerovski et al., 2013	• PCS • StDu: 6 months • CPV: Four visits with 6 weeks intervals during 6 months.	152	152	• BP control • % of patients with LS goals • AH AD • patient knowledge and satisfaction • modification of CV risk factors	WSU Own identification of hypertension/pre-hypertension diagnosis Aged 51 years (not reported if average or mean age)	• Counselling • BP measurement •Information-al materials • Diary • Referral to/contact with physician	BA, SGr	SPB: 1 mmHg ↓ DPB: 1 mmHg ↓
Svarstad *et al.*, 2013	• RCT • StDu: 12 months • IG CPV: Monthly INT visits for 6 months, follow-up 6 and 12 months from baseline • CG visits: Baseline visit, follow-up 6 and 12 months from baseline	576	493	• AH AD • BP control	African American patients with hypertension Mean age 53 years IG, 53 years CG	• Counselling • BP measurement •Information-al materials • Reminder aids • Referral to/contact with physician	CG, IG	IG: SBP: 14 mmHg ↓ DBP: 9 mmHg ↓ CG: SBP: 8 mmHg ↓ DBP: 7 mmHg ↓

Authors, year	Study design	Total number of patients	Number of patients completed	Outcome measures	Participants	Interventions	Comparisons	Outcomes (Mean BP change between baseline and final visit)
Pojskic *et al.*, 2014 (Pojskic, 2014a)	• RCT • StDu: 6 months • IG CPV: Monthly visits for 6 months • CG CPV: Monthly visits for 6 months	153	118	• BP control • AD AH therapy • smoking status and FQ • FQ of PE • BMI • drug costs • INT costs	• Patients with hypertension • Mean age 57 years IG, 57 years CG	• Counselling • BP measurement • Informational materials • Referral to/contact with physician	CG, IG	IG: SBP: 14 mmHg ↓ DBP: 6 mmHg ↓ CG: SBP: 5 mmHg ↓ DBP: 4 mmHg ↓
Stewart *et al.*, 2014	• RCT • StDu: 6 months • IG CPV: Baseline, 3 months, 6 months • CG CPV: Baseline, 6 months	395	354	• proportion self-reporting AH AD on AD questionnaires • BP control	• Patients with primary hypertension • Mean age 67 years PCG, 67 years UCG	• Counselling • BP measurement • Informational materials • Reminder aids • Referral to/contact with physician	PCG, UCG, SGr, HCG	UCG: SBP: 5 mmHg ↓ DBP: 4 mmHg ↓ PCG: SBP: 10 mmHg ↓ DBP: 5 mmHg ↓
Sharma et al., 2014	• BAS • StDu: 8 months • CPV: Baseline, 2 months, 4 months, 8 months	50	50	•change in knowledge and lifestyle practices (management of hypertension) • BP change	• Patients with hypertension diagnosis • Mean age 60 years	• Counselling • BP measurement • Informational materials	BA	SBP: 12 mmHg↓ DBP: 10 mmHg↓

Abbreviations for Table 2.1:

AD=Adherence; ADR=Adverse drug reaction; AH=Antihypertensive; BA=Before and After; BAS=Before and After Study; BMI=Body Mass Index; BP=Blood Pressure; CG=Control Group; CKD=chronic kidney disease; COPD=chronic obstructive pulmonary disease; CPV=Community pharmacy visits; CV=cardiovascular; DAA=Dose administration aid; DBP=Diastolic Blood Pressure; DRP=Drug-related problem; DTP=drug therapy-problem; EAP=Employee Assistance Program for disease management; ED=Educational; fin=final BP reading; FQ=Frequency; GP=General Practitioner; HBPM=home blood pressure monitoring; HCG=Hidden Control Group; HI=High-intensity; HMR=Home medicines review; IG=Intervention Group; ini=initial BP reading; INT=Intervention; LI=Low-intensity; LS=Lifestyle; MNCHP=Model Neighborhood Comprehensive Health Program, Inc.; MTM=Medication Therapy Management; MUR=Medication use review; NRCT=Non-randomised controlled trial; OC=Patients serve as their own control; PC=Pharmaceutical Care; PCG=Pharmacist Care Group; PCS=Prospective cohort study; PE=Physical Exercise; PHCU=primary health care unit; PMP=Patient medication profile; QoL=Quality of Life; RCT=Randomised controlled trial; RMS=Repeated measures study; RR=Refill reminder; S-A=Self-administer; SBP=Systolic Blood Pressure; SCS=Smoking cessation program; SD: Standard deviation; SG=Study group; SGr=Subgroup; StDu=Study duration; TABS=Tool for Adherence Behaviour Screening; TG=Test group; UCG=Usual Care Group; WB=Witness batch; WSU= Wayne State University employees participating in employer wellness plan

Since the meta-analysis was performed there have been identified 6 extra studies (3 RCTs, 1 BAS and 2 PCS) (see Table 2.2). Study duration varied from 2 weeks to 9 months. In total 734 patients completed these studies. The BP outcome across the studies in Table 2.2 was highly variable.

Table 2.2. Summary table of extra studies which have been identified since the meta-analysis was performed. The table displays authors, year of publication, study design, total number of patients, number of patients completed and outcomes (mean BP change between baseline and final visit). Author, year in italics=study not meeting EPOC study design criteria.

Authors, year	Study design	Total number of patients	Number of patients completed	Outcomes (Mean BP change between baseline and final visit)
Sookaneknun et al., 2004	• RCT • StDu: 9 months • Study sites: a university community pharmacy and two primary care units	235	227	IG: SBP: 23 mmHg ↓ DBP: 14 mmHg ↓ CG: SBP: 18 mmHg ↓ DBP: 12 mmHg ↓
Erhun et al., 2005	• PCS • StDu: 6 months	51	37	SBP: 42 mmHg↓ DBP: 22 mmHg↓
Oparah et al., 2006	• BAS • StDu: 6 months	42	36	SBP: 50 mmHg↓ DBP: 29 mmHg↓
DiDonato *et al.*, 2014	• RCT • StDu: 6 months	302	275	IG MS: SBP: 4 mmHg ↓ DBP: 2 mmHg ↓ IG ED: SBP: 10 mmHg ↓ DBP: 3 mmHg ↓ CG: SBP: 9 mmHg ↓ DBP: 3 mmHg ↓

Authors, year	Study design	Total number of patients	Number of patients completed	Outcomes (Mean BP change between baseline and final visit)
Pistja and Themeli, 2015a (Pistja and Themeli, 2015b)	• RCT • StDu: 9 months	200	120	IG: SBP: 6 mmHg ↓ DBP: 1 mmHg ↓ CG: SBP: 2 mmHg ↓ DBP: 1 mmHg ↓
Noble et al., 2016	• PCS • StDu: 2 weeks	39	39	SBP: 8 mmHg↓ DBP: 3 mmHg↓

Abbreviations for Table 2.2: BAS=Before and After Study; CG=Control Group; DBP=Diastolic Blood Pressure; IG=Intervention Group; IG ED=Intervention Group Education; IG MI=Intervention Group Medication Synchronization; PCS=Prospective cohort study; RCT=Randomised controlled trial; SBP=Systolic Blood Pressure; StDu=Study duration

2.6.3 Results of individual studies

A meta-analysis with odds ratios as an effect estimate was performed on 10 out of 21 studies with SBP and DBP as a combined outcome. Of 21 studies, 3 studies underwent a meta-analysis with odds ratios for SBP or DBP outcomes respectively.

Meta-analysis with mean difference was used as an effect estimate for 7 out of 21 included studies analysing both SBP and DBP respectively.

It was not possible to go forward with meta-analysis throughout all 21 studies because of study design or data not being available to support the calculation of effect estimates.

From Figures 2.2 to 2.6 all studies are relatively small-scale. The more modern studies appear to have a larger weighting. It is important to bear in mind when comparing the Forest plots scaling in each figure differ to present the data in an acceptable format.

2.6.3.1 Odds ratio

Examination of the Forest plots in Figures 2.2 to 2.4 shows the mean values for each study are in the control group area in the Forest plot with large confidence intervals observed in the older studies.

2.6.3.1.1 Systolic blood pressure (SBP) and diastolic blood pressure (DBP) as a combined outcome

Odds ratio as an effect estimate of SBP and DBP as a combined outcome is presented as a Forest plot in Figure 2.2. The meta-analysis for SBP and DBP as a combined outcome employed a random effects model including 1252 patients where the pooled effect of 0.33 mmHg increase in BP (95% CI, 0.23 mmHg to 0.47 mmHg, $p<0.00001$) implies no BP change. As seen in Figure 2.2, heterogeneity between studies relating to SBP and DBP as a combined outcome may not be relevant or is moderate ($\chi^2=15.32$, df=10, $p=0.12$, $I^2=35\%$).

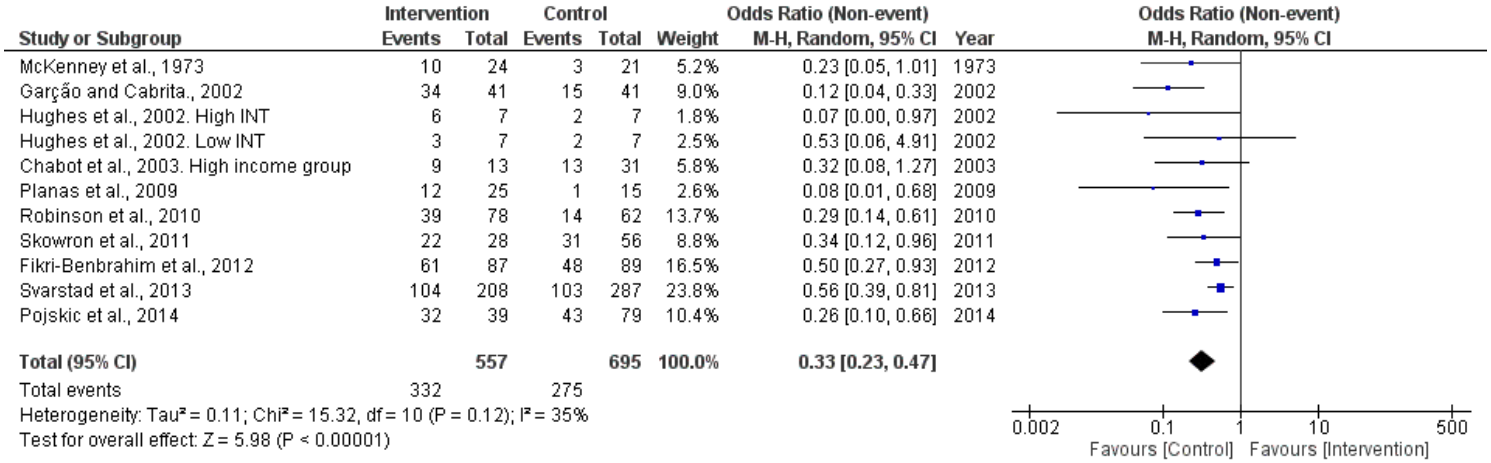


Figure 2.2. Odds ratio as an effect estimate with SBP and DBP as a combined outcome is displayed for each individual study as well as in a Forest plot. The pooled effect is presented both numerically and in the Forest plot. A random effects model was employed in this meta-analysis. Heterogeneity between studies is indicated as an I^2 value.

2.6.3.1.2 Systolic blood pressure (SBP)

Odds ratio as an effect estimate of SBP is presented as a Forest plot in Figure 2.3. The meta-analysis for SBP employed a random effects model including 263 patients where the pooled effect of 0.29 mmHg increase in SBP (95% CI, 0.12 mmHg to 0.72 mmHg, p=0.007) implies no SBP change. As seen in Figure 2.3. heterogeneity between studies relating to SBP is moderate (χ^2=3.78, df=2, p=0.15, I^2=47%).

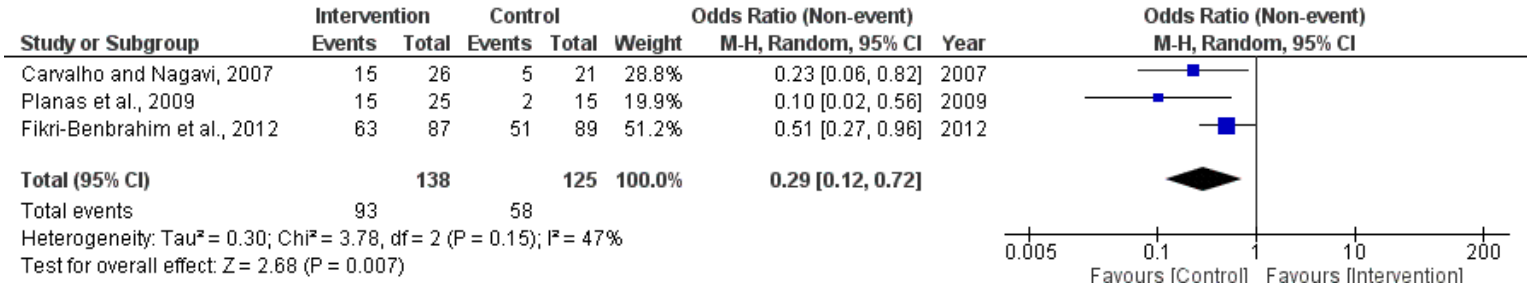


Figure 2.3. The odds ratio as an effect estimate of SBP is displayed for individual studies as well as in a Forest plot. The pooled effect is presented both numerically and in the Forest plot. A random effects model was employed in this meta-analysis. Heterogeneity between studies is indicated as an I^2 value.

2.6.3.1.3 Diastolic blood pressure (DBP)

Odds ratio as an effect estimate of DBP is presented as a Forest plot in Figure 2.4. The meta-analysis for DBP employed a random effects model including 263 patients where the pooled effect of 0.28 mmHg increase in DBP (95% CI, 0.04 mmHg to 2.08 mmHg, p=0.21) is indicative of no BP change. As seen in Figure 2.4 heterogeneity between studies relating to DBP is substantial (χ^2=9.20, df=2, p=0.01, I^2=78%).

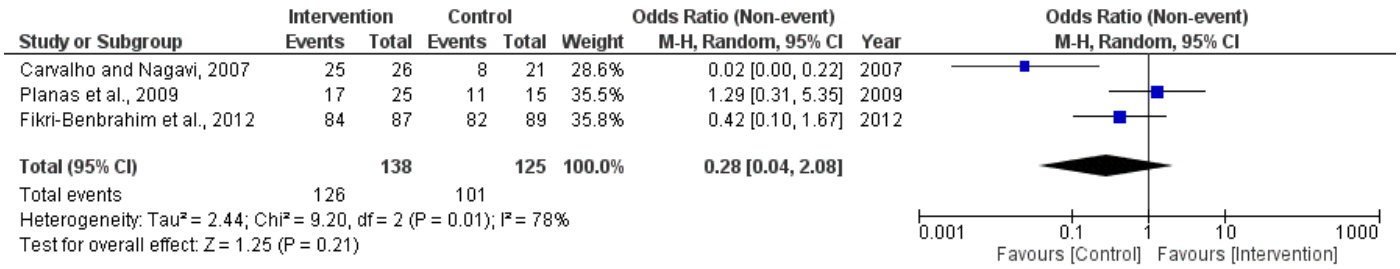


Figure 2.4. The odds ratio as an effect estimate of DBP is displayed for individual studies as well as in a Forest plot. The pooled effect is presented both numerically and in the Forest plot. A random effects model was employed in this meta-analysis. Heterogeneity between studies is indicated as an I^2 value.

2.6.3.2 Mean difference

2.6.3.2.1 Systolic blood pressure (SBP)

Mean difference as an effect estimate of SBP is presented as a Forest plot in Figure 2.5. The meta-analysis for SBP employed a random effects model including 1173 patients where the pooled effect is a 9.65 mmHg decrease in SBP (95% CI, -5.34 mmHg to -13.96 mmHg, $p<0.00001$). There is an indication of a positive effect when mean difference is plotted as an effect estimate for SBP. As seen in Figure 2.5 heterogeneity between studies relating to SBP is substantial ($\chi^2=20.52$, df=6, $p=0.002$, $I^2=71\%$).

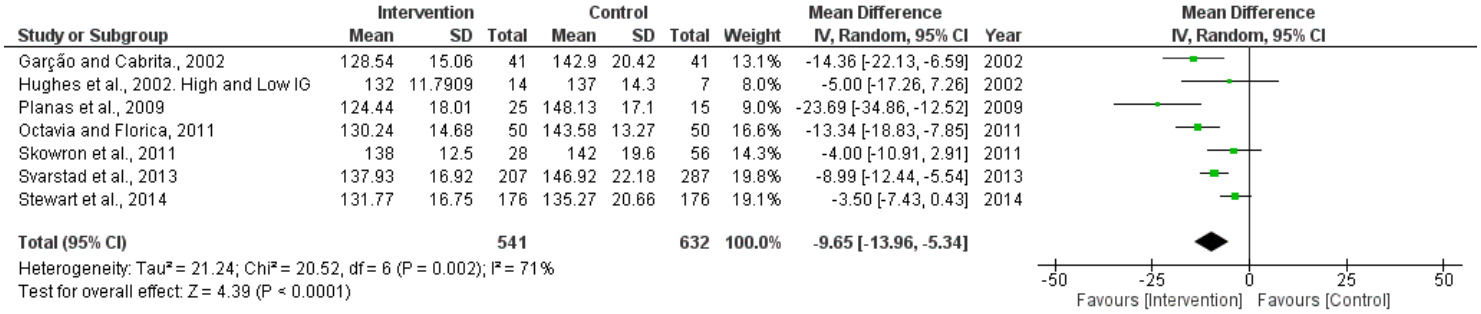


Figure 2.5. The mean difference as an effect estimate of SBP is displayed for individual studies as well as in a Forest plot. The pooled effect is presented both numerically and in the Forest plot. A random effects model was employed in this meta-analysis. Heterogeneity between studies is indicated as an I^2 value.

2.6.3.2.2 Diastolic blood pressure (DBP)

Mean difference as an effect estimate of DBP is presented as a Forest plot in Figure 2.6. The meta-analysis for DBP employed a random effects model including 1173 patients where the pooled effect is a 5.38 mmHg decrease in DBP (95% CI, -1.25 mmHg to -9.52 mmHg, p=0.01). There is an indication of a positive effect when mean difference is plotted as an effect estimate for DBP. As seen in Figure 2.6 heterogeneity between studies relating to DBP is substantial (χ^2=52.03, df=6, p<0.00001, I^2=88%).

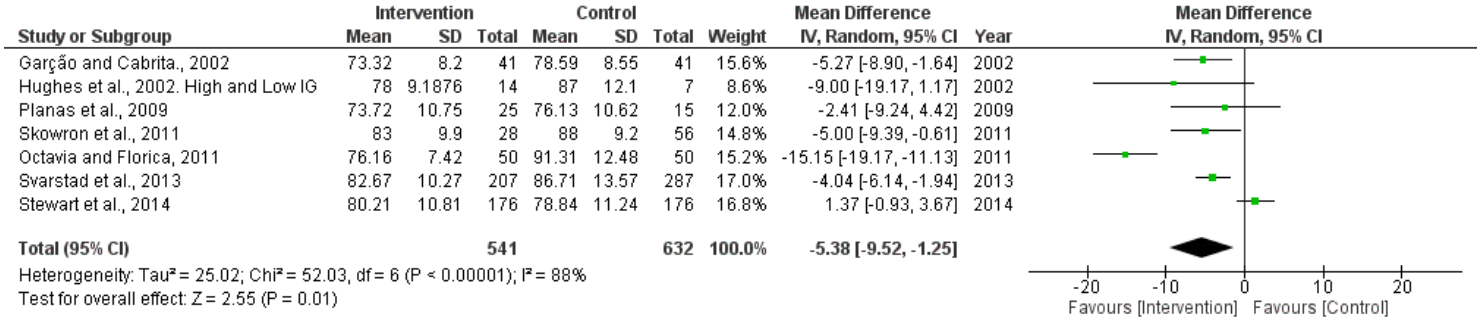


Figure 2.6. The mean difference as an effect estimate of DBP is displayed for individual studies as well as in a Forest plot. The pooled effect is presented both numerically and in the Forest plot. A random effects model was employed in this meta-analysis. Heterogeneity between studies is indicated as an I^2 value.

2.6.4 Additional analysis

2.6.4.1.1 Thematic analysis

The themes and corresponding sub-themes emanating from the review papers are presented in Table 2.3. Interventions, Outcomes and Study design are the most significant: sub-themes principally involve Population and Comparators. However, even though certain sub-themes are listed, they were not always evident in all studies.

Table 2.3. Themes and subthemes from the thematic analysis. Themes are displayed as headings. Bullet points show the sub-themes which occur in studies indicated as numbered references.

Population • *Hypertension* [1-21] • *Patient screening* [1-21] • *Population characteristics* [1-21] • *Therapy* [1-8, 10-21]* *not in [9]
Interventions • *Blood pressure* [1-21] • *Pharmaceutical care* [1-21] • *Resources* [1-21] • *Setting* [1-21] • *Staff* [1-21] • *Drug-related problems* [1-15, 17-21] *not in [16] • *Non-pharmacological treatment – lifestyle modification* [1-17, 19-21] *not in [18] • *Adherence* [1-7, 9-16, 18-21] *not in [8, 17] • *Guidelines* [2-8, 10-21] *not in [1, 9] • *Training* [2, 4-11, 13-15, 17-21]* *not in [1, 3, 12, 16] • *Quality of life* [2, 3, 7, 9, 12, 15, 17-19]* *not in [1, 4-6, 8, 10, 11, 13, 14, 16, 20, 21] • *Economy* [4, 7, 10, 11, 14, 18, 19, 21]* *not in [1-3, 5, 6, 8, 9, 12, 13, 15-17, 20]

Continuation of Table 2.3
Comparators • *Control* [2-7, 10, 12-15, 17-19]* *not in [1, 8, 9, 11, 16, 20, 21] • *Intervention* [3, 5-7, 13, 17, 18]* *not in [1, 2, 4, 8-12, 14-16, 19-21] • *Training* [14, 15, 17, 18]* *not in [1-13, 16, 19-21]
Outcomes • *Blood pressure* [1-21] • *Adherence* [1-7, 9-16, 18-21]* *not in [8, 17] • *Pharmacotherapy* [1, 2, 4-8, 10-15, 17-21]* *not in [3, 9, 16] • *Non-pharmacological treatment – lifestyle modification* [1-8, 10-12, 14, 16, 19]* *not in [9, 13, 15, 17, 18, 20, 21] • *Satisfaction with service* [3, 4, 7, 10, 11, 14, 17-20]* *not in [1, 2, 5, 6, 8, 9, 12, 13, 15, 16, 21] • *Cardiovascular risk* [1, 4, 7, 8, 11-14, 18]* *not in [2, 3, 5, 6, 9, 10, 15-17, 19-21] • *Quality of life* [2, 3, 7, 9, 12, 15, 17-19]* *not in [1, 4. 5, 6, 8, 10, 11, 13, 14, 16, 20, 21] • *Perceptions* [3, 4, 7, 11, 14, 18, 19]* *not in [1, 2, 5, 6, 8, 9, 10, 12, 13, 15-17, 20, 21] • *Economy* [4, 7, 14, 18, 19]* *not in [1-3, 5, 6, 8-13, 15-17, 20, 21] • *Knowledge* [3, 10, 11, 16, 17]* *not in [1, 2, 4-9, 12-15, 18-21] • *Health resource usage* [7, 21]* *not in [1-6, 8-20]
Study design • *Baseline characteristics* [1-21] • *Data collection* [1-21] • *Recruitment/screening* [1-21] • *Staff* [1-21] • *Study duration* [1-21] • *Barriers* [1, 2, 4, 6-11, 13-15, 18-21]* *not in [3, 5, 12, 16, 17] • *Ethics [3-9, 13-21]* * *not in [1, 2, 10-12] • *Bias* [2-7, 9, 11, 13-15, 18, 19, 21]* *not in [1, 8, 10, 12, 16, 17, 20] • *Funding* [1, 2, 5, 8, 11, 13, 15-21]* *not in [3, 4, 6, 7, 9, 10, 12, 14] • *Blinding* [3-6, 14, 18, 19, 21]* *not in [1, 2, 7-13, 15-17, 20] • *Intention-to-treat* [5, 13, 17-19, 21]* *not in [1-4, 6-12, 14-16, 20]

Numbered references in Table 2.3: **1.** Aguiar *et al.*, 2012; **2.** Aguwa *et al*., 2008; **3.** Carvalho and Nagavi, 2007; **4.** Chabot *et al*., 2003; **5.** Fikri-Benbrahim *et al*., 2012; **6.** Garção and Cabrita, 2002; **7.** Hughes *et al*., 2002; **8.** Júnior *et al*., 2008; **9.** Lai, 2007; **10.** McKenney *et al*., 1973: **11.** Nemerovski *et al*., 2013; **12.** Octavia and Florica, 2011; **13.** Planas, *et al*., 2009; **14.** Pojskic *et al*., 2014; **15.** Robinson *et al*., 2010; **16.** Sharma *et al*., 2014; **17.** Skowron *et al*., 2011; **18.** Stewart *et al*., 2014; **19.** Svarstad *et al*., 2013; **20.** Taylor *et al*., 2003; **21.** Zillich, *et al*., 2005

2.6.5 Risk of bias within studies

Risk of bias within the included studies with the dimension of bias (entry), the assessment of risk of bias (judgement) and the evidence for the assessment (support for judgement) with quotes and comments is presented in Table 5.1 in Appendix 5.2.

Risk of bias across studies is shown in Table 2.4. The overall risk among most of the studies involves high or unclear risk.

Table 2.4. Risk of bias across studies: an overall risk of bias assessment for each included study based on the risk of bias judgements made within the individual domains of The Cochrane Collaboration's tool for assessing risk of bias (see Table 5.1 in Appendix 5.2). Author, year in italics=study not meeting EPOC study design criteria.

Author, year	Overall risk
McKenney *et al.*, 1973	Unclear risk
Hughes *et al.*, 2002	Unclear risk
Garção and Cabrita., 2002	Unclear risk
Taylor et al., 2003	High risk
Chabot *et al.*, 2003	Unclear risk
Zillich et al., 2005	High risk
Carvalho and Nagavi, 2007	Unclear risk
Lai, 2007	High risk
Aguwa et al., 2008	High risk
Júnior et al., 2008	Unclear risk
Planas *et al.*, 2009	Unclear risk
Robinson *et al.*, 2010	High risk
Octavia and Florica, 2011	Unclear risk
Skowron *et al.*, 2011	Unclear risk
Aguiar et al., 2012	High risk
Fikri-Benbrahim *et al.*, 2012	High risk
Nemerovski et al., 2013	Unclear risk
Svarstad *et al.*, 2013	Low risk
Pojskic *et al.*, 2014 (Pojskic, 2014a)	High risk
Stewart *et al.*, 2014	Low risk
Sharma et al., 2014	High risk

2.6.7 Publication bias

A comparison of funnel plots based on effect estimates odds ratio and mean difference respectively with and without grey literature is demonstrated in this section.

2.6.7.1 Odds ratio: Systolic blood pressure (SBP) and diastolic blood pressure (DBP) as a combined outcome

2.6.7.1.1 Visual interpretation of the funnel plot including grey literature

Figure 2.7 displays a funnel plot based on odds ratio as an effect estimate of SBP and DBP as a combined outcome. Grey literature has been included the funnel plot. Visual inspection is suggestive of a funnel, but there is also clear asymmetry on the right-hand side. Consequently, the visual interpretation indicates publication bias is less likely to be present.

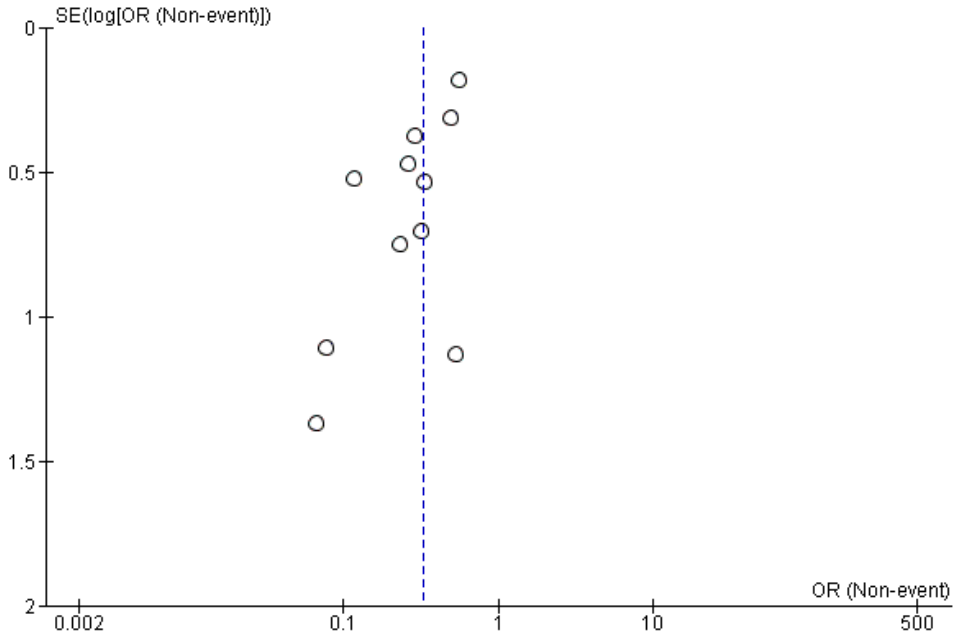


Figure 2.7. Funnel plot based on odds ratio as an effect estimate of SBP and DBP as a combined outcome. Grey literature has been included this funnel plot. Visual inspection is suggestive of a funnel, but there is also clear asymmetry on the right-hand side. Thus, this indicates publication bias is less likely to be present.

2.6.7.1.2 Statistical analysis of funnel plot asymmetry

The statistical analysis of funnel plot asymmetry shows a significant result (t=2.82, df=9, p=0.020) indicating asymmetry when grey literature is included the funnel plot.

2.6.7.1.3 Visual interpretation of the funnel plot excluding grey literature

Figure 2.8 demonstrates a funnel plot based on odds ratio as an effect estimate of SBP and DBP as a combined outcome. Grey literature has been excluded the funnel plot. Visual inspection is indicating a funnel, but clearly, there is asymmetry because there are only four studies.

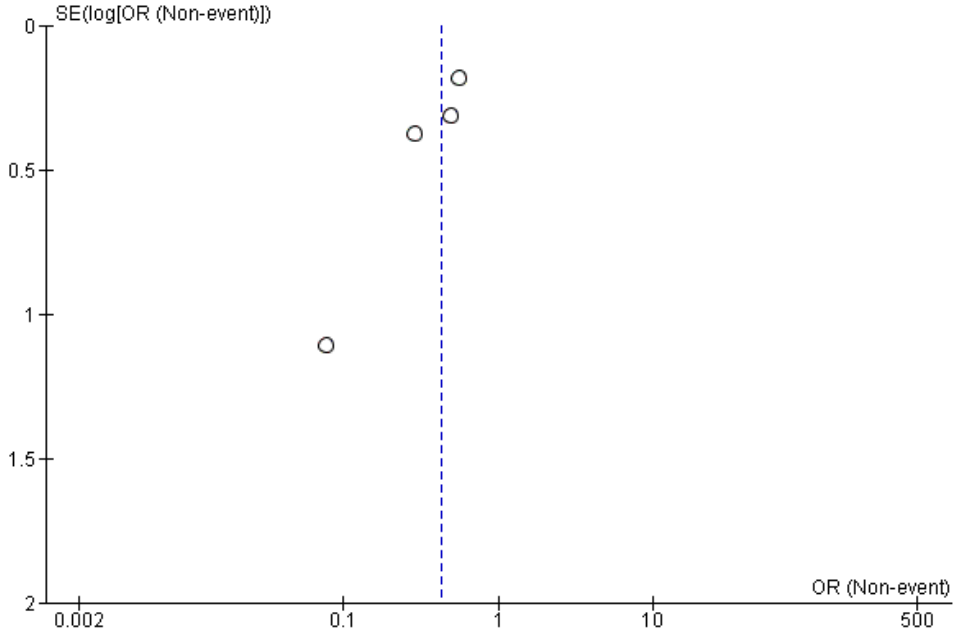


Figure 2.8. Funnel plot based on odds ratio as an effect estimate of SBP and DBP as a combined outcome. Grey literature has been excluded this funnel plot. Visual interpretation is indicating a funnel, but clearly, there is asymmetry because there are only four studies. Excluded grey literature consists of McKenney *et al*., 1973; Garção and Cabrita., 2002; Hughes *et al*., 2002. Low INT; Chabot *et al*., 2003. High income group; Skowron *et al*., 2011; Pojskic *et al*., 2014.

2.6.7.2 Mean difference

2.6.7.2.1 Systolic blood pressure (SBP)

2.6.7.2.1.1 Visual interpretation of the funnel plot including grey literature

Figure 2.9 displays a funnel plot based on mean difference as an effect estimate of SBP. Grey literature has been included the funnel plot. Visual inspection is suggestive of a funnel, but there is also asymmetry. This indicates publication bias is less likely to be present.

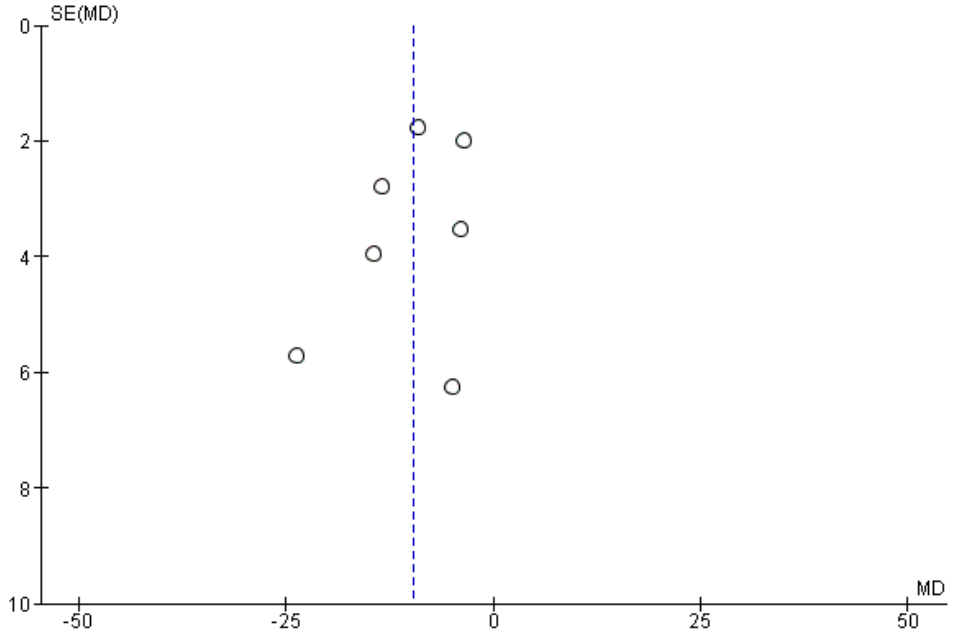


Figure 2.9. Funnel plot based on mean difference as an effect estimate of SBP. Grey literature has been included this funnel plot. There is a suggestion of a funnel, but there is also asymmetry. Consequently, there is an indication of publication bias less likely of being present.

2.6.7.2.1.2 Visual interpretation of the funnel plot excluding grey literature

Figure 2.10 demonstrates a funnel plot based on mean difference as an effect estimate of SBP. Grey literature has been excluded the funnel plot. Visual inspection is indicating a funnel, but clearly, there is asymmetry because there are only three studies.

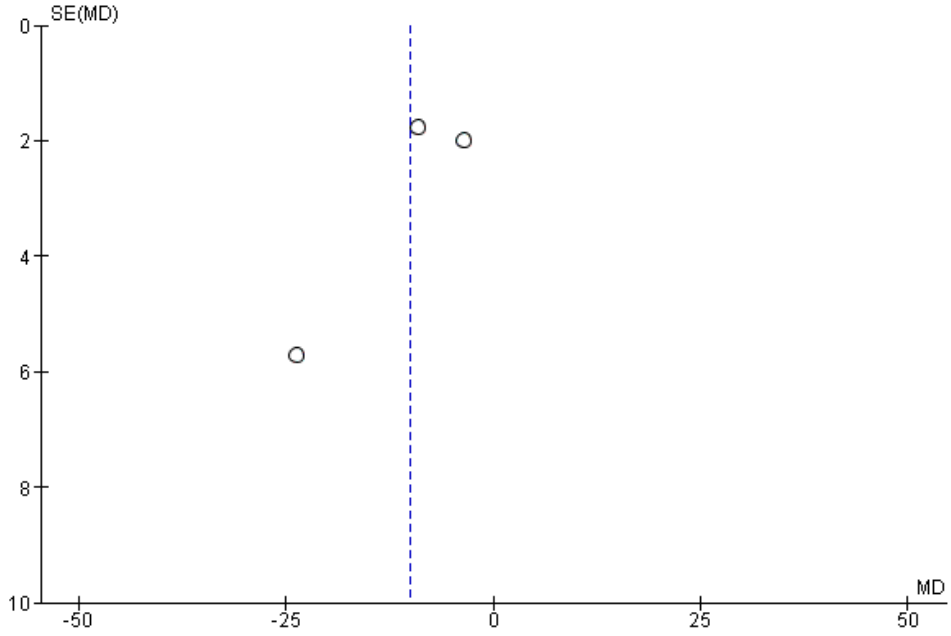


Figure 2.10. Funnel plot based on mean difference as an effect estimate of SBP. Grey literature has been excluded this funnel plot. Visual inspection is indicating a funnel, but clearly, there is asymmetry because there are only three studies. Excluded grey literature consists of Garção and Cabrita., 2002; Hughes *et al*., 2002. High and Low IG; Octavia and Florica, 2011; Skowron *et al*., 2011.

2.6.7.2.2 Diastolic blood pressure (DBP)

2.6.7.2.2.1 Visual interpretation of the funnel plot including grey literature

Figure 2.11 displays a funnel plot based on mean difference as an effect estimate of DBP. Grey literature has been included the funnel plot. Visual inspection is suggestive of funnel plot asymmetry.

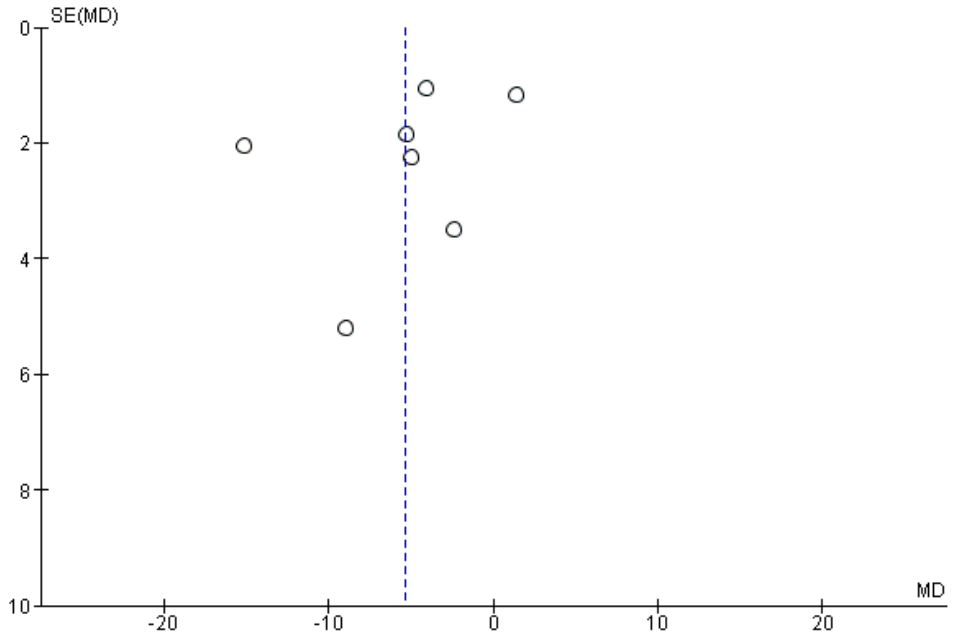


Figure 2.11. Funnel plot based on mean difference as an effect estimate of DBP. Grey literature has been included this funnel plot. Visual inspection is suggestive of funnel plot asymmetry.

2.6.7.2.2.2 Visual interpretation of the funnel plot excluding grey literature

Figure 2.12. demonstrates a funnel plot based on mean difference as an effect estimate of DBP. Grey literature has been excluded the funnel plot. Visual inspection is suggestive of funnel plot asymmetry when excluding grey literature.

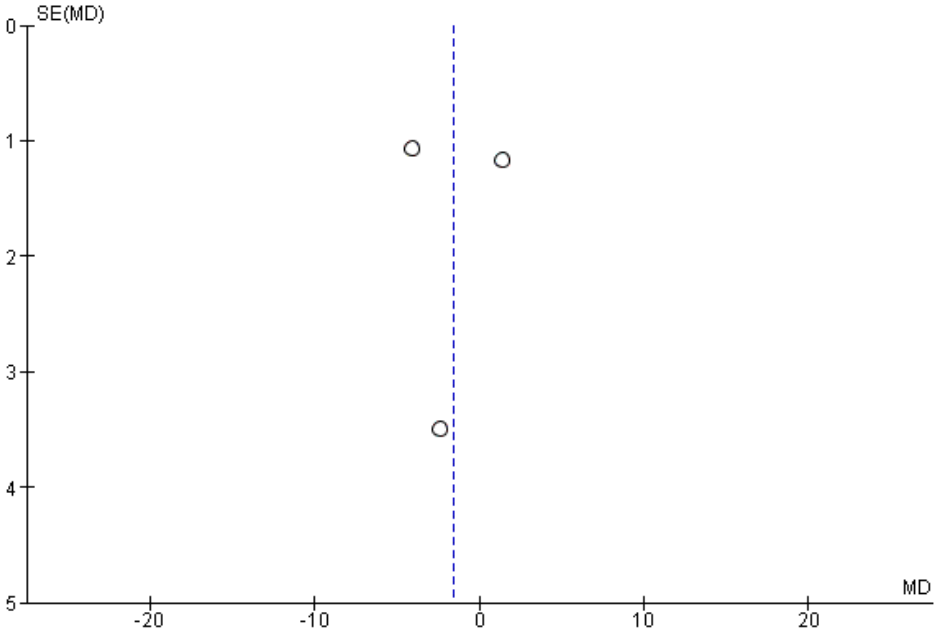


Figure 2.12. Funnel plot based on mean difference as an effect estimate of DBP. Grey literature has been excluded this funnel plot. Visual inspection is suggestive of funnel plot asymmetry. Excluded grey literature consists of Garção and Cabrita., 2002; Hughes *et al*., 2002. High and Low IG; Octavia and Florica, 2011; Skowron *et al*., 2011.

2.7 Discussion

This systematic review came about recognizing the need to identify and evaluate mixed-method studies on community pharmacist-led interventions within a community pharmacy setting aimed at blood pressure optimisation in patients undergoing oral antihypertensive medication therapy. The formulation of a structured question is a recommended pathway to conduct a systematic review (Khan *et al*., 2011). In contrast to what is somewhat considered a norm in the undertaking of systematic reviews, the present systematic review employed a mixed-method approach aiming to capture the evidence base in its entirety regardless of study design. Hadi and co-workers (2014) pinpoint that mixed-methods research would have a positive impact on pharmacy practice research (Hadi *et al*., 2014). To date and to what is known, this is the first comprehensive systematic review to have been undertaken within the current research domain using such an approach. Hence, this carries a risk in that there are studies containing a high risk of bias which could undermine the quality of the systematic review. Despite this, the present systematic review was primarily a scoping exercise constructed to explore the availability of evidence within the research domain.

2.7.1 Study selection process

Five different electronic biomedical databases were selected in which there was a varying quantity of search outputs, despite carefully selected MESH search term combinations tailored in accordance to each database. Interestingly, the grey literature provided a larger amount of records for screening compared to electronic databases.

Overall, the systematic review generated 21 studies for inclusion, a number which is moderate considering the time-scale since 1973. This could possibly reflect the change the pharmacist profession has undergone from preparation and dispensing of medications to working with patients in a pharmaceutical care perspective (Van Wijk *et al*., 2005).

2.7.2 Summary of the evidence

2.7.2.1 Participants

First and foremost, the patient screening process being the initial phase of the study is vital to recruit patients with the characteristics of interest. As studies have been performed on different ethnic groups, patients with differing socio-economic status, patients with comorbidity and a wide age span among patients of 50 or 60 years, the question remaining is how to screen patients in a standardized way to provide an individually tailored approach to the community pharmacy service. Thus, one approach could involve the creation of an algorithm in the context of patient characteristics, screening and recruitment process to establish which subsets of patients should be recruited in the light of a likely benefit from community-pharmacist-led intervention/s.

Secondly, across the time-scale from the older studies to the modern ones, there appears to be a trend towards inclusion of a larger number of patients in studies. Likewise, there is a varying number of patients completing the studies which is a known hurdle in clinical trials - to retain patients throughout the study. Indeed, this infers again that attention should be paid toward the screening process of patients at recruitment, to maximize the possibility of keeping the patients until study completion. A viable complementary approach to self-referred patients would be physician referral of patients to the community pharmacy service.

Thirdly, the finding that the pharmacotherapy sub-theme was not mentioned in any included studies inhibits knowledge of the pharmacotherapeutic factors contributing to blood pressure control, e.g. drug class, monotherapy, polypharmacy, duration of antihypertensive medication therapy. Indeed, apart from the pharmacotherapeutic data available at the community pharmacy, after obtaining the patient's consent, the community pharmacist/researcher should seek assistance from the physician to confirm relevant patient characteristics and pharmacotherapeutic data enabling the delivery of patient-centred and tailored intervention/s. The researcher/clinician approaching the patient during the screening/recruitment process will undoubtedly raise an awareness in the patient and may act as an intervention itself which potentially could be a Hawthorn effect. This is recognized in an Australian study by Bajorek and co-workers (2016) as BP measurement was performed as part of the patient screening process. The screening process could even have restricted patient recruitment (Bajorek *et al*., 2016). However, it is worthwhile to note that whilst this could have an impact on study results, it may be difficult in certain situations to avoid the BP measurement step of the patient screening process. What is more important is there being a setup in studies to evaluate potential covariates.

2.7.2.2 Interventions

To begin, the interventions among the studies consisted of referral to/contact with a physician, informational materials**,** counselling, BP measurement, reminders and diary keeping. In fact, the interventions appear to be applied generally to the hypertensive population, without acknowledgment of the highly individual attitude to drug-based therapies and which intervention is responsible for the blood pressure outcome. Among the studies in the present

systematic review, there is a complexity of interventions. In general, this agrees with a conclusion drawn in the year 2014 Cochrane review by Nieuwlaat and co-workers. Interventions to improve adherence to medications in a set of different medical conditions was investigated by an analysis of RCTs. The authors mention the steps of improving adherence to chronic medical conditions is currently complex (Nieuwlaat *et al*., 2014). In addition, the results from the meta-analysis of the current systematic review show that interventions do not produce any or only a minor positive effect. Thus, based on the evidence in the present systematic review, there is a need for standardization of interventions.

A systematic review was conducted by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) on interventions aiming at improving antihypertensive medication adherence in patients with essential hypertension. Publications ranging from the year 1979 to 2009 with various interventions and modes of delivering the interventions, as well as in various settings were included in their review. The authors bring forth several noteworthy limitations in studies aimed at improving antihypertensive medication adherence: interventions not being based on the determinants of non-adherence, not a proper description of the interventions, lack of consistency in adherence measurement, absence of studies relating antihypertensive medication adherence to blood pressure control, improper reporting of blood pressure and adherence. However, the authors mention that interventions which target medication knowledge among patients are likely to be clinically meaningful with regards to improving antihypertensive medication adherence. Nevertheless, it is unclear if this would result in blood pressure control. The authors also discuss there were some studies which included many interventions. In this situation, it is not clear whether a combination of

interventions or a single intervention leads to the positive outcome (Gwadry-Sridhar *et al*., 2013).

A Cochrane review by Schroeder and colleagues from 2004 aimed to assess the extent of different interventions in improving adherence to antihypertensive medications. The authors reviewed 38 RCTs including 58 different interventions in adult patients with hypertension in ambulatory care settings. They concluded that simplifying the dosing regimen is recommended as the primary step to improve adherence, although its effect on blood pressure outcome was not investigated. By contrast to the review by Gwadry-Sridhar and co-workers in 2013, educating the patient is not a promising strategy to optimising adherence. However, it is noted that because of the poor quality of included studies, their results should be interpreted with caution (Schroeder *et al*., 2004).

A Cochrane review from 2010 by Glynn and co-workers studied the effectiveness of interventions aimed at improving blood pressure control in hypertensive patients in ambulatory settings. Again, educational interventions alone were not successful, this time regarding achieving blood pressure control (Glynn *et al*., 2010).

Furthermore, the outcome of the thematic analysis shows that an appropriate level of community pharmacist competence is required when delivering interventions to hypertensive patients. It is vital that preparation of community pharmacists prior to delivering interventions is properly defined. Bajorek and co-workers (2015) evaluated a training programme preparing 17 community pharmacists for hypertension management. The study showed that simulated and inter-professional training using different methods was effective. However, training could be improved (Bajorek *et al*., 2015).

2.7.2.3 Comparators

From the time of the first study included in this systematic review, (1973) onward, the RCT was progressively introduced into community pharmacy research which included intervention and control groups. This type of comparison now dominates the evidence base. On a positive note, this brings about good study quality since RCT's will provide the lowest risk of bias. Another approach being taken is through a partition of intervention and control groups into subgroups when the groups possess variables of interest to be compared. Thus, this is a positive move toward individualized approach since BP outcomes may vary between different subsets of patients. By contrast, there are some studies which use a before-and-after study comparison which may increase the risk of bias, ultimately resulting in poor study quality (Khan *et al*., 2011; Wiffen *et al*., 2012).

2.7.2.4 Outcomes

2.7.2.4.1 Blood pressure (BP) outcome

First, the blood pressure outcome among the studies is highly variable reflecting the differences in study design. Indeed, the present meta-analysis shows conflicting outcomes depending on the mode of calculating effect estimates; either there is no effect or an intimation of a positive effect on blood pressure. This makes it valuable to bear in mind that an elongated positioning of the studies is obtained when plotting mean differences in comparison to only plotting odds ratios. Despite this, the contribution of some patients may be experiencing a mild degree of a white-coat effect could be making the blood pressure values not as optimal as they could be. Explanations to the outcome of the meta-analysis can be traced back to two possible factors: a) many of the pharmacy interventions relating to usage of

medicines are simplistic and as such do not work bearing in mind that some manoeuvres which community pharmacists take with a good intention could make matters worse and/or b) the quality of some studies is low, ultimately resulting in poor results. It is not thought that the identification of extra studies since the meta-analysis was performed in the present systematic review will change the direction of the meta-analytic outcome since the BP results in these extra studies are highly variable.

Secondly, it would appear that previous research is based on the premise that intervention/s lead to positive outcome/s. A systematic review by Cheema and co-workers (2014) reviewed community pharmacist-led interventions in blood pressure control, concluding that such actions provide a clinically important contribution to hypertension management (Cheema *et al*., 2014). The authors' approach of only including studies with randomized controlled design restricts the acquisition of the full evidence base within the research domain of community pharmacist-led interventions in optimizing blood pressure making it difficult to ensure comparability of BP outcome with the present systematic review.

Santschi and co-workers (2014) performed a meta-analysis by joining two previous systematic reviews. The analysis consisted of 39 RCTs with 14224 patients. The authors concluded that pharmacist interventions improved the management of BP. However, there was a spectrum of the efficacy of the interventions ranging from no effect to a large effect on BP. In addition, the analysis also included studies with study settings other than community pharmacy and in collaboration with other members of the healthcare team. Moreover, there was a substantial heterogeneity in BP between studies (Santschi *et al*., 2014).

Morgado and co-workers (2011) conducted a literature review and meta-analysis to evaluate the impact of pharmacist-led interventions on antihypertensive medication adherence and

blood pressure reduction. The review included 15 studies with different study designs including 3280 patients in total. Again, this review also included studies performed outside of a community pharmacy setting. Interventions which improved antihypertensive medication adherence resulted in significantly lowered BP. Furthermore, the authors noted that most interventions resulting in improved adherence were complex. The meta-analysis was performed on 8 studies including 2619 patients showing significant improvements in SBP, DBP and achieving BP control (Morgado *et al*., 2011).

In fact, the present systematic review shows there currently is no proper evidence to support the premise in earlier research of intervention/s leading to positive outcome/s. Therefore, interventions may have no impact or even a negative impact.

Thirdly, study settings other than community pharmacy is recurrent. This is also the case in the systematic review by Stewart and colleagues (2015) in which there were studies which had a focus on cardiovascular disease programs especially with relevance to antihypertensive medication adherence or persistence (Stewart *et al*., 2015). The method and location of BP measurement should be precise as this may have an impact on varying BP results, i.e. when BP is measured by a community pharmacist, another member of health care staff or the patient alone by home blood pressure measurement.

2.7.2.4.2 Other outcome measures

The evidence base points to an array of outcome measures. Thus, in some circumstances measuring several variables causes confusion into which target outcomes researchers intend to explore and what implications these outcomes would have on community pharmacy practice. The inclusion of non-pharmacologic treatment as an intervention should not be

underrepresented as this is a complement to the pharmacotherapeutic approach. However, researchers should instead be rigid in the choice of outcome measures with relevance to the development of a community pharmacy-based service. Previous systematic reviews, in general, support the evaluation of the economic aspect/cost-effectiveness of interventions (Glynn *et al*., 2010; Schroeder *et al*., 2004) Moreover, the evidence base lacks the assessment of attitudes to antihypertensive medication adherence as attitudes form an integral part of determining adherence, thus resulting in BP control. Further investigation is warranted into the impact of the community pharmacy interventions on quality of life of hypertensive patients. Future studies should ensure use of validated data collection tools for the purposes of obtaining reliable data.

2.7.2.5 Study design

The measures of consistency indicate the existence of heterogeneity between the included studies. Indeed, a large portion of the studies in the present systematic review are not well-designed. Study durations between 3-15 months and a varying frequency of study visits to the community pharmacy do not provide a clear picture of what is a standardized period of investigation or frequency of community pharmacy visits. Information on barriers surrounding current designs is lacking. Barriers should be highlighted to facilitate the development of improved study designs. Consequently, current designs are overly complicated and variable requiring standardization.

2.7.3 Risk of bias

There are studies in the present systematic review which are clearly at high risk of bias of which we cannot base practice and policy on. However, there are studies which are assessed to be unclear in risk: this type of evidence makes it difficult to plan policy since there is no evidence available to support the judgement. This renders studies in the present systematic review with unclear risk of bias to be suspect.

In addition, the thematic analysis has provided an indication of control groups not solely receiving usual care. The methodological approach of interventions being delivered to a control group during an ongoing study or towards study completion could possibly result in the advent of bias.

Moreover, the process of blinding patients in research on systems involving pharmaceutical interventions is not always achievable (Machado *et al*., 2007; Morgado *et al*., 2011; Mossialos *et al*., 2013). Thus, non-blinding of patients increases the likelihood of bias in studies. It can be inferred that standardising the study design will inherently reduce bias. In general, this proposition is supported by Nieuwlaat and co-workers, 2014 who indicated bias can be reduced by applying appropriate study designs (Nieuwlaat *et al*., 2014).

2.7.3.1 The Cochrane Collaboration's tool for assessing risk of bias versus other quality assessment tools

There exist various tools to assess bias in studies: older tools usually provide a summary score of bias for the study examined. The summary score method is simple in its approach. However, there have been raised issues concerning the summary score approach since it has been found to be inconsistent. Furthermore, such inconsistency causes an issue when bias is

being assessed in non-RCT studies. As such, The Cochrane Collaboration's tool for assessing risk of bias instead utilises a domain-specific approach to bias which includes a degree of flexibility when assessing the risk of bias without the requirement of providing a number to bias (Katikireddi *et al*., 2015).

The Cochrane Collaboration's tool for assessing risk of bias was employed in the present systematic review. Although this tool was constructed and validated for use in RCTs, the present systematic review did not restrict its use of this tool solely to RCTs. Being aware that there is an immediate high risk of bias in a non-RCT when using the tool, it really provides no reason not to be able to extend assessment for application into other study designs, even though there exist specific tools to assess bias in non-RCT studies such as the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I tool) (Sterne *et al*., 2016). Using different types of risk of bias assessment tools in the same systematic review would possibly provide non-comparable assessments between studies in the mixed-methods approach. Consequently, The Cochrane Collaboration Tool for risk of bias assessment was incorporated into the mixed-methods design.

2.7.3.2 Publication bias and funnel plot asymmetry

Visual interpretation of the funnel plots shows the presence of funnels and/or asymmetry in the funnels. However, the statistical test for assessing funnel plot asymmetry indicates asymmetry. It is known that visual interpretation of funnel plots is subjective. Hence, there is a possibility that there are reasons other than publication bias which could possibly explain the contrasting outcomes of the visual interpretation of the funnel plots and the statistical analysis of funnel plot asymmetry. In the literature, there have been suggested potential

reasons such as poor methodological quality, heterogeneity between studies and chance itself (Higgins and Green, 2011). Nevertheless, the importance of grey literature screening when performing a systematic review cannot be underestimated. The screening facilitates the retrieval of as many studies as possible which may reduce the risk of publication bias.

2.7.4 Limitations

The database searches retrieved certain outputs which were ostensibly very interesting but unfortunately did not meet the inclusion criteria for the systematic review. An example of this is seen in the paper by Blenkinsopp and co-workers which did not report any clinical values to substantiate adherence (Blenkinsopp *et al*., 2000). This is particularly disappointing with a condition such as hypertension, where there is a very clear relationship between the clinical markers, i.e. blood pressure and adherence itself. Amariles and co-workers in 2012 performed a study which included a community pharmacy-based pharmaceutical care process referred to as the "Dader Method" (Amariles *et al*., 2012). Although an interesting process, their study included a high-risk cardiovascular population not being representative for the present systematic review.

Some studies did not report data or consisted of a study design which did not make it possible to include the studies in the effect estimates calculations. Therefore, the present meta-analysis was narrowed to be performed on 13 out of 21 studies. When contact information was available for the author/s, attempts were made to contact the author/s to obtain supporting data to enable the calculation of the effect estimate, though this approach was not always successful. Because of this, it is of importance that when possible, data that is required to enable the calculation of effect estimates are reported. In some included studies, proportions

of patients were not separately reported for SBP and DBP. It might be argued that treating the outcomes SBP and DBP separately might be more robust, but since there was not much data, it was better to calculate something from the available data. The expectation is that SBP and DBP would increase or decrease in a linked manner. Rare exceptions to this aspect exist. However, the exceptions were unlikely to be met.

The analysis of funnel plot asymmetry could have been more robust: there was not sufficient data to create funnel plots for odds ratio of SBP and DBP respectively. Criteria for the statistical analysis of funnel plot asymmetry for continuous outcomes did not allow analysis of the funnel plot based on mean difference as an effect estimate of SBP or DBP.

Since the present study employed a mixed-methods approach, targeting the EPOC study design criteria in a pragmatic way was not always applicable to certain studies. There exists no structure such as PRISMA for reporting of research utilizing a mixed-methods approach (Hadi *et al*., 2014). However, the studies in the present systematic review which did not fully adhere to the EPOC study design criteria and/or PRISMA protocol have been indicated in the results section and it is considered that this limitation will not have an impact on the quantitative and qualitative outputs of this systematic review.

2.8 Conclusion

In conclusion, the evidence-base is not consistent on community pharmacist-led interventions which optimise blood pressure in patients undergoing oral antihypertensive medication therapy. A clear strategy to target patients who will likely have a benefit from the community pharmacy service is required. This could be facilitated by physicians referring patients to the community pharmacy as a complement to patient self-referral. A collaboration between the

community pharmacist and physician could contribute to confirming relevant clinical parameters in the patient.

Generic interventions for optimizing BP are being applied to the hypertensive patient population. In addition, together with previous systematic reviews aimed at improving blood pressure in hypertensive patients, it is clear from the evidence base of the present systematic review that there exists a multiplicity of interventions which are overly complex and do not indicate the effectiveness of different interventions. Blood pressure outcomes of the interventions do not point to a positive outcome. It is possible that certain interventions could result in no effect on BP or possibly even have a negative impact on BP. In addition, recommendations for interventions that are most appropriate under different circumstances is needed in future studies. Thus, ensuring a patient-centred approach by individually tailored interventions would pave the way for the provision of high-quality studies.

The existence of an array of study outcomes made it difficult to focus on what researchers wanted to achieve to develop an effective community pharmacy-based service. New well-designed studies providing evidence on outcomes at both community pharmacy and the patient level is required. Also needed is a standardized methodology with randomized controlled study design together with the standardisation of interventions. These measures would increase the likelihood of minimizing bias making it possible to form a solid foundation on which to build practice and policy.

3 A pilot study evaluating the impact of community pharmacist-led interventions to optimize antihypertensive medicines adherence

The findings from the general literature and systematic review were refined into the experimental methodological approach in this pilot study to evaluate the adherence subgroups.

3.1 Introduction

3.1.1 Pharmaceutical care service

The pharmacy profession has changed since the introduction of clinical pharmacy in the 1980s. The view has become more toward safe, effective, rational and individualizing therapy to the patient. Evolving technology has also resulted in a change in community pharmacy with examples such as mail-order and internet (Allen Jr *et al*., 2012). As the science of medication emerges and becomes more complex, an adequate number of community pharmacists with a specific level of knowledge is needed. The pharmacist is the logical choice to provide pharmaceutical care (Cipolle *et al*., 2012, Puspitasari *et al*., 2016). The human lifespan continues to increase resulting in polypharmacy as chronic illnesses evolve. Likewise, the number of prescribers is increasing. Thus, it is not foreign to understand this complexity leading to drug-related problems. At the patient level, the occurrence of drug-related problems and non-adherence reflect that medications are not properly managed. Here medication management has an essential role (Cipolle *et al*., 2012).

The concept of medication management is seen from two perspectives: the prescription-centred approach or a patient-centred approach. The latter is separated from the dispensing

process (Cipolle *et al.*, 2012). Disease state management forming the patient-centred approach looks at improving adherence to treatment for the individual patient. This encompasses planning in collaboration with patients and other healthcare staff, communication with the physician and documentation of the management of disease (Allen Jr *et al*., 2012). At the same time, the shift from the dispensing process and supplication of other pharmacy products to offering pharmaceutical care services presents its own challenges (Puspitasari *et al*., 2016). An attempt by the WHO has been made to provide guidance on investigations relating to a pharmacist-led, community pharmacy-based hypertension management program. The EuroPharm Forum and WHO CINDI Programme in 2005 produced a guidance document on pharmacy-based hypertension management. The reason is to increase blood pressure control in the community by including pharmacists to prevent, detect and manage hypertension. Continuous documentation of the activities and evaluation of the project are included (WHO, 2005). Despite this, the guideline does not recognize that patients have individual attitudes to therapy. Consequently, the outcome may not be the same in patients who receive the generic intervention.

3.1.2 Study design

The before-and-after study design is commonly used in pharmacy practice research. Data collection is performed on variable/s at baseline and at follow-up after the intervention. Following this, the before and after data is compared. Despite the study design is simplistic, there is no inclusion of a control group making it difficult to know if the changes are caused by the intervention or if confounding factors are involved. At the same time, the data

collection can be designed to confirm if other factors are involved in producing change (Smith, 2002; Tsuyuki *et al*., 2014).

A feasibility or pilot study provides an investigation on the efficacy and practical aspects of a study before going on to conducting a larger trial. Thus, any issues in the small-scale study can be captured and hopefully rectified before deciding to proceed with a larger study. In pharmacy research, it is common to employ triangulation. This will from different angles relate the study aims and objectives or validity of data to the combined use of various paths, methods and/or data within the same research investigation. Each single method used in triangulation will have its own pros and cons (Smith, 2002; Smith, 2010).

3.2 Methods

3.2.1 Research proposal

The original research proposal for this pilot study is found in Appendix 5.4.

3.2.2 Ethical approval

Ethical approval for this study was obtained from Regional Ethical Review Board in Uppsala, case number 2013/017 (Appendix 5.5).

3.2.3 Study design

This pilot study was an open-label, prospective, longitudinal before-and-after study of six-month duration with patients being their own control conducted in a single community pharmacy in Uppsala, Sweden.

3.2.4 Patient recruitment

Patients aged 18 and above, who had been prescribed at least one antihypertensive agent or fixed combination of antihypertensive medications, for at least 3 months were recruited. All participants could understand, write and speak Swedish. Medication refills were completed at the study pharmacy throughout the duration of the study. Patients who were not self-administering medicines or those participating in other clinical studies were excluded from the present investigation.

Patients presenting with prescriptions for antihypertensive agents were approached sequentially and were provided with the study patient information leaflet (Appendix 5.5) and invited to participate. They were given at least 24 hours to consider participation. If they expressed interest to participate, an appointment with the study pharmacist at the community pharmacy was done during which opportunity to ask questions about the study was given and they were asked to complete and sign a consent form (Appendix 5.6). This appointment also served as the baseline visit.

On entry into the study, each participant was assigned an individual three-digit participant code to anonymize data. Patient information was stored electronically protected by TrueCrypt data encryption technology.

3.2.5 Study visits

All study visits were performed in the community pharmacy with the study pharmacist.

3.2.5.1 Visit 0 (Baseline visit)

At the 40-minute baseline visit in the community pharmacy, participants completed an assessment of attitudes to antihypertensive medication adherence. This was performed through a triangulated approach using self-reported Morisky Medication Adherence Scale (8-item MMAS - in Swedish translation obtained from the original author), Medication Adherence Report Scale (MARS), and Belief about Medicines Questionnaire (BMQ). The latter 2 questionnaires were in Swedish translation with both forward and back translation approved by its original author (Holt *et al*., 2012; Horne *et al*., 1999; Krousel-Wood *et al*., 2009; Lehane and McCarthy, 2007; Mahler *et al*., 2010; Morisky *et al*., 2008; Mårdby *et al*., 2007; Ramanath *et al*., 2012).

Seated pulse, systolic and diastolic blood pressure measurements were made following 5 minutes' rest (Mancia *et al*., 2007; O'Brien *et al*., 2005; The British Hypertension Society, 2012). Measurements were made using a clinically validated electronic blood pressure monitor (model 705 IT OMRON HEALTHCARE Co., Ltd. Kyoto, Japan) and 3 readings were made to check for conformity (The British Hypertension Society, 2012; The British Hypertension Society, 2016). It is considered the patient was most relaxed during the last repeat blood pressure measurement. The participant was informed about the results from the blood pressure and pulse measurement.

3.2.5.2 Visit 1 (Interventions) – 3-months from baseline

3.2.5.2.1 Adherence screening questionnaire scoring

The scale scoring for the questionnaires was performed in accordance with instructions from the original authors. Low adherence on the 8-item MMAS was considered as a scale score of

<6, medium adherence 6 to <8, and high adherence at the maximum 8-item MMAS score of 8. Ranges of the adherence scale score and adjusted mean score in the MARS questionnaire were between 5-25 and 1-5 respectively. For the BMQ, each of the four subscales could have a scale score range of 1-5.

Participants were allocated into one of four adherence groups: adherent (A), intentional non-adherent rational (IR), intentional non-adherent irrational (II) and unintentional non-adherent (U). However, as the categorization of patients progressed, it became apparent that a small number of patients could be allocated to two adherence subgroups simultaneously.

3.2.5.2.2 The adherence subgroup categorization process

Patients were assigned to the A subgroup when maximum adherence scores were obtained on both the 8-item MMAS and MARS. Both the MARS and 8-item MMAS consist of questions dealing with intentional and unintentional non-adherence. Moreover, these questions can be categorized from the perspective of rationality or irrationality. Figures 3.1 to 3.3. set out a schematic illustration on how the questionnaires used during the adherence screening enabled adherence subgroup categorization.

Suspicions of non-adherence were always considered when the scores on the 8-item MMAS and MARS were below maximum. In these circumstances, the study pharmacist reviewed questionnaire responses to identify where the patient had provided answers that reduced the adherence score. These questions were then categorized as intentional or unintentional non-adherence. The set thresholds in questionnaire scores for the adherence subgroup categorization process were based on intuition. Consequently, the occurrence of the

intentional versus unintentional non-adherence among these questions determined if the patient was intentional or unintentional non-adherent.

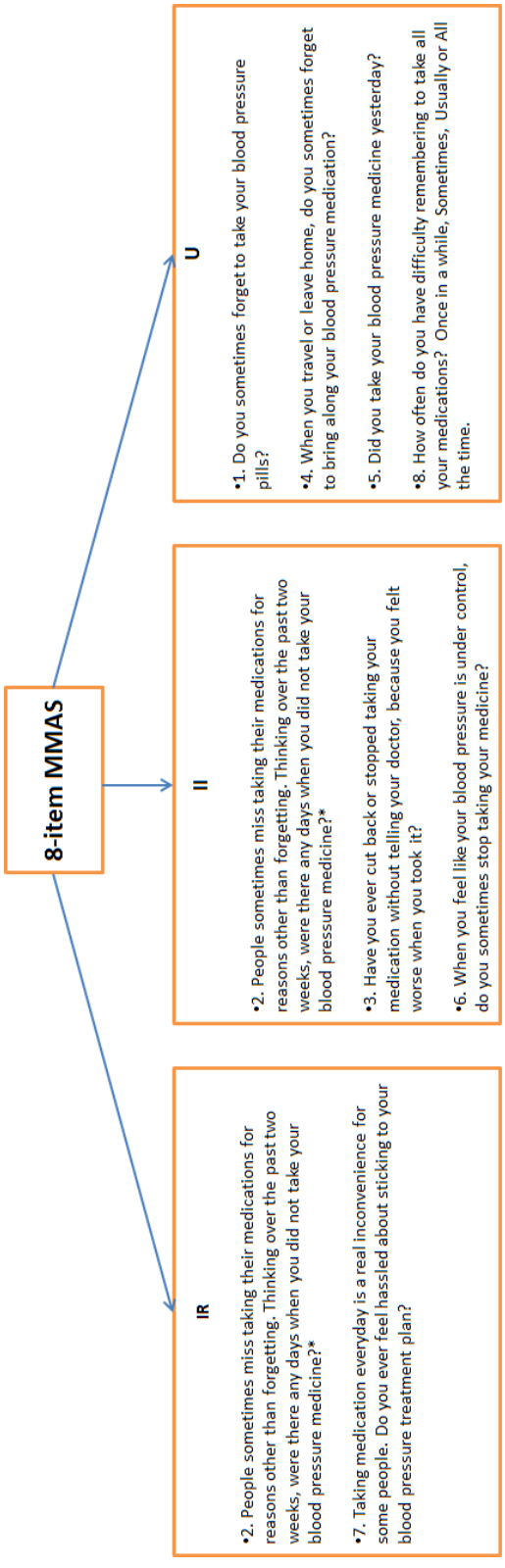


Figure 3.1. Categorization of the 8-item MMAS responses into sub-types of adherence. Number codes set before the questions indicate the numbering of the question in the actual 8-item MMAS questionnaire. The categorization follows into intentional non-adherent rational (IR), intentional non-adherent irrational (II) or unintentional non-adherent (U) adherence sub-types based on the responses the patient has provided in the questionnaire. Use of the ©MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E. Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772.

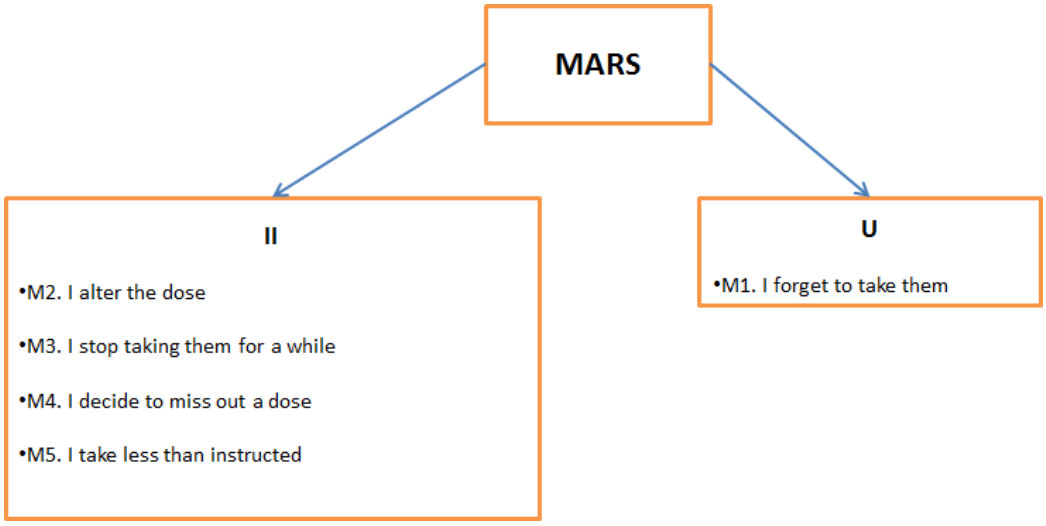


Figure 3.2. Categorization of MARS responses into sub-types of adherence. Codes before each statement indicate the numbering of the statement in the MARS questionnaire. The categorization into intentional non-adherent irrational (II) or unintentional non-adherent (U) adherence sub-types was based on the responses the patient provided in the questionnaire.

For example, the patient may have responded that they had forgotten to take their blood pressure medication and that taking medication caused the patient to worry. This indicated unintentional non-adherent behavior resulting in allocation to the U subgroup.

The division into rational or irrational was performed after the study pharmacist again looked at each question in MARS and 8-item MMAS to which the patient had provided answers that reduced the adherence score. Each question was noted as either rational or irrational. Thus, the occurrence of rationality versus irrationality questions was a deciding factor into the categorization. In addition, this categorization was further refined by the patient's BMQ responses. This was done by the study pharmacist by examining the individual scale scores and the responses from the necessity, concern, overuse and harm scales (Figure 3.3).

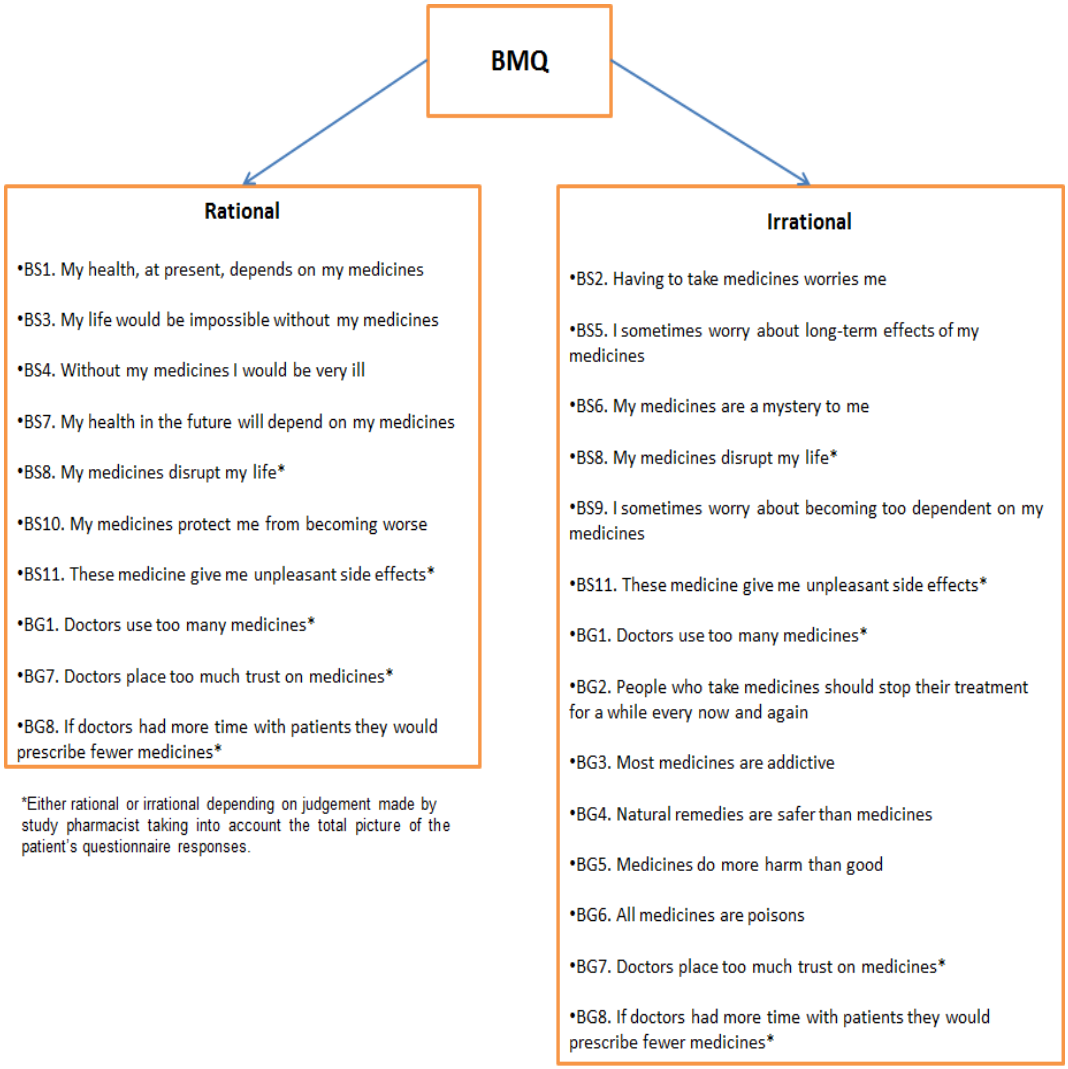


Figure 3.3. Categorization of BMQ responses into rational or irrational. Code before the belief statement indicates the numbering of the statement in the BMQ questionnaire. The categorization into rational or irrational was based on the responses the patient provided in the questionnaire. Some belief responses were regarded as either rational or irrational depending on a judgement made by the study pharmacist when the entire perspective of the patient's questionnaire responses was examined.

The necessity beliefs were all assessed as being rational beliefs. Therefore, the occurrence of a score of 4-5 (Agree – Strongly Agree) on the necessity scale pointed toward rationality. However, if the score was between 3-1 (Uncertain – Strongly Disagree) it was a pointer that the patient was more toward the irrational side. The beliefs which made up the concern,

overuse and harm scales were assessed as being irrational. Hence, a score of 4-5 would indicate irrationality whereas scores 3-1 would point toward rationality.

Thus, we can see that the frequency of intentional versus unintentional non-adherence responses on the 8-item MMAS, MARS and rationality versus irrationality on the 8-item MMAS, MARS and BMQ decided the adherence subgroup categorization.

3.2.5.2.3 Interventions

At a study visit to the study community pharmacy three months from baseline, interventions intuitively designed to optimize adherence were delivered to each patient based on their individual results received on the 8-item MMAS, MARS and BMQ adherence screens. Participants received one of the following interventions provided by the study pharmacist according to their adherence subgroup categorization:

- A: patients visited the community pharmacy to receive a generic patient medication explanation leaflet (I) describing facts on adherence to antihypertensive medication therapy and steps to be taken to improve adherence (Appendix 5.7).

- IR: patients visited the community pharmacy to receive a patient medication explanation leaflet (I).

- II: patients received targeted counselling (C) explaining their condition, medication mechanism, importance and outcomes of adherence (this targeted counselling took place in a separate, calm and quiet room in the pharmacy building). Counselling was

completed in a maximum 30 minutes per patient. The patient was during the counselling session also given a patient medication explanation leaflet (I).

- U: patients received targeted counselling (C). Patients also received a patient medication explanation leaflet (I) and a reminder sheet (R) for use at home in a convenient, prominent position. The reminder sheet was customized to each patient, featuring tick boxes to demonstrate if and when a dose was taken (Appendix 5.8).

3.2.5.2.4 Deviations from the intervention protocol

There were situations necessitating deviation from the intervention protocol in which an alternative intervention or combinations of interventions were used. Such situations arose when questionnaire data was equivocal and indicated to address particular adherence issues.

3.2.5.2.5 Patients requesting BP and pulse measurement at visit 1

At visit 1 there were patients who requested for BP and pulse measurement, despite this not being a part of the study protocol.

3.2.5.3 Visit 2 (Final visit) – 6 months from baseline

At a final 40-minute study visit to the community pharmacy, patients completed 8-item MMAS, MARS and BMQ questionnaires. Blood pressure and pulse measurements were recorded.

3.2.6 Statistics

3.2.6.1 Power calculation

The calculation for the approximate sample sizes that would be required in each adherence subgroup for 80% power at the 5% significance level when comparing various proportions was performed in Microsoft Excel 2010 (Microsoft Corporation, 2010). The chosen success rate was titrated to the number of patients considered to be recruited in the authentic practice situation, i.e. the number of patients required in each adherence subgroup for 80% power at 5% significance level: 70% success, 30% failure for intervention was 25 patients in each adherence subgroup.

3.2.6.2 Statistical software

Microsoft Excel 2010 was used to perform the calculations of the descriptive statistics (Microsoft Corporation, 2010). IBM SPSS Statistics version 22 was used to perform all the other statistical analysis (IBM Corp., 2013).

3.2.6.3 Significance levels

The definitions for the significance levels are: *significant* when $p<0.05$, *very significant* when $p<0.01$ and *highly significant* when $p<0.001$.

3.2.6.4 Descriptive statistics

Descriptive statistics including mean, median, standard deviation (StDev) and standard error (SE) were calculated in Microsoft Excel 2010 (Microsoft Corporation, 2010).

3.2.6.5 The Shapiro-Wilk test of normality and the Wilcoxon-signed rank test

The Shapiro-Wilk test of normality was performed to obtain information on whether the blood pressure and pulse data at visit 0 and visit 2 followed a normal distribution. The blood pressure and pulse data at visit 0 and visit 2 did not fully comply to follow a normal distribution. Because of this, the nonparametric Wilcoxon signed-rank test was performed to analyse the mean changes in systolic BP (SBP), diastolic BP (DBP) and pulse between visit 0 and visit 2. P values of <0.05 were taken as significant for both the Shapiro-Wilk test of normality and the Wilcoxon-signed rank test.

3.2.6.6 Spearman correlation

A Spearman correlation was performed to see if a correlation existed between the scores from the adherence screens (8-item MMAS, MARS and BMQ) and the outcomes SBP, DBP and pulse. This was performed in the overall study population, A and U subgroups. The correlation was not performed for the other subgroups as the patient numbers were too low. Raw data from each of the adherence screens (Morisky, MARS, BMQ) were treated as a continuum ($0 \rightarrow x$) and a Spearman correlation was performed with the outcomes SBP, DBP and pulse (repeat measurements, last repeat measurements) at visit 0 and visit 2 respectively. The statistic was two-tailed with significance levels $p<0.01$ and $p<0.05$.

3.2.6.7 Multivariate analysis of variance (MANOVA) and multivariate analysis of covariance (MANCOVA)

Multivariate analysis of variance (MANOVA) was performed to analyse between-groups differences at visit 0 and visit 2 respectively. For visit 0 the independent variable was the adherence subgroups, whereas for visit 2 the statistic was performed with the adherence subgroups and allocated interventions as independent variables. The mean values of blood pressure and pulse repeats were the dependent variables. Post-hoc analysis with Tukey's HSD and Bonferroni was performed to explore statistically significant univariate outcomes.

To test potential covariates which could influence the blood pressure and pulse results, multivariate analysis of covariance (MANCOVA) was performed to test the relationship between groups and possibly influencing covariates. MANCOVA was performed sequentially for each covariate (SBP based on repeat measurements at visit 0, DBP based on repeat measurements at visit 0, pulse based on repeat measurements at visit 0, medication group, month at visit 0, gender of patient, age of patient at visit 0, patient on monotherapy/polypharmacy) to either establish them or reject them as possibly interfering factors. Post-hoc analysis of univariate outcomes was carried out with Bonferroni adjustment.

The multivariate analysis was separately taken in the light of the following criteria for MANOVA and MANCOVA (Mayers, 2013):

MANOVA

- categorical independent variables
- normally distributed dependent variables
- not too many deviations
- acceptable correlation between dependent variables

- homogeneity of variance between groups
- equal correlation between dependent variables between groups
- not too many dependent variables

MANCOVA

- correlation between the covariate and dependent variables
- if the covariate is dependent on independent variables
- covariates measured before interventions
- covariate and dependent variables normally distributed
- enough sample sizes and equal sample sizes
- homogeneity of regression slopes (covariate and dependent variable)

Both MANOVA and MANCOVA were planned to be performed on a pragmatic basis. However, all criteria were not always met and the interpretations of the MANOVA and MANCOVA results should be taken considering these constraints. In addition, ANOVA is a statistic which can stand medium level of deviation from normality (Petrie and Sabin, 2009).

For MANOVA and MANCOVA p-values of <0.05 were taken as significant.

3.3 Results

3.3.1 Study duration

The study lasted from March 27th, 2013 to December 9th, 2014. Results were analyzed on an intention-to-treat basis.

3.3.2 Study population

The overall study population was 153 patients of which 147 patients completed all study visits. Six patients withdrew after visit 0. Reasons for withdrawal were that patient number 517 and 518 cited time constraints, patient 562 halted antihypertensive pharmacotherapy according to the physician's recommendation, patient 651 cited personal circumstances, whereas patient 652 cited both personal circumstances and time constraints. Patient 532 did not provide a reason for study withdrawal.

In the overall study population, there were 77 male and 76 female patients. Mean age of the overall patient population was 66 years. There were 73 patients on monotherapy and 80 patients on polypharmacy.

The overall study population is presented in Table 3.1. in which the changes in SBP, DBP and pulse between visit 0 and visit 2 are shown. The desired outcome was a blood pressure change >0 equating to a reduction in mean SBP and DBP between visit 0 and 2. A blood pressure change <0 equated to an increase in mean SBP and DBP between visit 0 and 2. The antihypertensive pharmacotherapy for each patient is classified according to medication groups. In addition, adherence subgroup and the interventions delivered for each patient are shown.

Blood pressure and pulse results in the results section are all based on repeat measurements unless otherwise stated.

From Table 3.1, changes in BP for patients on mono or dual therapy indicate a positive change: a blood pressure reduction occurring between visit 0 and 2. Patients on triple, quadruple and quintuple therapies mainly have a negative change in blood pressure, i.e. their blood pressure getting worse.

Table 3.1. Overall study populations with change in SBP, DBP and pulse between visit 0 and visit 2, their antihypertensive pharmacotherapy classified according to medication groups, adherence subgroups and the allocated intervention. Participants highlighted in italics are patient drop-outs.

PN	ChSBP	ChDBP	ChPulse	AHMG	ADSG	INT
500	38	17	8	TD+(ACEinh)*	II	C+I
568	-11	-24	6	LD	II	C+I
522	-6	10	17	TPSD	A AND II	C+I
630	-6	-1	3	TPSD	U	C+I+R
506	-6	-10	4	BB	U	C+I+R
507	5	-3	-7	BB	A AND IR	C+I
523	-7	3	2	BB	A	C+I
534	6	6	7	BB	U	C+I+R
540	21	3	-4	BB+(ARB)* +(ARBHCT)*	U	C+I+R
542	12	12	2	BB	A	I
549	15	8	-4	BB	A	I
561	-3	-4	2	BB	A	C+I
567	15	11	1	BB	U	C+I+R
596	14	3	6	BB	A	I
617	-1	0	0	BB	II	C+I
620	2	-5	-7	BB	A	I
626	-6	-13	-1	BB	A	I
518				*CCB*		
519	5	13	10	CCB	U	C+I+R
545	0	-1	-8	CCB	A	I
553	12	11	-6	CCB	A	I

Continuation of Table 3.1

PN	ChSBP	ChDBP	ChPulse	AHMG	ADSG	INT
557	-21	-15	3	CCB	U	C+I+R
563	7	7	11	CCB	U	C+I+R
577	17	8	8	CCB	U	C+I+R
580	-6	-5	11	CCB	A	I
587	6	5	-7	CCB	A	C+I
592	32	23	28	CCB+(BB)*	A	C+I
610	-7	-5	-1	CCB	U	C+I+R
614	-3	1	-2	CCB	U	C+I+R
618	-9	-5	-5	CCB	A	I
638	17	11	-11	CCB	A	I
646	1	-1	5	CCB	U	C+I+R
648	-3	-10	-9	CCB	U	C+I+R
514	5	0	0	ACEinh	U	C+I+R
527	-21	-6	3	ACEinh	A AND IR	I
551	8	6	-3	ACEinh	U	C+I+R
569	-25	-6	2	ACEinh	A	I
582	3	-3	11	ACEinh	U	C+I+R
586	-20	-16	10	ACEinh	A	I
589	-8	-6	-2	ACEinh	II AND U	C+I+R
590	-8	-5	6	ACEinh	A	C+I
600	-10	-3	1	ACEinh	U	C+I+R
601	-14	-10	-5	ACEinh	U	C+I+R
604	15	18	5	ACEinh	U	C+I+R
607	3	5	2	ACEinh	IR AND U	C+I+R

Continuation of Table 3.1

PN	ChSBP	ChDBP	ChPulse	AHMG	ADSG	INT
611	-8	-4	4	ACEinh	U	C+I+R
612	4	-1	-2	ACEinh	II AND U	C+I+R
644	-13	-6	3	ACEinh	A	I
647	-16	-11	0	ACEinh	A	I
652				*ACEinh*		
503	-4	-2	-4	ACEinhHCT	A AND IR	I
521	25	17	-18	ACEinhHCT	U	C+I+R
539	-11	-9	0	ACEinhHCT	U	C+I+R
555	11	2	23	ACEinhHCT	U	C+I+R
574	7	2	-3	ACEinhHCT	U	C+I+R
616	18	7	-9	ACEinhHCT	U	C+I+R
541	-9	-8	5	ARB	U	C+I+R
558	-3	0	-7	ARB	A	C+I
562				*ARB*		
564	-12	-8	8	ARB	U	C+I+R
571	-10	-11	3	ARB	U	C+I+R
572	6	7	-3	ARB	A	C+I
619	17	-5	-8	ARB	A	I
629	29	4	-18	ARB	A	I
632	24	13	2	ARB	U	C+I+R
633	35	18	3	ARB	A	I
641	23	1	-3	ARB	A	I
512	-2	2	-2	ARBHCT	A	I
547	-10	-5	13	ARBHCT	U	C+I+R
578	15	9	-8	ARBHCT	U	C+I+R

Continuation of Table 3.1

PN	ChSBP	ChDBP	ChPulse	AHMG	ADSG	INT
591	-18	-1	5	ARBHCT	A	I
595	-4	-6	-18	ARBHCT	U	C+I+R
628	29	15	-8	ARBHCT	A	I
556	16	-2	-20	TD+ACEinh	A	I
643	24	12	-12	TD+ACEinh	U	C+I+R
621	-3	-6	1	TD+ARB	U	C+I+R
516	-3	-8	0	LD+TPSD	II	C+I+R
588	9	1	3	LD+BB	U	C+I+R
536	17	2	-3	LD+CCB	II	C+I
505	36	8	7	LD+ACEinh	U	C+I+R
529	3	4	4	LD+ACEinhHCT	A AND II	C+I
502	14	9	-8	PSD+BB	A	I
613	6	5	5	PSD+ARB	A	I
520	-2	-2	4	TPSD+ACEinh	A	I
513	-3	5	-3	BB+CCB	A AND II	C+I
537	-10	-8	-9	BB+CCB	U	C+I+R
552	13	4	21	BB+CCB	A	C+I
575	-5	-8	2	BB+CCB	A	C+I
609	8	4	3	BB+CCB	A	C+I
636	12	8	-4	BB+CCB	U	C+I+R
650	-5	-7	-8	BB+CCB	U	C+I+R
544	28	1	1	BB+ACEinh	A	I
550	3	0	12	BB+ACEinh	A	C+I
585	19	5	-8	BB+ACEinh	A	C+I
602	14	12	-5	BB+ACEinh+(ARB)*	A	I

Continuation of Table 3.1

PN	ChSBP	ChDBP	ChPulse	AHMG	ADSG	INT
606	8	8	1	BB+ACEinh	A	C+I
608	3	5	1	BB+ACEinh	U	C+I+R
627	15	-2	-11	BB+ACEinh	A	I
640	-5	-1	-7	BB+ACEinh	A	I
525	15	10	-3	BB+ARB	U	C+I+R
528	-23	-18	-19	BB+ARB	U	C+I+R
603	-6	-7	6	BB+ARB	A	C+I
631	3	-10	3	BB+ARB	A	C+I
634	3	-1	0	BB+ARB	A	I
583	-1	1	-3	BB+ARBHCT	II	C+I
649	-15	-3	-6	BB+ARBHCT	A	C+I
511	0	-4	8	CCB+ACEinh	A	I
535	13	6	13	CCB+ACEinh	U	C+I+R
573	-22	-5	10	CCB+ACEinh	A	I
570	-20	-9	-7	CCB+ACEinhHCT	A	C+I
581	-6	-5	-17	CCB+ACEinhHCT	U	C+I+R
598	1	1	-3	CCB+ACEinhHCT	U	C+I+R
615	15	7	-24	CCB+ACEinhHCT	A	I
622	2	6	1	CCB+ACEinhHCT	U	C+I+R
645	31	15	-3	CCB+ACEinhHCT	II	C+I
504	18	9	1	CCB+ARB +(ARBHCT)*	U	C+I+R
510	-46	-24	-6	CCB+ARB	II	C+I
524	0	10	1	CCB+ARB	A	I
543	12	2	13	CCB+ARB	U	C+I+R
501	30	19	-8	CCB+ARBHCT	A	I

Continuation of Table 3.1

PN	ChSBP	ChDBP	ChPulse	AHMG	ADSG	INT
526	13	9	4	CCB+ARBHCT	A	I
531	12	9	3	CCB+ARBHCT	A	I
559	6	1	-5	CCB+ARBHCT	II	C+I
593	-10	-7	16	CCB+ARBHCT+(BB)*	II	I
594	1	-6	-12	CCB+ARBHCT	A	I
599	-1	11	0	CCB+ARBHCT	U	C+I+R
625	-28	-17	-5	TD+LD+CCB +(TPSD)*+(ACEinh)*	II	C+I
538	-18	-18	0	TD+BB+ARB	U	C+I+R
565	5	1	5	TD+BB+ARB	A	I
548	-5	-12	-14	TD+CCB+ACEinh	A	C+I
532				*LD+PSD+ARB*		
554	13	2	3	LD+BB+ACEinh	II	C+I
639	-2	-7	-3	LD+BB+ARB	A AND II	C+I
576	7	12	7	TPSD+CCB+ARB	U	C+I+R
508	-6	-9	-2	BB+CCB+ACEinh	A AND IR	I
517				*BB+CCB+ACEinh*		
560	12	1	3	BB+CCB+ACEinh	A	C+I
566	-10	-1	-7	BB+CCB+ACEinh	U	C+I+R
623	-9	-13	-9	BB+CCB+ACEinh	U	C+I+R
635	6	4	-25	BB+CCB+ACEinh	A AND II	C+I
651				*BB+CCB+ACEinh*		
515	-1	-5	4	BB+CCB+ACEinhHCT	A	I
584	7	0	-5	BB+CCB+ACEinhHCT	U	C+I+R
597	14	5	-2	BB+CCB+ARBHCT	IR AND U	C+I+R

Continuation of Table 3.1

PN	ChSBP	ChDBP	ChPulse	AHMG	ADSG	INT
624	20	9	-5	BB+CCB+ARBHCT	U	C+I+R
637	-7	-3	-1	TD+PSD+CCB+ARB	A	I
509	2	-6	-8	LD+PSD+BB+ACEinh	U	C+I+R
530	-11	-11	-11	LD+PSD+BB+ACEinh	U	C+I+R
605	-14	0	0	LD+PSD+BB+ACEinh	A	C+I
533	-10	-4	9	TPSD+CCB+ACEinh +ARB	A	I
546	-6	5	6	TD+LD+BB+CCB +ACEinh	II	C+I
642	10	-2	0	LD+TPSD+BB+CCB +ACEinh	U	C+I+R
579	-13	-8	-14	PSD+CCB+ACEinh +BBCCB+Alpha	U	C+I+R

Abbreviations for Table 3.1: ACEinh=Angiotensin Converting Enzyme (ACE) inhibitor; ACEinhHCT= Angiotensin Converting Enzyme (ACE) inhibitor and hydrochlorothiazide; ADSG=Adherence subgroup; AHMG=Antihypertensive medication group; Alpha=Alpha blocker; ARB=Angiotensin-II receptor blocker; ARBHCT=Angiotensin-II receptor blocker and hydrochlorothiazide; BB=Beta-blocker; BBCCB=Beta-blocker and calcium channel blocker; CCB=Calcium-channel blocker; ChDBP=Change in diastolic blood pressure; ChPulse=Change in pulse; ChSBP=Change in systolic blood pressure; INT=Intervention; LD=Loop diuretic; PN=Participant number; PSD=Potassium-sparing diuretic; TD=Thiazide diuretic; TPSD=Thiazide and potassium-sparing diuretic; (xy)*=Add-on drug after visit 0

3.3.2.1 Adherence subgroups

These are the 8 adherence subgroups with the n values for each subgroup (Table 3.2). The largest adherence subgroups are the A (n=62) and U (n=59) subgroups being similar in patient numbers. These are followed by the II (n=13) subgroup. The (A and IR) (n=4) and (A and II) (n=5) subgroups are also similar with small patient numbers. The (IR and U) and (II and U) subgroups are very small each consisting of 2 patients.

Table 3.2. Number (n) of patients in each adherence subgroup. The largest adherence subgroups are the A (n=62) and U (n=59) subgroups, followed by II (n=13). They are then followed by the smaller subgroups A and II (n=5), A and IR (n=4). The (IR and U) and (II and U) subgroups consist of very small numbers, n=2 in each subgroup.

Adherence subgroups	n
A	62
A AND IR	4
A AND II	5
II	13
IR AND U	2
II AND U	2
U	59

A=adherent; IR=intentional non-adherent rational; II=intentional non-adherent irrational; U=unintentional non-adherent

3.3.3 Deviations from study protocol

For a few patients, there were a small number of deviations from the study protocol to accommodate the authentic community pharmacy practice situation. At the request of three patients: participants 501, 502 and 539, rather than measuring the BP at the community pharmacy, they were measured in the patients' domiciliary environment. It was acknowledged that a patient may be more relaxed in their home compared to the community pharmacy.

For participant 605 a larger cuff size was used since a smaller cuff size was not comfortable. Patient 535 had almost a 7-month study duration to facilitate the scheduling of the last study

visit. Participant 588 had to stop administering antihypertensive medication 14 days prior to visit 2 by request of the physician. Similarly, participant 625 stopped administering antihypertensive medication 4 weeks prior to visit 2, though this patient intended to contact the physician to restart the therapy. Despite this, on examination of the results there really no difference in their results and performance, so they were included in the cohort.

3.3.4 Baseline (visit 0) analysis

The multivariate analysis at visit 0 showed the between-group difference in blood pressure and pulse at visit 0 to be significant ($p<0.05$). The p-values of the four different test statistics in the multivariate analysis are shown in Table 3.3. Univariate analysis showed a significant difference for pulse at visit 0 ($p<0.05$). See the test statistic for the univariate analysis in Table 3.3.

Table 3.3. MANOVA at visit 0. Multivariate analysis showed a significant between-group difference ($p<0.05$) on BP and pulse at visit 0 as shown by four test statistics: Pillai's Trace, Wilk's λ, Hotelling's Trace and Roy's Largest Root. The univariate analysis displayed a significant difference ($p<0.05$) for pulse at visit 0.

MANOVA visit 0		
Multivariate	**F statistic**	**p value**
Pillai's Trace=0.095	F(6, 270)=2.24	0.040
Wilk's λ=0.91	F(6, 268)=2.25	0.039
Hotelling's Trace=0.10	F(6, 266)=2.27	0.038
Roy's Largest Root=0.089	F(3, 135)=4.00	0.009
Univariate	**F statistic**	**p value**
Pulse visit 0	F(2, 136)=4.30	0.015

3.3.5 Deviation from intervention protocol

A deviation from the intervention protocol was necessary for 25 patients. Table 3.4 indicates to which patients these deviations occurred and on what basis the deviation was done. In general, deviations were more common for adherence subgroup A.

Table 3.4. Patients to which deviations occurred from the intervention protocol. The evidence for the deviations is shown. Codes for the questions and statements in the actual adherence screening questionnaires are indicated in this table.

A subgroup, Participant number	**Intervention**	**8-item MMAS***	**MARS**	**BMQ**
523	C+I			Specific Necessity score 1.4
548	C+I			Specific Necessity score 2.8
550	C+I			Specific Necessity score 3.6
552	C+I			Agree BS5, General Overuse score 3, Agree BG1
558	C+I			Strongly Agree BS2, Uncertain BS5, BS9, Agree BG1, BG7, Uncertain BG8
560	C+I			Uncertain BS2, BS5, Agree BS11, General Overuse score 3.3, Agree BG8
561	C+I			Specific Necessity score 2.4, Agree BS2, BS11, Uncertain BS5, Agree BG8
570	C+I			Specific Necessity score 2.6, Agree BS2, BS5, BS9, Gen Overuse score 3, General Harm score 2.6
572	C+I			Specific Necessity score 3.4, Agree BS2, BS5, BS9, Uncertain BG7, BG8
575	C+I			Specific Necessity score 3, Uncertain BS9, General Overuse score 4.3, General Harm score 3.2
585	C+I			Specific Necessity score 2.6, Uncertain BS6, BS9, General Overuse score 3, General Harm score 2.6
587	C+I			Specific Necessity score 2, Uncertain BG7, BG8
590	C+I			Specific Necessity score 3.4, Specific Concerns score 2.5, Agree BS2, BS9, Agree BG1, BG8.
592	C+I			Strongly Disagree BS3, Uncertain BS2, BS9, BS11, Agree BS5, Strongly Agree BG1, Agree BG3, BG6, BG8, Uncertain BG7

Continuation of Table 3.4				
A subgroup, Participant number	**Intervention**	**8-item MMAS***	**MARS**	**BMQ**
603	C+I			Specific Necessity score 2.6, Specific Concerns score 2.7, General Overuse score 4
605	C+I			Uncertain BS6, BS11, BG7
606	C+I			Specific Necessity score 3, Specific Concerns score 2.8, Agree BS5, General Overuse score 3.7 (Agree BG7, BG 8, participant note on BG7, BG8: not always/sometimes)
609	C+I			Uncertain BS2, Agree BS5, BS9, BS11. General Overuse score 2.7
631	C+I			Specific Necessity score 2.4, Specific Concerns score 2.5, Agree BS2, General Overuse score 3
649	C+I			Specific Concerns score 3, Agree BS5, BS8, BS9, General Overuse score 3
A and IR subgroup, Participant number	**Intervention**	**8-item MMAS***	**MARS**	**BMQ**
507	C+I			Specific Necessity score 2.6, Strongly Agree BG5
II subgroup, Participant number	**Intervention**	**8-item MMAS***	**MARS**	**BMQ**
516	C+I+R	Yes, on question number 3	Rarely M3	

Abbreviations for Table 3.4: C=counselling; I=medication explanation leaflet; R=reminder sheet.
*Use of the ©MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E. Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772.

3.3.6 Patients requesting blood pressure (BP) and pulse measurement at visit 1

There were 30 patients who requested BP and pulse measurement during visit 1. However, the readings for these measurements are not reported in this thesis since they do not contribute to the study aims and objectives.

3.3.7 Blood pressure (BP) and pulse results

The BP and pulse results at visit 0 and visit 2 for the cohort and each adherence subgroup is shown in the following section. The results are based on *repeat* BP measurements or *last repeat* BP measurement as noted in each figure/table.

3.3.7.1 Cohort (n=153)

Table 3.5 shows two different ways of representing the BP and pulse results based on either a) repeat measurements or b) the last repeat measurement.

In general, the BP and pulse results at visit 0 based on repeat measurements do not differ when compared to the last repeat measurement. The BP and pulse results at visit 0 and visit 2 are displayed in Table 3.5. SBP at visit 0 is around 140 mmHg, DBP at around 80 mmHg and a pulse surrounding 70 beats/minute. When reaching visit 2 the SBP reaches 137 mmHg, a DBP still around 80 mmHg and pulse at about 70 beats/minute.

The change in blood pressure and pulse between visit 0 and visit 2 is displayed in Table 3.6. A statistically significant result was obtained on the change in SBP between visit 0 and 2 for the overall study population based on repeat blood pressure measurements. There was no change in DBP, almost no change in pulse. In addition, there was BP control in the cohort.

Table 3.5. BP and pulse results for the cohort (n=153) at visit 0 and visit 2 respectively.

Visit 0 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)	Visit 2 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	140	79	69	**Mean**	137	79	69
Median	139	79	67	**Median**	136	80	68
StDev	17	10	12	**StDev**	16	10	11
SE	1	1	1	**SE**	1	1	1

Visit 0 (last repeat)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)	Visit 2 (last repeat)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	138	79	69	**Mean**	137	78	69
Median	138	78	68	**Median**	135	79	67
StDev	17	10	12	**StDev**	16	10	11
SE	1	1	1	**SE**	1	1	1

Abbreviations: StDev: Standard deviation; SE=Standard error

Table 3.6. Changes in SBP, DBP and pulse between visit 0 and visit 2 are shown for the cohort (n=153).

Change between visit 0 and visit 2 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	3*	0	-1
Median	2	0	0
StDev	14	9	9
SE	1	1	1
Change between visit 0 and visit 2 (last repeat)	**SBP (mmHg)**	**DBP (mmHg)**	**Pulse (beats/minute)**
Mean	2	0	0
Median	2	1	0
StDev	15	10	8
SE	1	1	1

*Statistically significant (Wilcoxon signed-rank test: p=0.049)
Abbreviations: StDev: Standard deviation; SE=Standard error

3.3.7.2 Adherent (A) subgroup (n=62)

Table 3.7. shows two different ways of representing the BP and pulse results based on a) repeat measurements or b) the last repeat measurement. In general, the BP and pulse results at visit 0 based on repeat measurements do not differ when compared to the last repeat measurement.

Table 3.7 displays the BP and pulse results at visit 0 and visit 2. The SBP at visit 0 is around 140 mmHg, DBP at around 80 mmHg and a pulse surrounding 70 beats/minute. When reaching visit 2 the SBP reaches a level of 136 mmHg, a DBP almost remaining at 80 mmHg and a pulse at about 70 beats/minute.

Changes in blood pressure and pulse between visit 0 and visit 2 is displayed in Table 3.8. The A subgroup generally showed small improvements in SBP and DBP and almost no change in pulse between visit 0 and visit 2. This adherence subgroup had a stable BP control.

Table 3.7. BP and pulse results for the A subgroup (n=62) at visit 0 and visit 2 respectively.

Visit 0 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)	Visit 2 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	140	79	69	**Mean**	136	78	70
Median	138	80	68	**Median**	136	78	69
StDev	18	10	12	**StDev**	14	9	11
SE	2	1	2	**SE**	2	1	1

Visit 0 (last repeat)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)	Visit 2 (last repeat)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	139	78	70	**Mean**	136	78	70
Median	137	79	68	**Median**	137	79	68
StDev	17	10	12	**StDev**	15	10	11
SE	2	1	2	**SE**	2	1	1

Abbreviations: StDev: Standard deviation; SE=Standard error

Table 3.8. Changes in SBP, DBP and pulse between visit 0 and visit 2 are shown for A subgroup (n=62).

Change between visit 0 and visit 2 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	4	1	-1
Median	3	0	1
StDev	14	8	9
SE	2	1	1
Change between visit 0 and visit 2 (last repeat)	**SBP (mmHg)**	**DBP (mmHg)**	**Pulse (beats/minute)**
Mean	3	1	0
Median	2	1	1
StDev	15	9	8
SE	2	1	1

Abbreviations: StDev: Standard deviation; SE=Standard error

3.3.7.2.1 Within-group blood pressure (BP) changes in Adherent (A) subgroup

The changes in SBP and DBP between visit 0 and visit 2 for each patient in subgroup A (n=62) are demonstrated in Figures 3.4 (repeat measurements) and 3.5 (last repeat measurement). It is shown that subgroup A generally has small improvements in SBP and DBP. Patients in this subgroup exhibit a stable BP control. Apart from the clinically acceptable -10 to +10 mmHg band, there is seen a large variability in BP results between patients reaching up to about 70 mmHg in SBP and 20 mmHg in DBP.

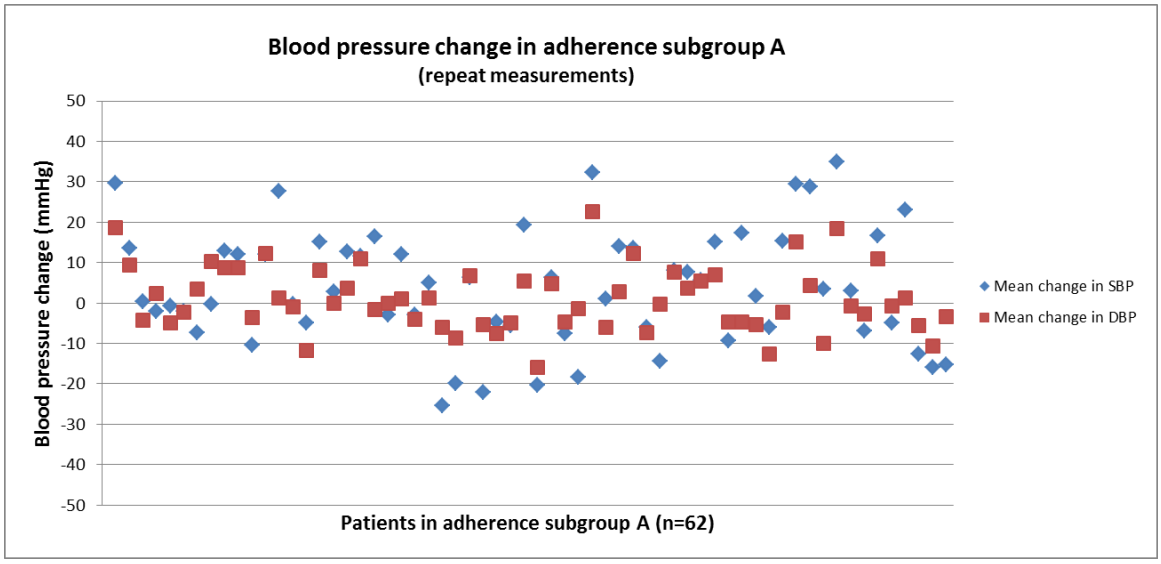


Figure 3.4. Change in SBP and DBP between visit 0 and visit 2 based on repeat BP measurements for each patient in adherence subgroup A (n=62).

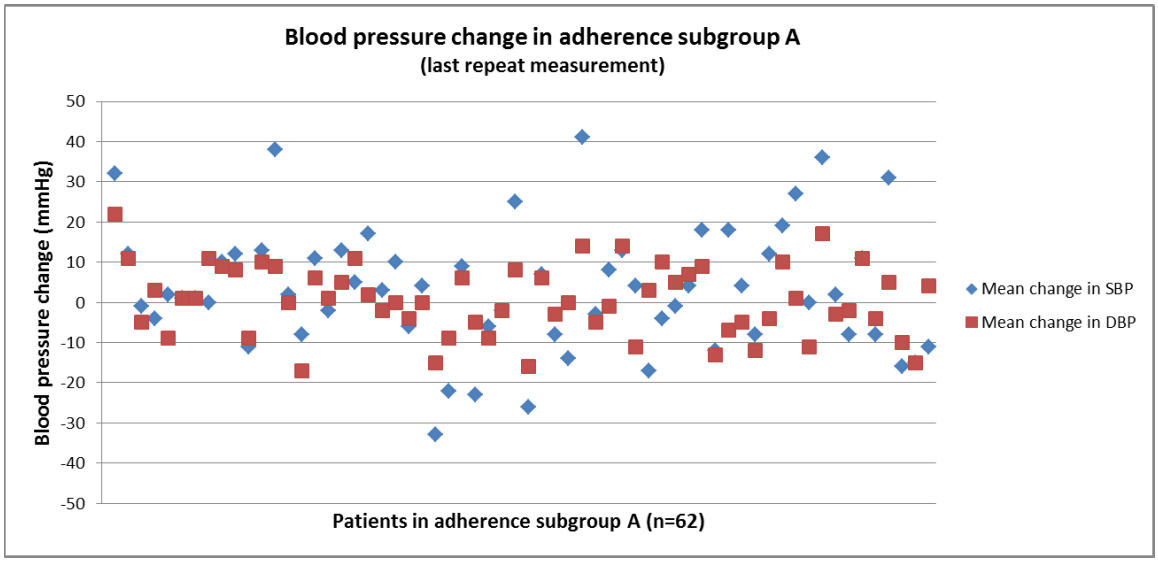


Figure 3.5. Change in SBP and DBP between visit 0 and visit 2 based on last repeat BP measurement for each patient in adherence subgroup A (n=62).

3.3.7.3 Adherent and Intentional non-adherent rational (A and IR) subgroup (n=4)

Table 3.9 shows two different ways of representing the BP and pulse results based on a) repeat measurements or b) the last repeat measurement. In general, the BP and pulse results based on repeat measurements do not differ when compared to the last repeat measurement.

Table 3.9 displays the BP and pulse results at visit 0 and visit 2. SBP at visit 0 is around 130 mmHg, DBP at around 70 mmHg and a pulse at 61 beats/minute. When reaching visit 2 the SBP reaches a level of about 140 mmHg, a DBP almost at 75 mmHg and a pulse at 64 beats/minute.

The change in blood pressure and pulse between visit 0 and visit 2 is displayed in Table 3.10**.** The A and IR subgroup showed a worsening in BP and pulse between visit 0 and 2. Despite this, there is a stable BP control in this adherence subgroup in relation to the target SBP <140 mmHg and DBP <90 mmHg.

Table 3.9. BP and pulse results for the A and IR subgroup (n=4) at visit 0 and visit 2 respectively.

Visit 0 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)	Visit 2 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	132	69	61	**Mean**	138	74	64
Median	131	70	64	**Median**	140	76	65
StDev	11	11	13	**StDev**	5	11	10
SE	6	6	8	**SE**	3	6	6

Visit 0 (last repeat)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)	Visit 2 (last repeat)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	131	68	61	**Mean**	140	73	64
Median	131	69	64	**Median**	142	75	65
StDev	13	11	13	**StDev**	10	11	9
SE	7	6	7	**SE**	6	6	5

Abbreviations: StDev: Standard deviation; SE=Standard error

Table 3.10. Changes in SBP, DBP and pulse between visit 0 and visit 2 are shown for A and IR subgroup (n=4).

Change between visit 0 and visit 2 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	-7	-5	-3
Median	-5	-4	-3
StDev	11	3	4
SE	6	2	2
Change between visit 0 and visit 2 (last repeat)	**SBP (mmHg)**	**DBP (mmHg)**	**Pulse (beats/minute)**
Mean	-9	-5	-3
Median	-7	-4	-4
StDev	14	2	4
SE	8	1	3

Abbreviations: StDev: Standard deviation; SE=Standard error

3.3.7.3.1 Blood pressure (BP) levels at visit 0 and visit 2 in Adherent and Intentional non-adherent rational (A and IR) subgroup

The SBP and DBP at visit 0 and visit 2 for each patient in subgroup A and IR (n=4) are demonstrated in Figures 3.6 and 3.7. The figures highlight the SBP at visit 0 is around 130 mmHg, DBP at around 70 mmHg. When reaching visit 2 the SBP reaches a level of about 140 mmHg, a DBP almost at 75 mmHg. In general, there is a stable BP control in the A and IR subgroup in relation to the target SBP <140 mmHg and DBP <90 mmHg, despite there being a worsening in BP between visit 0 and visit 2.

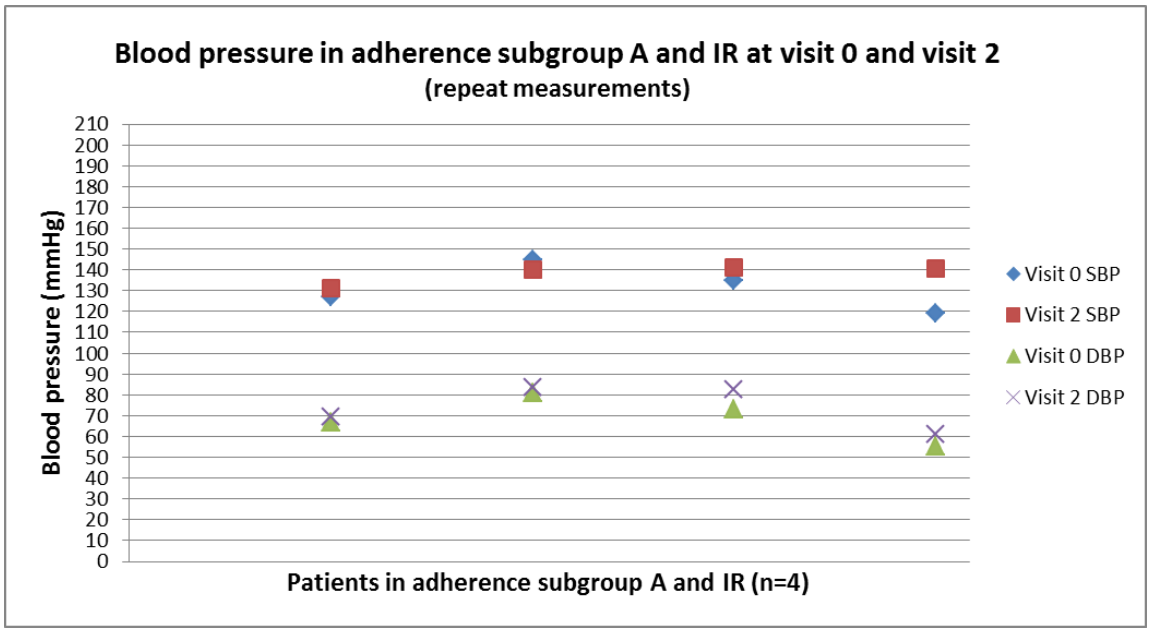


Figure 3.6. SBP and DBP at visit 0 and visit 2 based on repeat BP measurements for each patient in adherence subgroup A and IR (n=4).

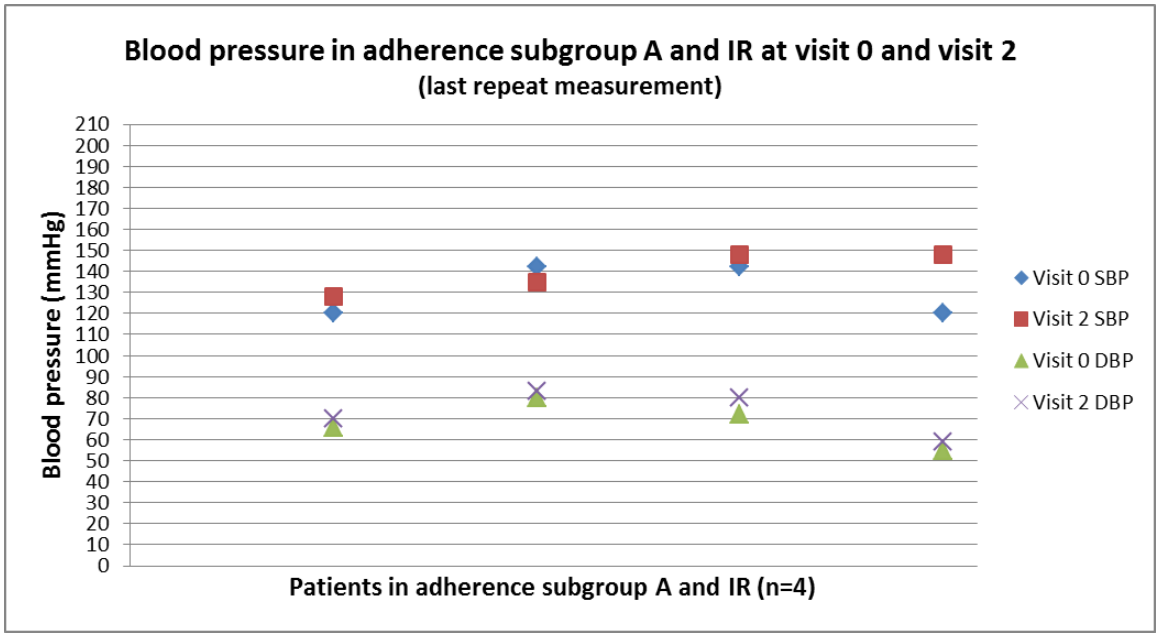


Figure 3.7. SBP and DBP at visit 0 and visit 2 based on last repeat BP measurement for each patient in adherence subgroup A and IR (n=4).

3.3.7.3.2 Within-group blood pressure (BP) changes between visit 0 and visit 2 in Adherent and Intentional non-adherent rational (A and IR) subgroup

The changes in SBP and DBP between visit 0 and visit 2 for each patient in subgroup A and IR (n=4) are demonstrated in Figures 3.8 and 3.9. There is a worsening in BP and pulse between visit 0 and visit 2. Despite this, there is generally a stable BP control in the A and IR subgroup in relation to the target SBP <140 mmHg and DBP <90 mmHg.

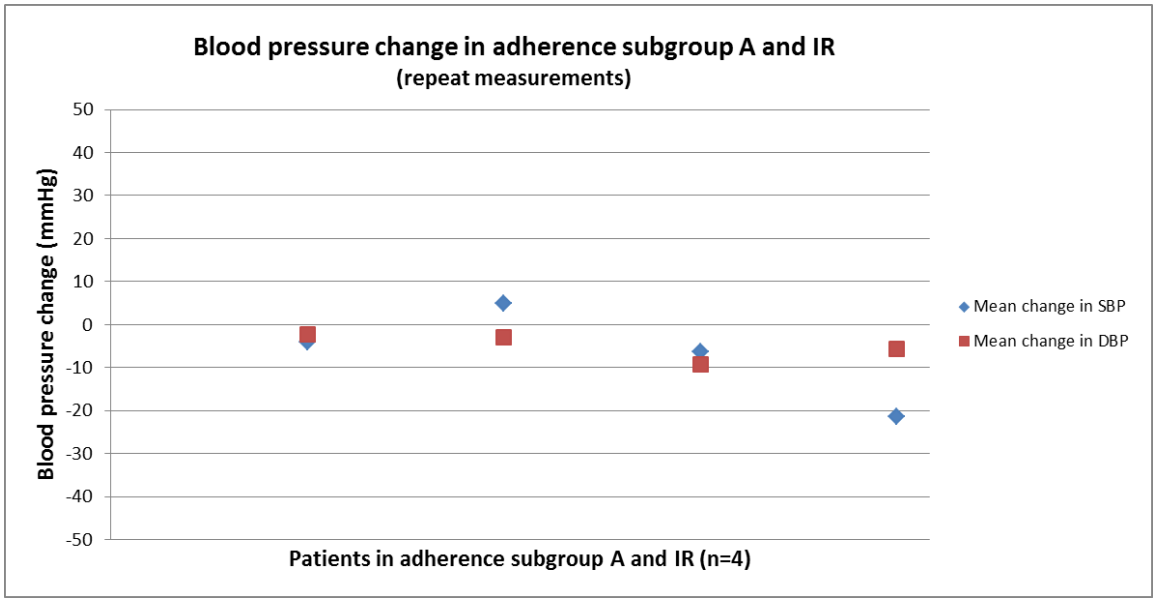


Figure 3.8. Change in SBP and DBP between visit 0 and visit 2 based on repeat BP measurements for each patient in adherence subgroup A and IR (n=4).

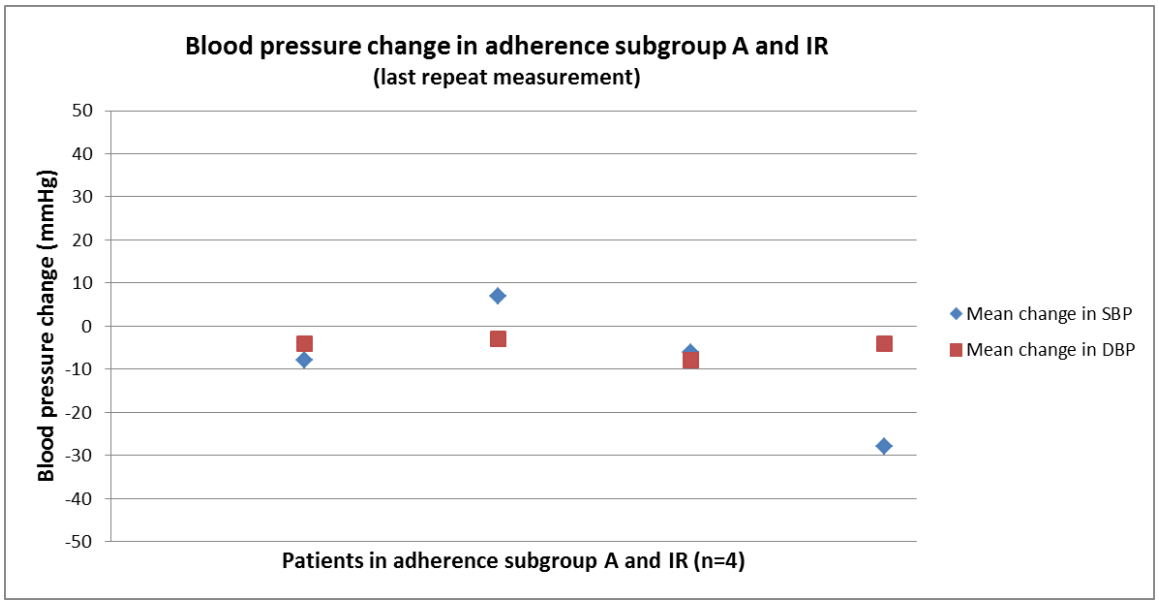


Figure 3.9. Change in SBP and DBP between visit 0 and visit 2 based on last repeat BP measurement for each patient in adherence subgroup A and IR (n=4).

3.3.7.4 Adherent and Intentional non-adherent irrational (A and II) subgroup (n=5)

Table 3.11 shows two different ways of representing the BP and pulse results based on a) repeat measurements or b) the last repeat measurement. In general, the BP and pulse results at visit 0 based on repeat measurements do not differ when compared to the last repeat measurement.

The BP and pulse results at visit 0 and visit 2 are displayed in Table 3.11. SBP at visit 0 is around 140 mmHg, DBP at around 80 mmHg and a pulse around 70 beats/minute. There is a slight difference in BP results at visit 2 based on repeat measurements or the last repeat measurement. Considering the repeat measurements, when reaching visit 2 the SBP reaches 140 mmHg, a DBP of 74 mmHg and a pulse of 70 beats/minute. At visit 2 the last repeat measurement displays an SBP of 136 mmHg, DBP at 70 mmHg and a pulse of 71 beats/minute.

The change in blood pressure and pulse between visit 0 and visit 2 is displayed in Table 3.12. The A and II subgroup had mixed outcome in SBP – some improvement and some worsening, an improvement in DBP and almost no change in pulse between visit 0 and visit 2. Despite this, there is a stable BP control in the A and II subgroup in relation to the target SBP <140 mmHg and DBP <90 mmHg.

Table 3.11. BP and pulse results for the A and II subgroup (n=5) at visit 0 and visit 2 respectively.

Visit 0 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)	Visit 2 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	139	77	68	**Mean**	140	74	70
Median	138	74	64	**Median**	137	72	72
StDev	10	7	13	**StDev**	13	8	7
SE	5	3	7	**SE**	6	4	4

Visit 0 (last repeat)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)	Visit 2 (last repeat)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	139	80	69	**Mean**	136	70	71
Median	142	78	66	**Median**	134	71	72
StDev	9	6	13	**StDev**	13	8	6
SE	5	3	6	**SE**	7	4	3

Abbreviations: StDev: Standard deviation; SE=Standard error

Table 3.12. Changes in SBP, DBP and pulse between visit 0 and visit 2 are shown A and II subgroup (n=5).

Change between visit 0 and visit 2 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	-1	3	-2
Median	-2	4	-3
StDev	5	6	15
SE	2	3	8
Change between visit 0 and visit 2 (last repeat)	**SBP (mmHg)**	**DBP (mmHg)**	**Pulse (beats/minute)**
Mean	2	10	-2
Median	7	8	0
StDev	8	6	15
SE	4	3	7

Abbreviations: StDev: Standard deviation; SE=Standard error

3.3.7.4.1 Blood pressure (BP) levels at visit 0 and visit 2 in Adherent and Intentional non-adherent irrational (A and II) subgroup

The SBP and DBP at visit 0 and visit 2 for each patient in subgroup A and II (n=5) are demonstrated in Figures 3.10 and 3.11. There is a mix of SBP levels between patients at both visit 0 and visit 2. It is also about the two different ways of representing the BP as either being based on repeat measurements or last repeat measurement. However, the DBP is generally ≤90 mmHg. Nonetheless, overall there is a stable BP control in the A and II subgroup in relation to the target SBP <140 mmHg and DBP <90 mmHg.

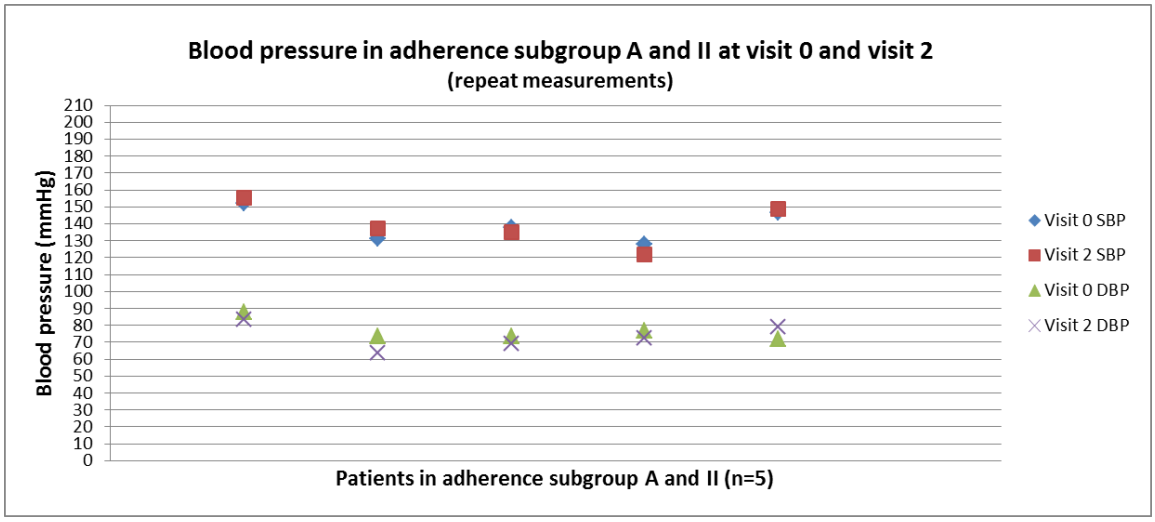


Figure 3.10. SBP and DBP at visit 0 and visit 2 based on repeat BP measurements for each patient in adherence subgroup A and II (n=5).

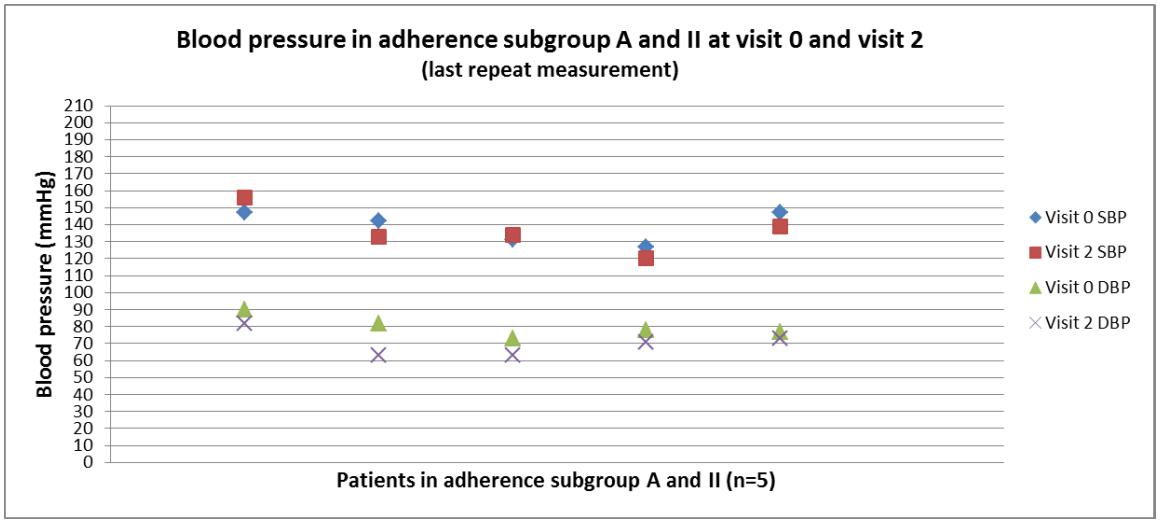


Figure 3.11. SBP and DBP at visit 0 and visit 2 based on last repeat BP measurement for each patient in adherence subgroup A and II (n=5).

3.3.7.4.2 Within-group blood pressure (BP) changes between visit 0 and visit 2 in Adherent and Intentional non-adherent irrational (A and II) subgroup

The changes in SBP and DBP between visit 0 and visit 2 for each patient in subgroup A and II (n=5) are demonstrated in Figures 3.12. and 3.13. In some patients, there is an improvement in SBP, whereas some patients have a worsening in SBP. This is also about the two different ways of representing the BP as either being based on repeat measurements or last repeat measurement. Overall, there is an improvement in DBP in this adherence subgroup. Despite this, generally, there is a stable BP control in the A and II subgroup in relation to the target SBP <140 mmHg and DBP <90 mmHg.

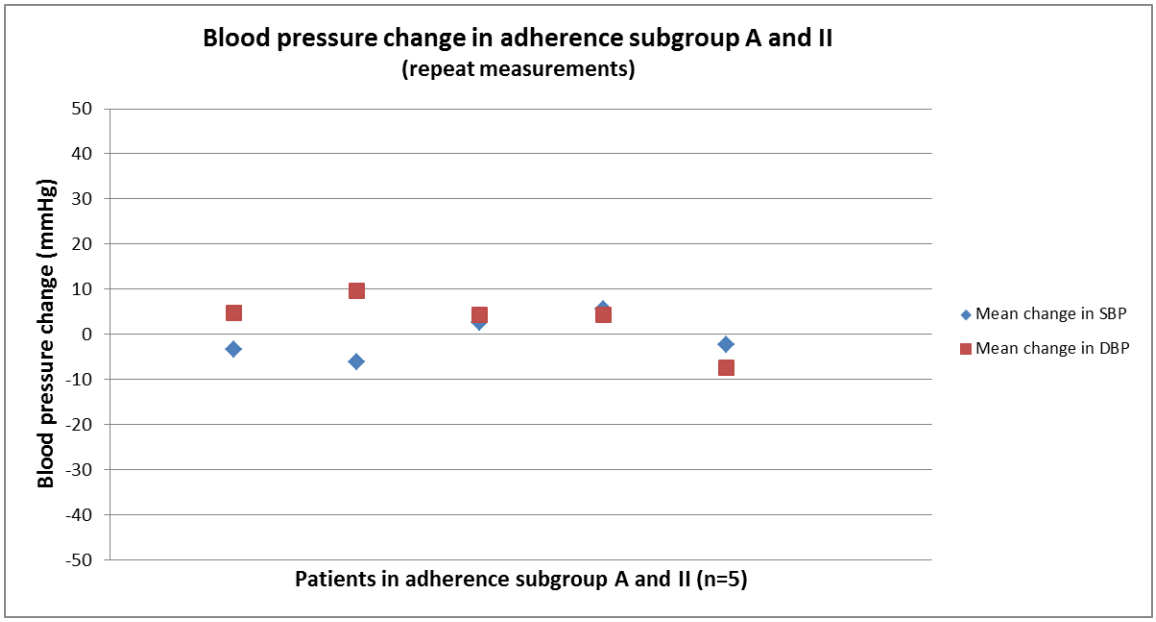


Figure 3.12. Change in SBP and DBP between visit 0 and visit 2 based on repeat BP measurements for each patient in adherence subgroup A and II (n=5).

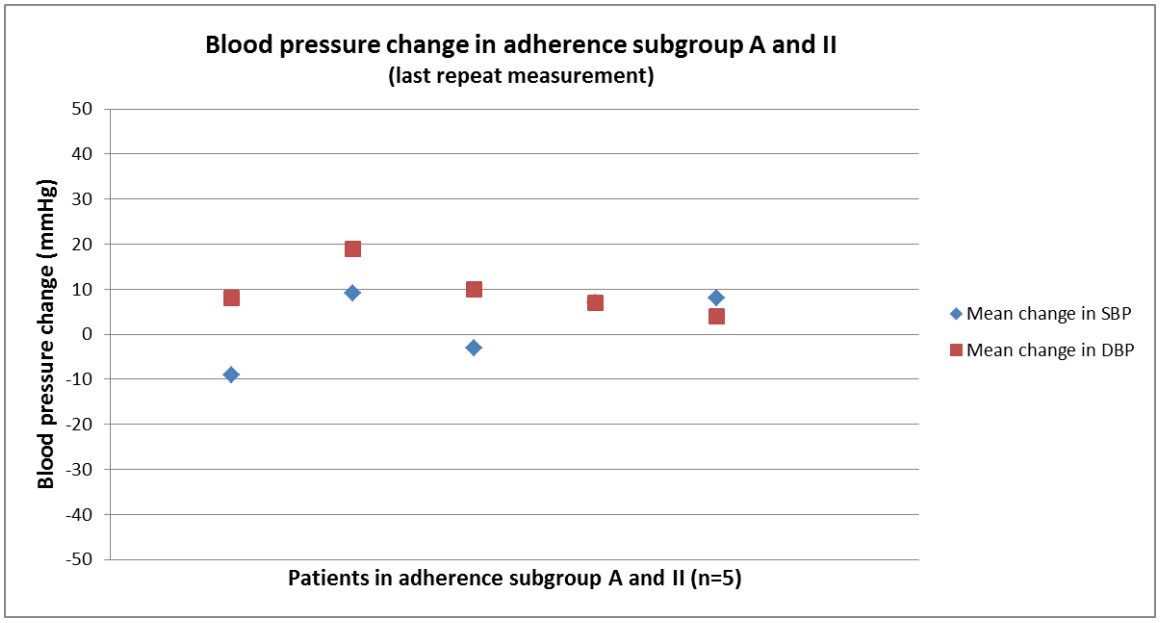


Figure 3.13. Change in SBP and DBP between visit 0 and visit 2 based on last repeat BP measurement for each patient in adherence subgroup A and II (n=5).

3.3.7.5 Intentional non-adherent irrational (II) subgroup (n=13)

Table 3.13. shows two different ways of representing the BP and pulse results based on a) repeat measurements or b) the last repeat measurement.

In general, the BP and pulse results at visit 0 based on repeat measurements do not differ when compared to the last repeat measurement.

BP and pulse results at visit 0 and visit 2 are displayed in Table 3.13. SBP at visit 0 is around 150 mmHg, DBP at around 80 mmHg and a pulse around 70 beats/minute. At visit 2 the SBP remains around 150 mmHg, DBP has increased to about 85 mmHg and a pulse at 67 beats/minute. As these results show, there is no BP control in subgroup II.

The change in blood pressure and pulse between visit 0 and visit 2 is displayed in Table 3.14. The II subgroup showed almost no change in SBP, a small worsening in DBP and a small improvement in pulse between visit 0 and visit 2.

Table 3.13. BP and pulse results for the II subgroup (n=13) at visit 0 and visit 2 respectively.

Visit 0 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)	Visit 2 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	151	83	68	**Mean**	151	86	67
Median	142	82	67	**Median**	144	89	67
StDev	24	13	12	**StDev**	28	11	8
SE	7	4	3	**SE**	8	3	2

Visit 0 (last repeat)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)	Visit 2 (last repeat)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	150	81	68	**Mean**	149	85	67
Median	142	79	68	**Median**	143	87	68
StDev	23	12	12	**StDev**	27	10	9
SE	7	4	3	**SE**	8	3	2

Abbreviations: StDev: Standard deviation; SE=Standard error

Table 3.14. Changes in SBP, DBP and pulse between visit 0 and visit 2 are shown for II subgroup (n=13).

Change between visit 0 and visit 2 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	0	-3	1
Median	-1	1	0
StDev	22	13	7
SE	6	4	2
Change between visit 0 and visit 2 (last repeat)	**SBP (mmHg)**	**DBP (mmHg)**	**Pulse (beats/minute)**
Mean	1	-3	1
Median	3	0	-2
StDev	23	13	7
SE	7	4	2

Abbreviations: StDev: Standard deviation; SE=Standard error

3.3.7.5.1 Blood pressure (BP) levels at visit 0 and visit 2 in Intentional non-adherent irrational (II) subgroup

The SBP and DBP at visit 0 and visit 2 for each patient in subgroup II (n=13) are demonstrated in Figures 3.14 and 3.15. The figures indicate an SBP at visit 0 around 150 mmHg and DBP being around 80 mmHg. At visit 2 the SBP remains around 150 mmHg, whereas DBP has increased to about 85 mmHg. As seen in Figures 3.14 and 3.15, patients in the II subgroup had high SBP values at both visit 0 and visit 2, thereby having no BP control.

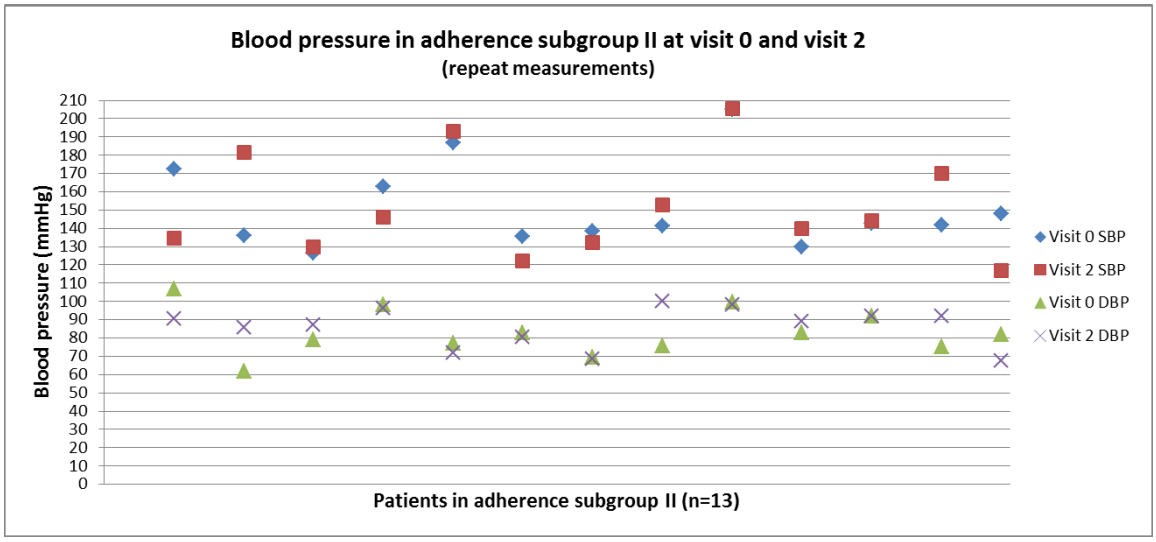


Figure 3.14. SBP and DBP at visit 0 and visit 2 based on repeat BP measurements for each patient in adherence subgroup II (n=13).

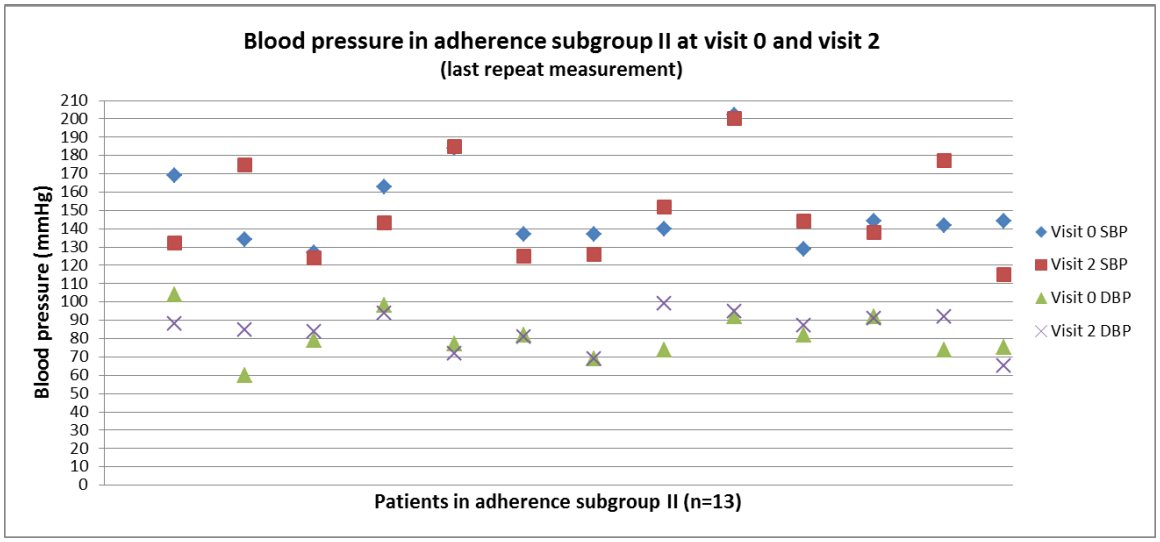


Figure 3.15. SBP and DBP at visit 0 and visit 2 based on last repeat BP measurement for each patient in adherence subgroup II (n=13).

3.3.7.5.2 Within-group blood pressure (BP) changes between visit 0 and visit 2 in Intentional non-adherent irrational (II) subgroup

The changes in SBP and DBP between visit 0 and visit 2 for each patient in subgroup II (n=13) are demonstrated in Figures 3.16 and 3.17. The II subgroup showed almost no change in SBP, a small worsening in DBP. Subgroup II did not exhibit BP control.

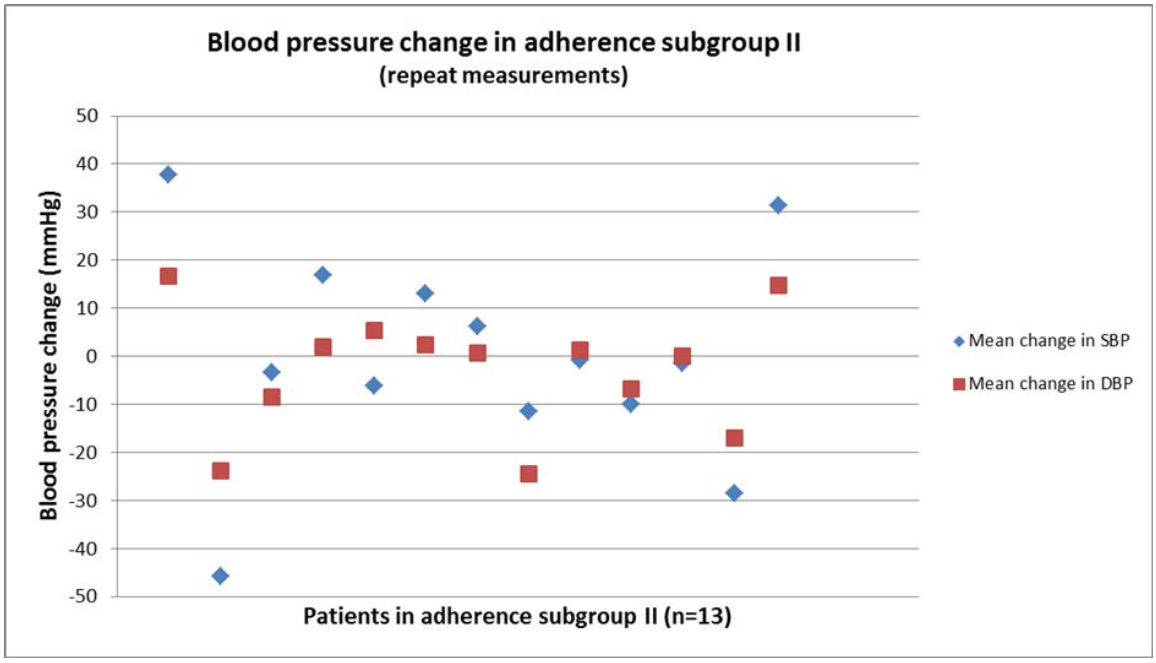


Figure 3.16. Change in SBP and DBP between visit 0 and 2 based on repeat BP measurements for each patient in adherence subgroup II (n=13).

.

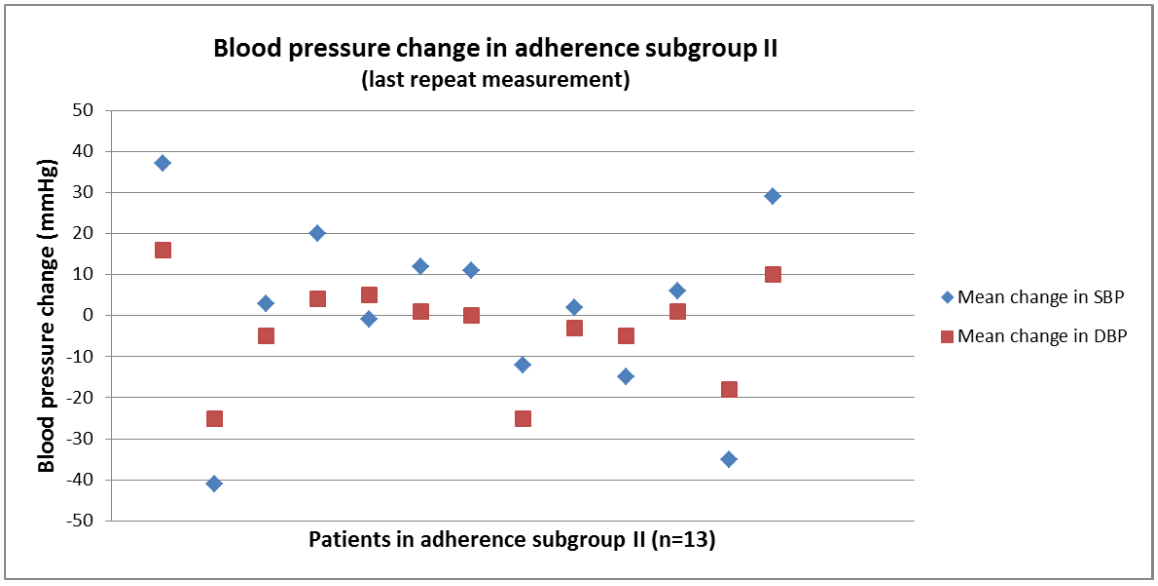


Figure 3.17. Change in SBP and DBP between visit 0 and 2 based on last repeat BP measurement for each patient in adherence subgroup II (n=13).

3.3.7.6 Intentional non-adherent rational and Unintentional non-adherent (IR and U) subgroup (n=2)

Table 3.15. shows two different ways of representing the BP and pulse results based on a) repeat measurements or b) the last repeat measurement. SBP at visit 0 and visit 2 based on repeat measurements differed when compared to the last repeat measurement results. This did not apply to DBP or pulse results. BP and pulse results at visit 0 and visit 2 are displayed in Table 3.15. Considering repeat measurements, the SBP at visit 0 is 140 mmHg, whereas at visit 2 SBP is 131 mmHg. Based on last repeat measurement SBP at visit 0 is 133 mmHg and drops to 128 mmHg at visit 2.

Overall, DBP at visit 0 is around 70 mmHg and a pulse around 60-65 beats/minute. At visit 2 the DBP drops to around 65 mmHg and a pulse at 63 beats/minute. The BP results indicate a BP control in subgroup IR and U.

The change in blood pressure and pulse between visit 0 and visit 2 is displayed in Table 3.16. The IR and U subgroup showed an improvement in BP and almost no change in pulse between visit 0 and visit 2.

Table 3.15. BP and pulse results for the IR and U subgroup (n=2) at visit 0 and visit 2 respectively.

Visit 0 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)	Visit 2 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	140	71	62	**Mean**	131	66	63
Median	140	71	62	**Median**	131	66	63
StDev	18	1	19	**StDev**	25	0	16
SE	18	1	19	**SE**	25	0	16

Visit 0 (last repeat)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)	Visit 2 (last repeat)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	133	70	64	**Mean**	128	65	63
Median	133	70	64	**Median**	128	65	63
StDev	18	1	19	**StDev**	25	2	16
SE	18	1	19	**SE**	25	2	16

Abbreviations: StDev: Standard deviation; SE=Standard error

Table 3.16. Changes in SBP, DBP and pulse between visit 0 and visit 2 are shown for IR and U subgroup (n=2).

Change between visit 0 and visit 2 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	9	5	0
Median	9	5	0
StDev	8	0	3
SE	8	0	3
Change between visit 0 and visit 2 (last repeat)	**SBP (mmHg)**	**DBP (mmHg)**	**Pulse (beats/minute)**
Mean	5	5	1
Median	5	5	1
StDev	8	3	3
SE	8	3	3

Abbreviations: StDev: Standard deviation; SE=Standard error

3.3.7.6.1 Blood pressure (BP) levels at visit 0 and visit 2 in Intentional non-adherent rational and Unintentional non-adherent (IR and U) subgroup

The SBP and DBP at visit 0 and visit 2 for each patient in subgroup IR and U (n=2) are demonstrated in Figures 3.18 and 3.19. There is a difference when SBP at visit 0 and visit 2 is displayed as either being based on repeat measurements or the last repeat measurement. However, this did not apply to the DBP and pulse results. The mean value of SBP at visit 0 is 140 mmHg, whereas at visit 2 the SBP drops to 131 mmHg. Based on last repeat measurement, the mean value of SBP at visit 0 is 133 mmHg and drops to 128 mmHg at visit 2. Overall, DBP at visit 0 is around 70 mmHg, whereas at visit 2 the DBP drops to around 65 mmHg. The results indicate a BP control in this adherence subgroup.

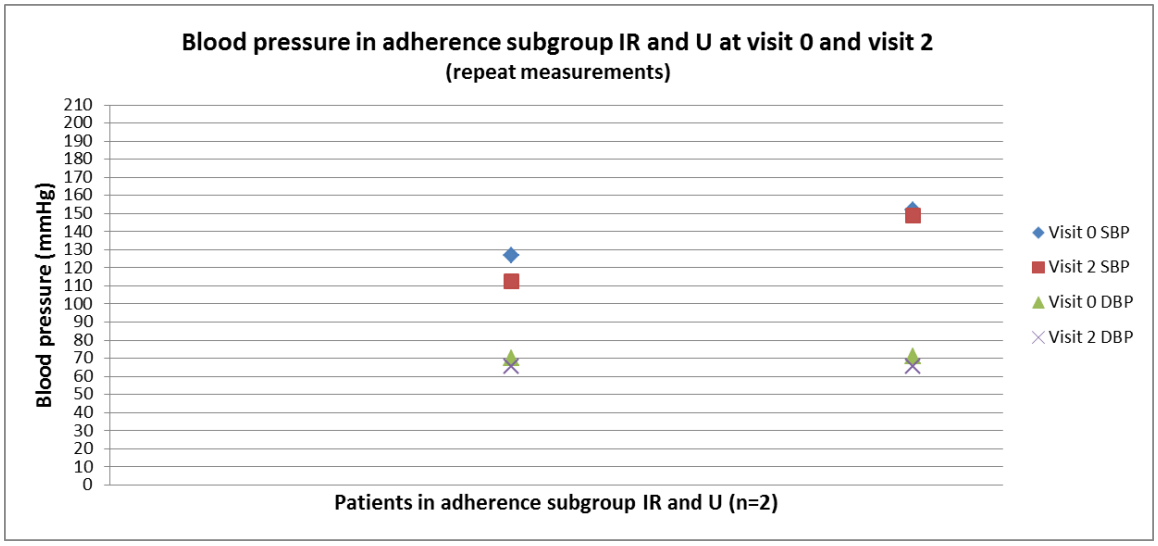


Figure 3.18. SBP and DBP at visit 0 and visit 2 based on repeat BP measurements for each patient in adherence subgroup IR and U (n=2).

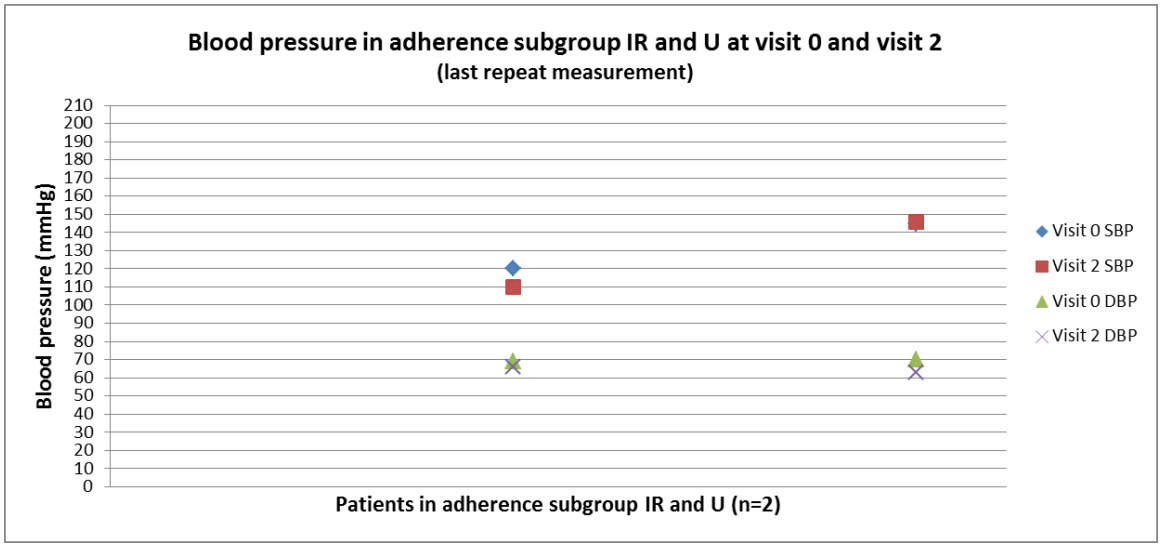


Figure 3.19. SBP and DBP at visit 0 and visit 2 based on last repeat BP measurement for each patient in adherence subgroup IR and U (n=2).

3.3.7.6.2 Within-group blood pressure (BP) changes between visit 0 and visit 2 in Intentional non-adherent rational and Unintentional non-adherent (IR and U) subgroup

The changes in SBP and DBP between visit 0 and visit 2 for each patient in subgroup IR and U (n=2) are demonstrated in Figures 3.20 and 3.21. The IR and U subgroup showed an improvement in BP control between visit 0 and visit 2. The results indicate a BP control in this adherence subgroup.

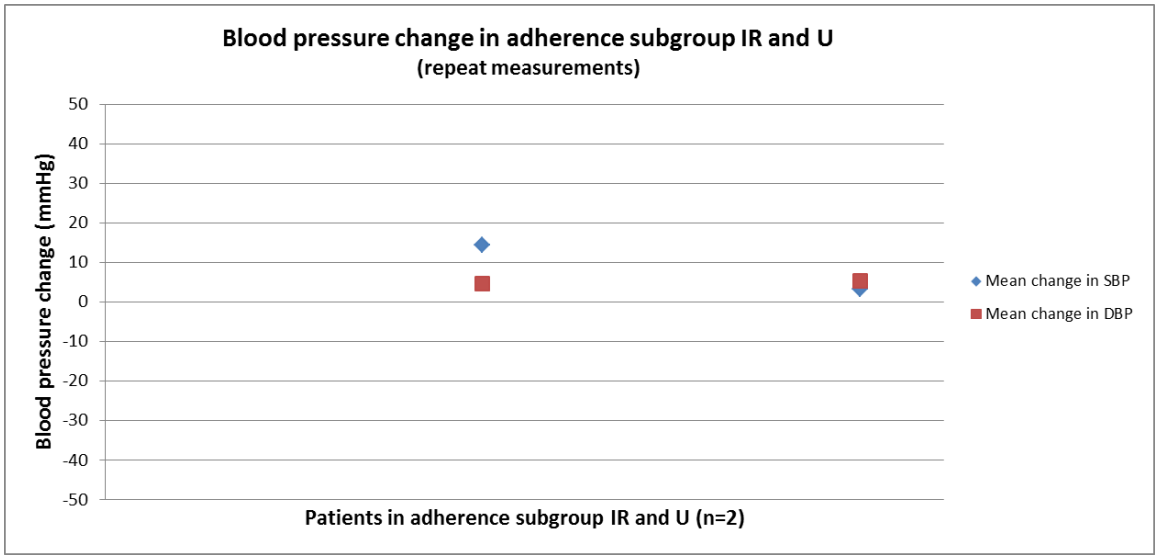


Figure 3.20. Change in SBP and DBP between visit 0 and 2 based on repeat BP measurements for each patient in adherence subgroup IR and U (n=2).

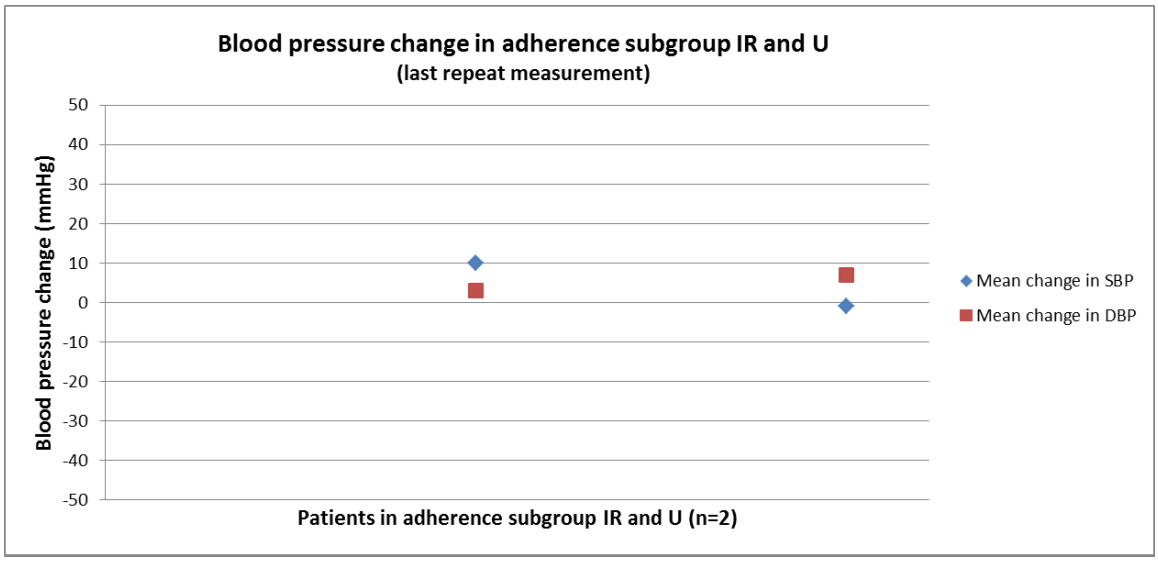


Figure 3.21. Change in SBP and DBP between visit 0 and 2 based on last repeat BP measurement for each patient in adherence subgroup IR and U (n=2).

3.3.7.7 Intentional non-adherent irrational and Unintentional non-adherent (II and U) subgroup (n=2)

Table 3.17. shows two different ways of representing the BP and pulse results based on a) repeat measurements or b) the last repeat measurement. In general, there was a difference based on repeat measurements in comparison to the last repeat measurement results. BP and pulse results at visit 0 and visit 2 are displayed in Table 3.17. Considering repeat measurements, the SBP at visit 0 is 127 mmHg, DBP 75 mmHg and pulse at 73 beats/minute. At visit 2 the SBP is 129 mmHg, DBP 78 mmHg and a pulse at 75 beats/minute. Based on last repeat measurement, SBP at visit 0 is 117 mmHg, DBP at 75 mmHg and pulse at 72 beats/minute. At visit 2 the SBP is 129 mmHg, DBP at 81 mmHg and pulse at 78 beats/minute. The BP results indicate a BP control in subgroup II and U.

The change in blood pressure and pulse between visit 0 and visit 2 is displayed in Table 3.18. The II and U subgroup showed a worsening in BP and pulse between visit 0 and visit 2.

Table 3.17. BP and pulse results for the II and U subgroup (n=2) at visit 0 and visit 2 respectively.

Visit 0 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)	Visit 2 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	127	75	73	**Mean**	129	78	75
Median	127	75	73	**Median**	129	78	75
StDev	9	0	13	**StDev**	0	3	14
SE	9	0	13	**SE**	0	3	14

Visit 0 (last repeat)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)	Visit 2 (last repeat)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	117	75	72	**Mean**	129	81	78
Median	117	75	72	**Median**	129	81	78
StDev	10	3	14	**StDev**	0	5	15
SE	10	3	14	**SE**	0	5	15

Abbreviations: StDev: Standard deviation; SE=Standard error

Table 3.18. Changes in SBP, DBP and pulse between visit 0 and visit 2 are shown for II and U subgroup (n=2).

Change between visit 0 and visit 2 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	-2	-3	-2
Median	-2	-3	-2
StDev	8	3	0
SE	8	3	0
Change between visit 0 and visit 2 (last repeat)	**SBP (mmHg)**	**DBP (mmHg)**	**Pulse (beats/minute)**
Mean	-12	-6	-6
Median	-12	-6	-6
StDev	10	2	1
SE	10	2	1

Abbreviations: StDev: Standard deviation; SE=Standard error

3.3.7.7.1 Blood pressure (BP) levels at visit 0 and visit 2 in Intentional non-adherent irrational and Unintentional non-adherent (II and U) subgroup

The SBP and DBP at visit 0 and visit 2 for each patient in subgroup II and U (n=2) are demonstrated in Figures 3.22 and 3.21. There is a general difference in BP results based on the way the results are being portrayed – either as repeat measurements or last repeat measurement. Considering repeat measurements, the mean value of SBP at visit 0 is 127 mmHg and DBP 75 mmHg. At visit 2 the SBP is 129 mmHg and DBP 78 mmHg. Based on last repeat measurement, mean value of SBP at visit 0 is 117 mmHg and DBP 75 mmHg. At visit 2 the SBP is 129 mmHg and DBP 81 mmHg. The results indicate a BP control in this adherence subgroup.

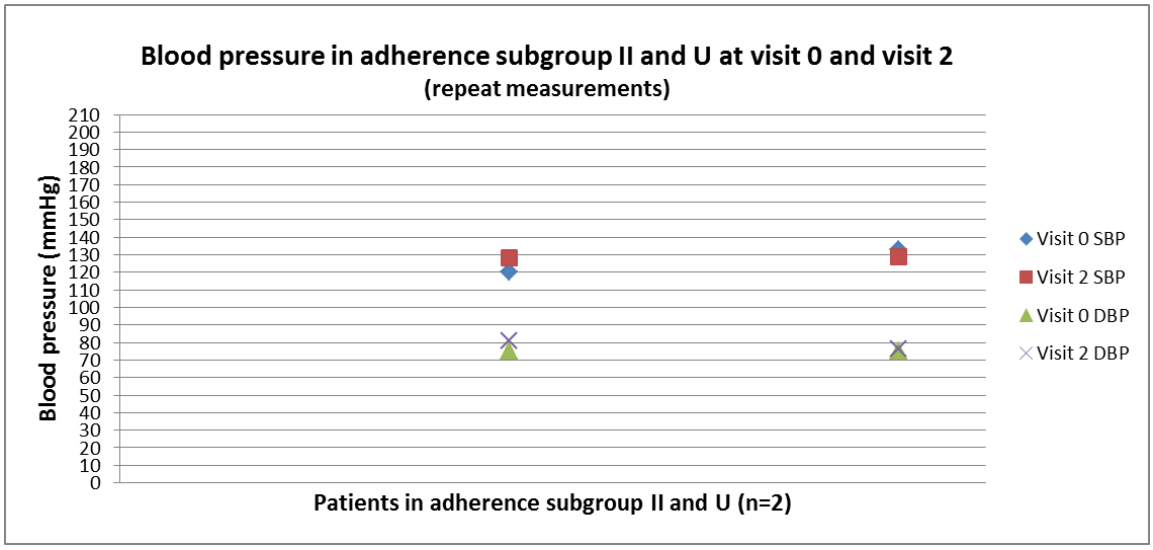


Figure 3.22. SBP and DBP at visit 0 and visit 2 based on repeat BP measurements for each patient in adherence subgroup II and U.

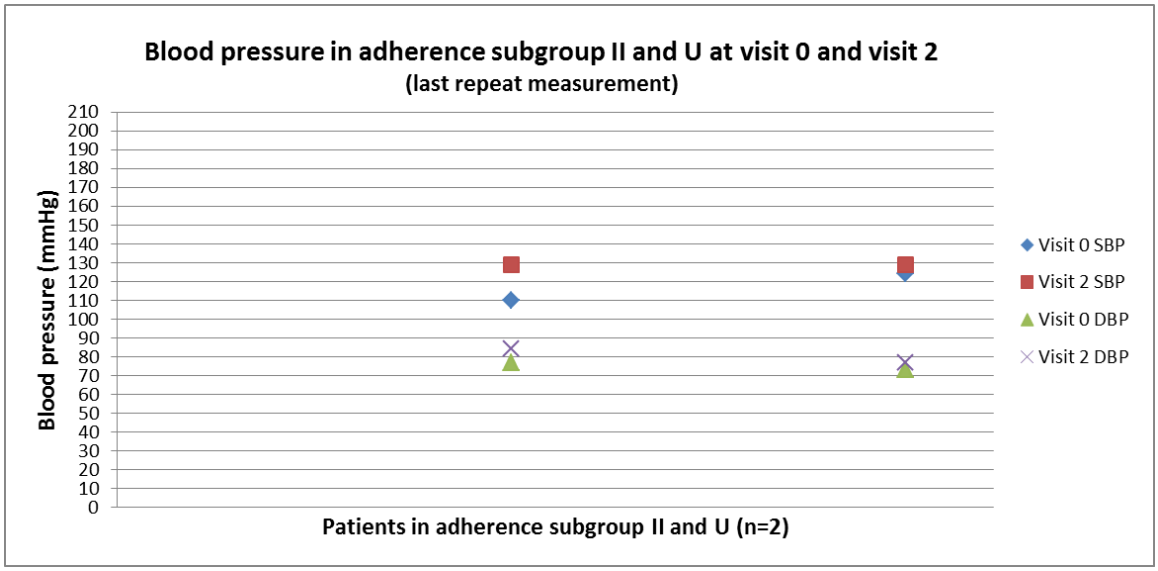


Figure 3.23. SBP and DBP at visit 0 and visit 2 based on last repeat BP measurement for each patient in adherence subgroup II and U (n=2).

3.3.7.7.2 Within-group blood pressure (BP) changes between visit 0 and visit 2 in Intentional non-adherent irrational and Unintentional non-adherent (II and U) subgroup

The changes in SBP and DBP between visit 0 and visit 2 for each patient in subgroup II and U (n=2) are demonstrated in Figures 3.24 and 3.25. The II and U subgroup showed a worsening in BP between visit 0 and visit 2. However, the results indicate a BP control in this adherence subgroup.

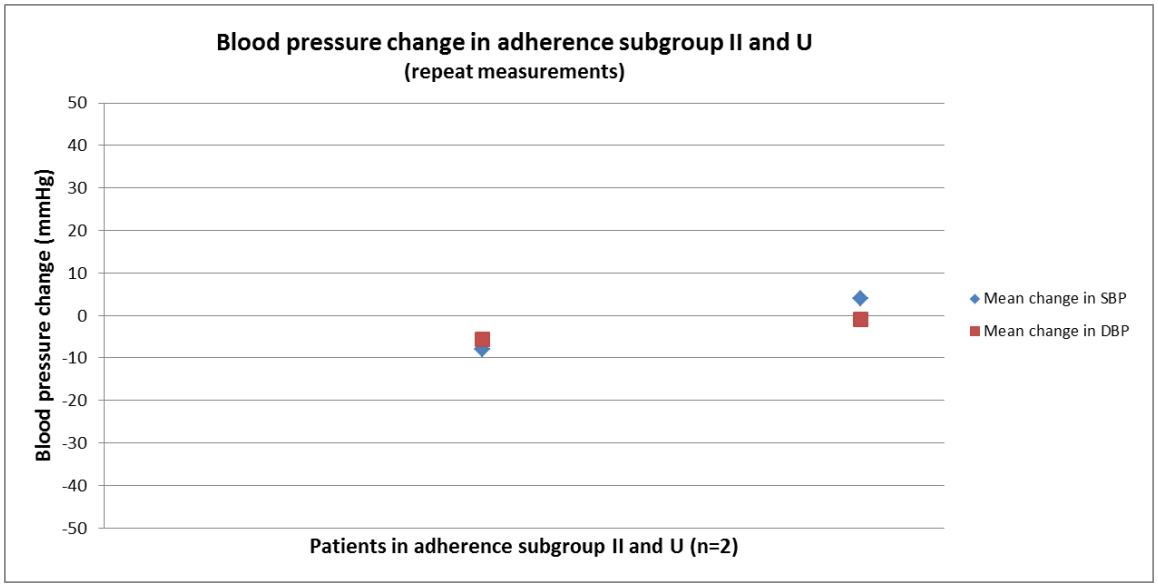


Figure 3.24. Change in SBP and DBP (between visit 0 and 2) based on repeat BP measurements for each patient in adherence subgroup II and U (n=2).

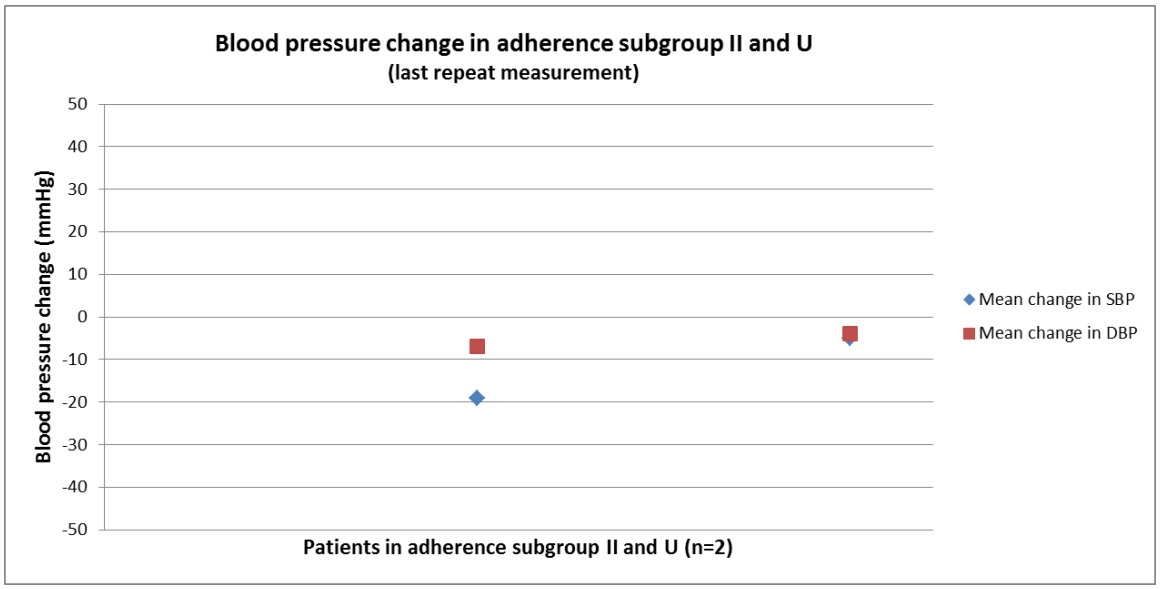


Figure 3.25. Change in SBP and DBP (between visit 0 and 2) based on last repeat BP measurement for each patient in adherence subgroup II and U.

3.3.7.8 Unintentional non-adherent (U) subgroup (n=59)

Table 3.19 shows two different ways of representing the BP and pulse results based on a) repeat measurements or b) the last repeat measurement. There was basically was no difference in BP and pulse based on repeat measurements in comparison to the last repeat measurement. BP and pulse results at visit 0 and visit 2 are displayed in Table 3.19. The table shows the SBP at visit 0 being around 140 mmHg, DBP at 80 mmHg and pulse at 69 beats/minute. At visit 2 the SBP is 135 mmHg, DBP 80 mmHg and a pulse around 70 beats/minute. The U subgroup had BP control.

The change in blood pressure and pulse between visit 0 and visit 2 is displayed in Table 3.20. There was in the U subgroup a small improvement in SBP and almost no change in DBP or pulse between visit 0 and visit 2**.**

Table 3.19. BP and pulse results for the U subgroup (n=59) at visit 0 and visit 2 respectively.

Visit 0 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)	Visit 2 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	138	80	69	**Mean**	135	80	70
Median	140	80	67	**Median**	135	81	68
StDev	13	8	12	**StDev**	13	10	12
SE	2	1	2	**SE**	2	1	2

Visit 0 (last repeat)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)	Visit 2 (last repeat)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	137	80	69	**Mean**	135	80	69
Median	138	80	68	**Median**	135	79	66
StDev	13	9	12	**StDev**	13	10	12
SE	2	1	2	**SE**	2	1	2

Abbreviations: StDev: Standard deviation; SE=Standard error

Table 3.20. Changes in SBP, DBP and pulse between visit 0 and visit 2 are shown for U subgroup (n=59).

Change between visit 0 and visit 2 (repeats)	SBP (mmHg)	DBP (mmHg)	Pulse (beats/minute)
Mean	3	0	-1
Median	2	0	0
StDev	13	9	9
SE	2	1	1
Change between visit 0 and visit 2 (last repeat)	**SBP (mmHg)**	**DBP (mmHg)**	**Pulse (beats/minute)**
Mean	2	1	0
Median	1	1	1
StDev	13	10	9
SE	2	1	1

Abbreviations: StDev: Standard deviation; SE=Standard error

3.3.7.8.1 Within-group blood pressure (BP) changes between visit 0 and visit 2 in Unintentional non-adherent subgroup (U)

The changes in SBP and DBP between visit 0 and visit 2 for each patient in subgroup U (n=59) are demonstrated in Figures 3.26 and 3.27. There was in the U subgroup a small improvement in SBP and almost no change in DBP. This adherence subgroup had a BP control.

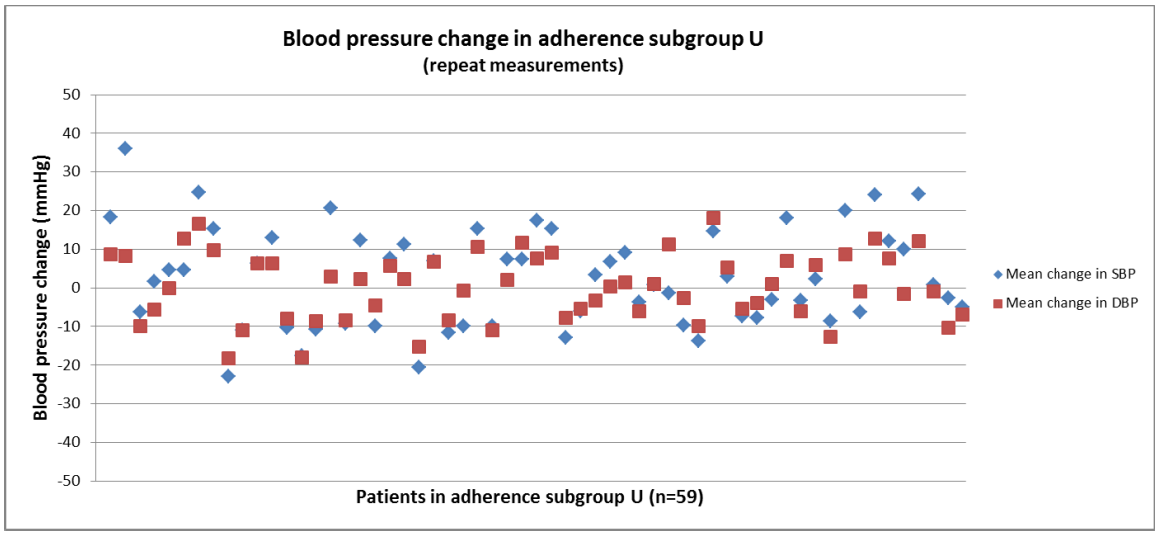


Figure 3.26. Change in SBP and DBP (between visit 0 and 2) based on repeat BP measurements for each patient in adherence subgroup U.

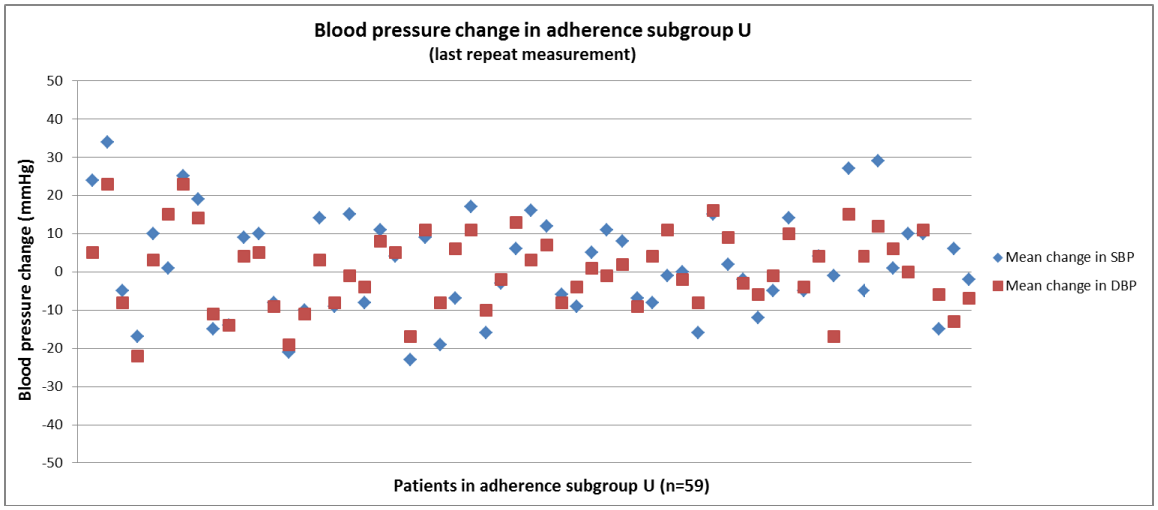


Figure 3.27. Change in SBP and DBP (between visit 0 and 2) based on last repeat BP measurement for each patient in adherence subgroup U.

3.3.7.9 Comparison on between-group blood pressure (BP) results: subgroups Adherent (A) (n=62) and Unintentional non-adherent (U) (n=59)

Subgroups A (n=62) and U (n=59) are pretty much matched groups with similar sizes. It is worthwhile to do a comparison on these subgroups to determine between-group differences in SBP and DBP at visit 0 and visit 2 respectively.

The SBP and DBP at visit 0 for each patient in subgroups A or U are demonstrated in Figures 3.28 and 3.30. Likewise, the SBP and DBP at visit 2 is demonstrated in Figures 3.29 and 3.31.

For subgroup A, the mean value of SBP at visit 0 is around 140 mmHg and DBP around 80 mmHg (Figures 3.28 and 3.30). When reaching visit 2 the mean value of SBP reaches a level of 136 mmHg and a DBP almost remaining at 80 mmHg (Figures 3.29 and 3.31). Thus, this adherence subgroup has a stable BP control.

Subgroup U had at visit 0 an SBP at around 140 mmHg and a DBP at 80 mmHg (Figures 3.28 and 3.30). At visit 2 the SBP is 135 mmHg and DBP at 80 mmHg (Figures 3.29 and 3.31). Thus, the U subgroup had BP control.

Figures 3.28, 3.29, 3.30 and 3.31 confirm that there is a wider scatter in BP data in the A subgroup in comparison to the U subgroup.

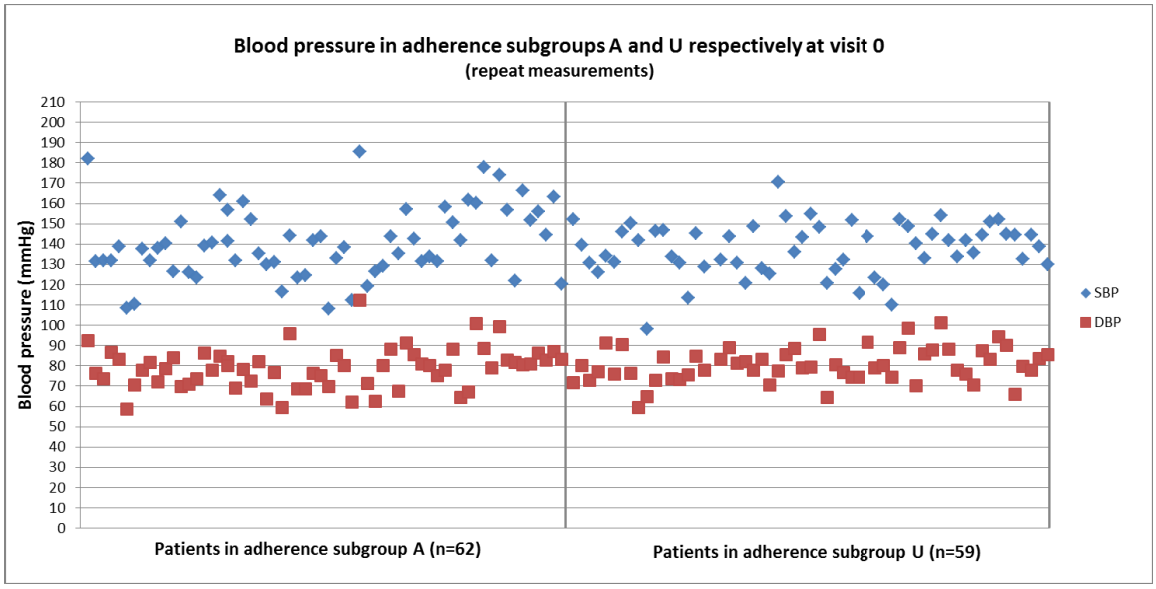


Figure 3.28. SBP and DBP at visit 0 based on repeat BP measurements for each patient in adherence subgroups A (n=62) and U (n=59).

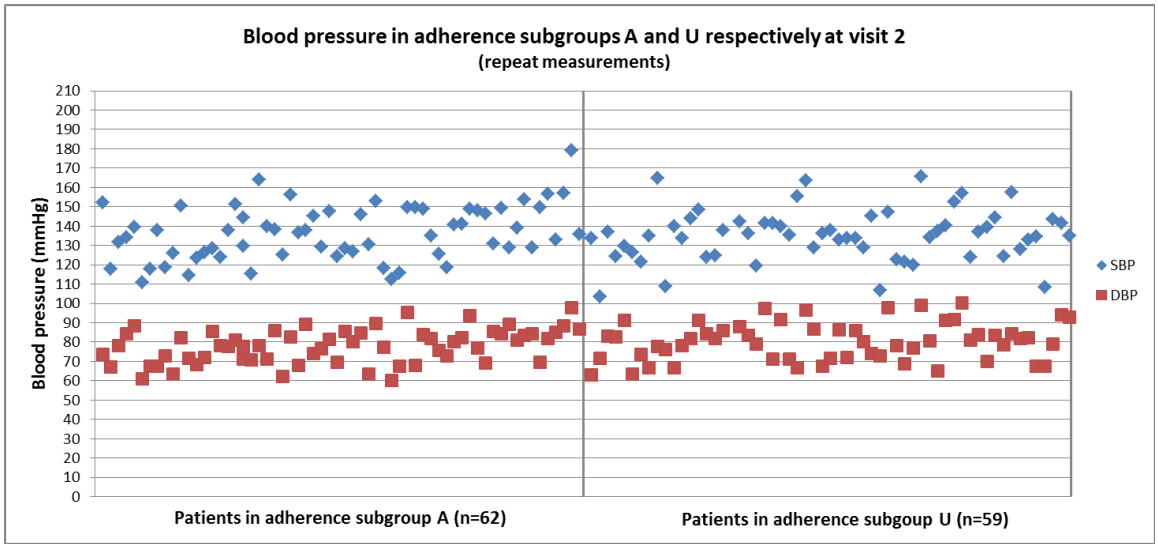


Figure 3.29. SBP and DBP at visit 2 based on repeat BP measurements for each patient in adherence subgroups A (n=62) and U (n=59).

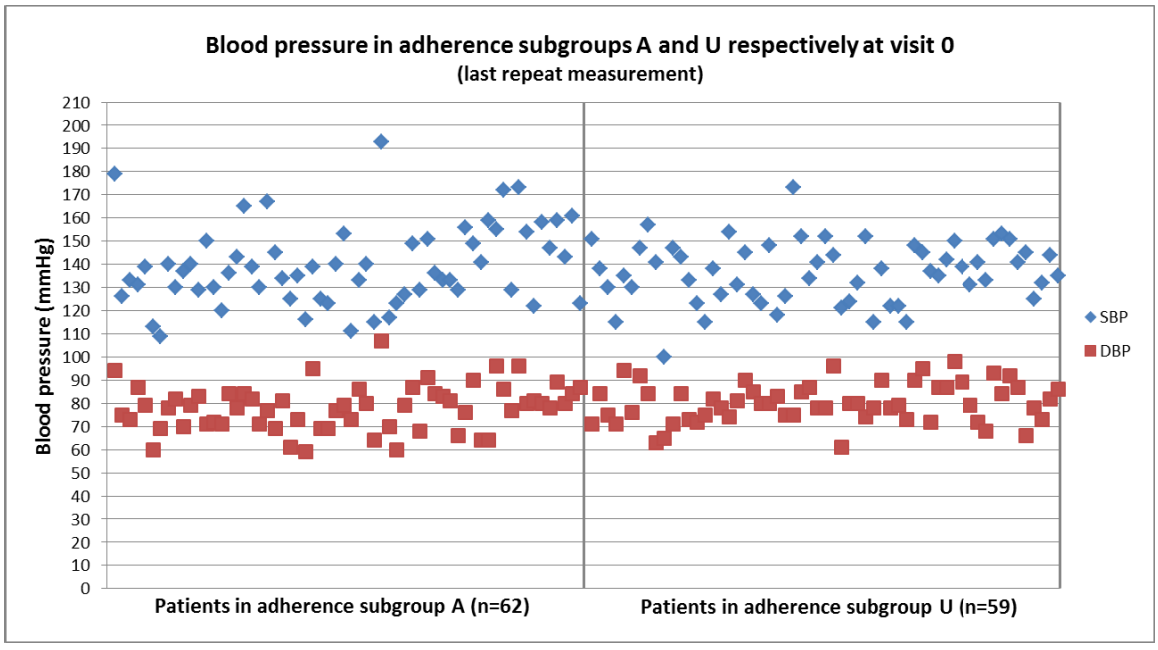


Figure 3.30. SBP and DBP at visit 0 based on last repeat BP measurement for each patient in adherence subgroups A (n=62) and U (n=59).

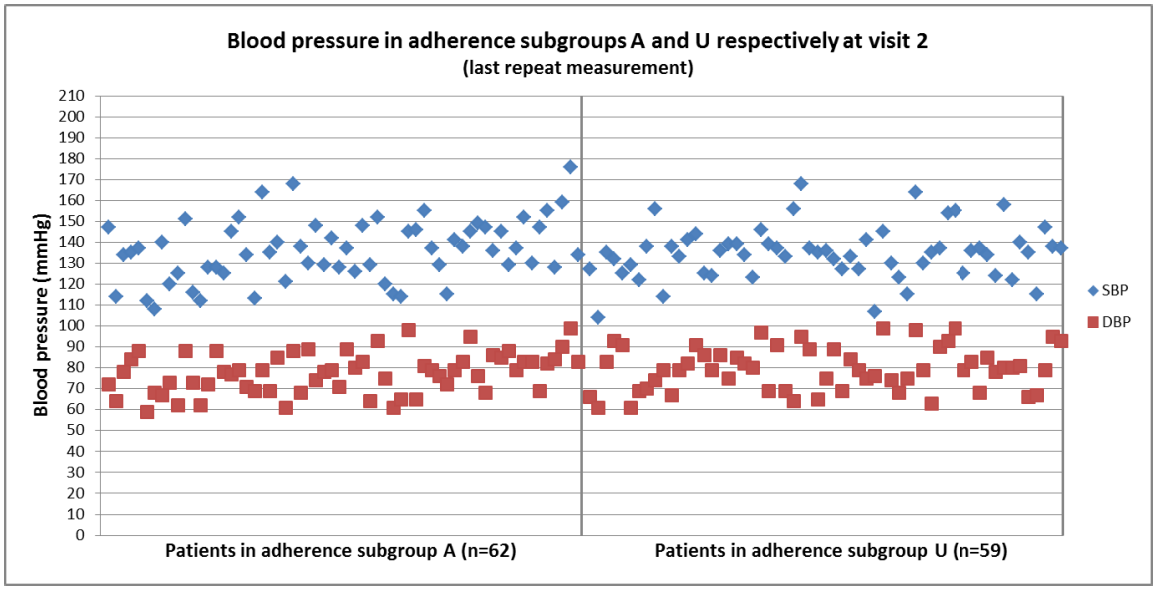


Figure 3.31. SBP and DBP at visit 2 based on last repeat BP measurement for each patient in adherence subgroups A (n=62) and U (n=59).

3.3.8 Scores from adherence screens

Scores from questionnaires used in adherence screens at visit 0 and visit 2 are presented in Table 3.21 as mean values for the overall study population and each adherence subgroup. When everything was piled together to compare the results on adherence screens from visit 0 with visit 2, there is really no difference.

Table 3.21. Mean values of scores from questionnaires used in adherence screens for the cohort and each adherence subgroup. There is really no difference when everything is piled together comparing the scores at visit 0 and visit 2.

Visit 0

	8-item MMAS[1*]	MARS score[2]	MARS adj.[3]	BMQN[4]	BMQC[5]	BMQO[6]	BMQH[7]
Cohort (n=153)	7.5	24.3	4.9	3.7	2.1	3.0	2.1
A (n=62)	8.0	25.0	5.0	3.7	1.9	2.9	2.0
A and IR (n=4)	8.0	25.0	5.0	3.8	2.1	2.4	2.2
A and II (n=5)	8.0	25.0	5.0	3.8	2.6	3.2	2.8
II (n=13)	6.9	22.9	4.6	3.8	2.7	3.4	2.5
IR and U (n=2)	6.5	23.0	4.6	4.3	2.0	3.5	1.9
II and U (n=2)	7.5	21.5	4.3	3.0	1.8	3.5	1.6
U (n=59)	7.0	23.9	4.8	3.6	2.1	3.0	2.2

Visit 2

	8-item MMAS[1*]	MARS score[2]	MARS adj.[3]	BMQN[4]	BMQC[5]	BMQO[6]	BMQH[7]
Cohort (n=153)	7.6	24.4	5.0	3.6	2.0	3.1	2.1
A (n=62)	7.9	24.7	4.9	3.6	1.9	3.0	1.9
A and IR (n=4)	8.0	25.0	5.0	3.4	2.2	2.4	2.0
A and II (n=5)	8.0	25.0	5.0	4.2	2.3	3.2	2.4
II (n=13)	7.6	24.1	4.8	3.8	2.5	3.3	2.3
IR and U (n=2)	8.0	25.0	5.0	3.9	2.3	3.3	2.4
II and U (n=2)	6.5	23.5	4.7	3.3	1.9	3.4	1.7
U (n=59)	7.4	23.9	5.2	3.5	2.0	3.1	2.1

[1]8-item Morisky Medication Adherence Scale score [2]Medication Adherence Report Scale score [3]Medication Adherence Report Scale adjusted mean score [4]Beliefs about Medicines Questionnaire Specific Necessity score [5]Beliefs about Medicines Questionnaire Specific Concerns score [6]Beliefs about Medicines Questionnaire General Overuse score [7]Beliefs about Medicines Questionnaire Harm score *Use of the ©MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E. Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772.

3.3.9 Spearman correlation

Spearman correlation was performed to see if a correlation existed between the scores from the adherence screens (8-item MMAS, MARS, and BMQ) and the outcomes SBP, DBP, and pulse. Inspection of the results showed that BMQ scale scores were dominant with significant and very significant correlations to SBP, DBP and pulse outcomes. The significant and very significant results from this analysis are displayed in Tables 3.22 and 3.23 (see asterisks).

Table 3.22. Significant and very significant results from Spearman correlations for the cohort (n=153). A Spearman correlation was performed with the scores from the adherence screening questionnaires and the SBP, DBP and pulse outcomes (repeat measurements, last repeat measurements) at visit 0 and visit 2 respectively.

Cohort (n=153)

Adherence screen	Repeat measurements Visit 0	Spearman's rho	p value	n
8-item MMAS[1]	**DBP**	-0.17**	0.033	153
BMQ Necessity scale	**DBP**	-0.22*	0.006	153
BMQ Necessity scale	**Pulse**	0.19**	0.018	153
BMQ Concerns scale	**DBP**	0.22*	0.005	153
BMQ Overuse scale	**SBP**	0.26*	0.001	153
BMQ Overuse scale	**DBP**	0.23*	0.005	153

Adherence screen	Repeat measurements Visit 2	Spearman's rho	p value	n
8-item MMAS[1]	**SBP**	0.17**	0.036	147

Adherence screen	Last repeat measurement Visit 0	Spearman's rho	p value	n
MARS score	**DBP**	-0.16**	0.048	153
MARS adjusted mean score	**DBP**	-0.16**	0.048	153
BMQ Necessity scale	**DBP**	-0.19**	0.016	153
BMQ Necessity scale	**Pulse**	0.19**	0.022	153
BMQ Concerns scale	**DBP**	0.23*	0.005	153
BMQ Overuse scale	**SBP**	0.28*	<0.001	153
BMQ Overuse scale	**DBP**	0.24*	0.003	153
BMQ Harm scale	**SBP**	0.16**	0.043	153

Adherence screen	Last repeat measurement Visit 2	Spearman's rho	p value	n
8-item MMAS[1]	**SBP**	0.19**	0.022	147

**=statistically significant at the 0.01 level (2-tailed) **=statistically significant at the 0.05 level (2-tailed)*

[1]Use of the ©MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E. Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772.

Table 3.23. Statistically significant results from Spearman correlations for adherence subgroups A (n=62) and U (n=59). A Spearman correlation was performed with the scores from the adherence screening questionnaires and the SBP, DBP and pulse outcomes (repeat measurements, last repeat measurements) at visit 0 and visit 2 respectively.

A subgroup (n=62)

Adherence screen	Repeat measurements Visit 0	Spearman's rho	p value	n
BMQ Concerns scale	**DBP**	0.29**	0.023	62
BMQ Concerns scale	**Pulse**	-0.35*	0.005	62
Adherence screen	**Last repeat measurement Visit 0**	**Spearman's rho**	**p value**	**n**
BMQ Concerns scale	**DBP**	0.26**	0.043	62
BMQ Concerns scale	**Pulse**	-0.36*	0.004	62

U subgroup (n=59)

Adherence screen	Repeat measurements Visit 0	Spearman's rho	p value	n
BMQ Necessity scale	**SBP**	-0.34*	0.008	59
BMQ Overuse scale	**DBP**	0.31**	0.017	59
Adherence screen	**Last repeat measurement Visit 0**	**Spearman's rho**	**p value**	**n**
BMQ Necessity scale	**SBP**	-0.36*	0.005	59
BMQ Concerns scale	**DBP**	0.29**	0.028	59
BMQ Overuse scale	**DBP**	0.34*	0.008	59

*****=*statistically significant at the 0.01 level (2-tailed)* ******=*statistically significant at the 0.05 level (2-tailed)*

3.3.10 Multivariate analysis of variance (MANOVA)

Post-hoc analysis with Tukey's HSD and Bonferroni showed significantly higher SBP ($p<0.05$) in II subgroup compared to subgroups A or U. The post-hoc analysis also showed patients who received interventions C+I had significantly higher SBP ($p<0.05$) in comparison to patients receiving either of the interventions I or C+I+R (Table 3.24).

Table 3.24. Post-hoc analysis for MANOVA at visit 2. The post-hoc analysis with Tukey's HSD and Bonferroni showed a significantly higher SBP ($p<0.05$) in II subgroup compared to A and U subgroups. Patients who received interventions C+I had significantly higher SBP ($p<0.05$) compared to patients receiving interventions I or C+I+R.

Post-hoc analysis (Tukey's HSD) adherence subgroups	**Mean difference in visit 2 SBP (mmHg)**	**Standard error**	**p value**
Subgroup II - Subgroup A	15	5	0.030
Subgroup II - Subgroup U	16	5	0.016
Post-hoc analysis (Bonferroni) adherence subgroups	**Mean difference in visit 2 SBP (mmHg)**	**Standard error**	**p value**
Subgroup II - Subgroup A	15	5	0.040
Subgroup II - Subgroup U	16	5	0.020
Post-hoc analysis (Tukey's HSD) interventions	**Mean difference in visit 2 SBP (mmHg)**	**Standard error**	**p value**
Interventions C+I - Interventions I	8	3	0.047
Interventions C+I - Interventions C+I+R	9	3	0.020
Post-hoc analysis (Bonferroni) interventions	**Mean difference in visit 2 SBP (mmHg)**	**Standard error**	**p value**
Interventions C+I - Interventions C+I+R	9	3	0.022

3.3.11 Multivariate analysis of covariance (MANCOVA)

Post-hoc analysis with Bonferroni adjustment showed significantly higher DBP ($p<0.05$) in II subgroup compared to subgroup IR and U when having monotherapy/polypharmacy as a covariate (Table 3.25).

Table 3.25. Post-hoc analysis with monotherapy/polypharmacy as a covariate. The post-hoc analysis with Bonferroni adjustment showed a significantly higher DBP ($p<0.05$) in II subgroup compared to subgroup IR and U.

Post-hoc analysis (Bonferroni) adherence subgroups	Mean difference in visit 2 DBP (mmHg)	Standard error	p value
Subgroup II - Subgroup IR and U	24	8	0.040

3.4 Discussion

3.4.1 Screening of antihypertensive medication adherence and blood pressure (BP) assessment of community pharmacy hypertensive patients

The present pilot study sought to I) assess the feasibility of performing adherence screening in community pharmacy hypertensive patients, II) to deliver community pharmacist-led interventions targeting adherence status according to adherence subgroups to optimise blood pressure (BP) and III) establish (a) any issues with the adherence screen (b) any indications of outcomes from the allocated interventions (c) any indication if certain interventions were detrimental.

This pilot study shows potential value in screening antihypertensive adherence in community pharmacy. Patients can be categorized into different adherence subgroups. In addition, the present study indicates that generic interventions might not suit all patients. Certain adherence subgroups appear to react negatively to the pharmaceutical interventions used, possibly with detrimental outcomes on adherence and their blood pressure control.

The power calculation should be interpreted in the light of the present study is a feasibility study. Despite some subgroups not reaching the 25-patient target, the target number of patients was achieved for the A and U subgroups. Results from the present study show that there exist subgroups which are more definitive than others. This is reflected by the number of patients in each subgroup. The A (n=62), II (n=13), U (n=59) subgroups all appear to be discrete groupings. By contrast, the IR subgroup (n=0) appears not to be discrete. In addition, there is a cross-over between subgroups A and IR (n=4), A and II (n=5), IR and U (n=2), II and U (n=2). The subgroups with the smaller numbers of patients appear to be the more problematic groups. Intuitively, the smaller subgroups consist of patients with more issues,

e.g. patients who may worry about their medicines and those patients who change their views. The findings from this study indicate that patients who appear to conform to specific adherence sub-type groups are likely to require personalised interventions to facilitate the enhancement of their adherence. It is likely that these interventions will differ depending on the subgroup attribution. However, the exact nature of the optimal intervention requires further confirmation studies.

Tracking results of the changes in SBP and DBP across adherence subgroups results often deviate from the clinically acceptable -10 to +10 mmHg band, exhibiting more extreme changes as indicators of patient adherence worsen. This confirms that poor medication adherence results in unsatisfactory blood pressure control in the present pilot study.

3.4.2 Patients requesting for blood pressure (BP) and pulse measurement at visit 1

BP and pulse measurement at visit 1 demonstrates the importance of the community pharmacist as a provider of information and extended clinical services in healthcare, i.e. a clinician with the competence of performing hands-on examinations and making clinical decisions. The present study also demonstrates examples of patients requesting a hands-on physical examination involving diagnostics from community pharmacists.

3.4.3 Blood pressure (BP) outcome in the cohort

The mean age of the patients in the study cohort was 66 years, an age group with high SBP probably resulting at least in part from arterial stiffness increasing with age. The obtained statistical significant SBP change between visit 0 and 2 is clinically meaningful as SBP is the most important BP marker regarding cardiovascular risk (Kaplan *et al*., 2015; Warrell, 2010).

Elevated SBP has a larger effect on angina, myocardial infarction, and peripheral arterial disease. However, compared to SBP, an elevated DBP has a stronger effect on abdominal aortic aneurysm (Rapsomaniki *et al*., 2014).

3.4.4 Blood pressure (BP) outcome in adherence subgroups

3.4.4.1 Adherent (A) subgroup (n=62)

Patients in subgroup A generally exhibited blood pressure change between -10 to +10 mmHg over the study period and therefore appear to be adherent: their adequate blood pressure control reflecting the use of antihypertensive medication in an appropriate, stable manner. However, the present study results indicate that targeted pharmacist intervention may produce some additional benefits in blood pressure control even in this adherent group. A significant number of patients in the A subgroup exhibited optimal blood pressure control. However, there was a significant level of noise in the blood pressure data. The variance in BP readings in the A subgroup could possibly be explained if some patients have deliberately manipulated their responses in assessments of their attitudes towards adherence, which is a known limitation of self-reported adherence screening (Wiffen *et al*., 2012).

3.4.4.2 Intentional non-adherent rational (IR) subgroup (n=0)

The IR subgroup did not appear to be a discrete grouping making it appropriate to consider possible flaws in the adherence subgroup categorization. The adherence screening questionnaires may not accurately assess these patients. However, another explanation is that pharmacological management is generally adequate in the patient cohort.

It is postulated that in an efficient healthcare system, the extent of any IR subgroup would be low: findings otherwise might imply poor prescribing. Almost 50% of patients discontinue administering their antihypertensive medication during the first year of treatment (Kaplan *et al*., 2015; Mancia *et al*., 2013). Therefore, the likelihood of identifying patients who conform to an IR group type, from patients newly commenced on antihypertensive therapy would be higher compared to those who have already been stabilized on antihypertensive pharmacotherapy for a significant period.

3.4.4.3 Intentional non-adherent irrational (II) subgroup (n=13)

Patients in the intentional non-adherent irrational subgroup exhibited highly variable blood pressure control (some worse, some better). Post-hoc analysis from MANOVA at visit 2 showed that in this subgroup there was a significantly higher SBP compared to A and U subgroups. It is likely that II patients have a higher blood pressure, which indicates they are probably not taking their therapy. The present pilot study may well indicate that community pharmacist intervention in those patients with irrational beliefs about antihypertensive medicines (the II subgroup) could reinforce such misbeliefs leading to further deterioration in their blood pressure control.

As clinical practitioners, pharmacists need to be aware that practice interventions are not necessarily universally good in outcome in certain subsets of the patient population. Hence, the present pilot study indicates the proposition for targeted interventions on an individual basis. Working on the ethical principle "*primum non nocere*" (first do no harm), this aspect of improving patient adherence requires further study in terms of identifying risks associated with pharmaceutical interventions.

3.4.4.4 Mixed subgroups: Adherent and Intentional non-adherent rational (A and IR) (n=4); Adherent and Intentional non-adherent irrational (A and II) (n=5); Intentional non-adherent rational and Unintentional non-adherent (IR and U) (n=2); Intentional non-adherent irrational and Unintentional non-adherent (II and U) (n=2)

The inconsistency in adherence subgroup allocation resulting from the application of the 8-item MMAS, MARS and BMQ necessitated some patients being simultaneously assigned into four different mixed adherence categories: A and IR; A and II; IR and U; II and U.

Patients who were allocated to subgroups A and IR or A and II appeared to exhibit stable BP control; generally, these patients were close to being fully adherent.

Subgroup IR and U showed an improvement in BP, whereas the II and U subgroup had a worsening in BP. A possible explanation is that the IR and U subgroup may have benefited from the intervention. Also, it could be that the scope of IR is diminished in comparison to U within this subgroup considering there being good therapeutics in the entire cohort. The explanation for a worsening in BP for the II and U subgroup could possibly be traced back to the reasoning for the BP outcome in the II subgroup. In any case, the patient numbers were very low in the IR and U, II and U subgroups. Hence, the blood pressure results for these two mixed adherence subgroups should be interpreted with caution.

3.4.4.5 Unintentional non-adherent (U) subgroup (n=59)

The present study indicates the potential for improvements in blood pressure control through targeted pharmaceutical intervention in those patients appearing to be unintentionally non-adherent. The intervention package provided to this adherence subgroup shows it may be effective in reaching blood pressure reduction.

3.4.5 Comparability with other studies and covariates influencing blood pressure (BP) outcome

Comparability of study results has not been carried out since no other studies have been found reporting similar results. Therefore, it is difficult to pinpoint definite reasons for the obtained BP results in this pilot study. However, examining factors which determine blood pressure variability provide a possible guidance to reasons although not being definite.

There are numerous factors that could affect blood pressure. Some patients would have controlled BP due to being adherent to the oral antihypertensive medication therapy and good antihypertensive therapeutics. In those patients where there is a reduction in BP, patients may, for example, commence an exercise regimen or implement a dietary measure to reduce sodium intake. By contrast, a BP elevation could be caused by a white-coat effect or stress prior to or during the study visit. Moreover, in Sweden, there is a long season with a cold climate. The fact that visit 0 and/or visit 2 could have occurred during the cold season may have contributed to increased peripheral resistance in some patients, thereby causing a BP elevation.

As there is an indication of significance to a covariate such as monotherapy/polypharmacy, a larger study would probably show some significant issues with covariates which are of importance in future planning of adherence research and in the therapy and assessment of hypertension. Consequently, some of the variations in blood pressure might be explained by factors not controlled for in the study design. Nonetheless, the results are strongly suggestive that patients with hypertension can be routinely allocated to generic adherence subtypes in a community pharmacy, with the intent of targeting appropriate interventions to optimize antihypertensive medication adherence.

It has been shown that with some disease states, increasing polypharmacy results in lower adherence for various reasons (Anthierens *et al*., 2010; Lehane and McCarthy, 2007; WHO, 2003; Volpe *et al*., 2010). By large, the interventions C+I+R or C+I was provided to patients on more than two antihypertensive drugs. These patients had a worsening in BP, showing these interventions were provided when non-adherence was present. This suggests that it may well be medication non-adherence that causes the negative values in blood pressure. Despite non-adherence, it should be investigated if there are pathophysiological factors contributing to the resistant hypertensive state. This would best be done by the pharmacist referring the patient to a specialist hypertension clinic.

3.4.6 Interventions and blood pressure (BP) outcome

The questionnaire scores from adherence screens at visit 0 and 2 strictly underpin the hypothesis that any adherence intervention probably will not work for everybody. Besides, the post-hoc analysis in MANOVA at visit 2 showed that to patients which interventions C+I was delivered exhibited a worsening in blood pressure outcome. This being intuitively correct since C+I was to a great extent delivered to the II subgroup, whereas intervention I was targeted to the A subgroup and C+I+R to the U subgroup, suggesting there is a possibility that reinforcement of multiple interventions in those patients who are accepting of these methods may be the best way forward. Consequently, there are indications in the present study that in patients who are adherent, informatics and basic reminder interventions may be suitable and in patients who are intentionally or unintentionally non-adherent, reminders could be effective.

3.4.7 Variability in blood pressure (BP) and pulse results

The reflection of a significant statistical between-group difference at visit 0 and a non-significant between-group difference at visit 2 in a pragmatic approach portrays the variability in the BP and pulse results that are leading to flaws in the statistics which need to be interpreted with caution.

Inspection of the numerical values of BP and pulse results at visit 0 and visit 2 display a numerical variation. See examples 1-3 in Figures 3.32 to 3.37.

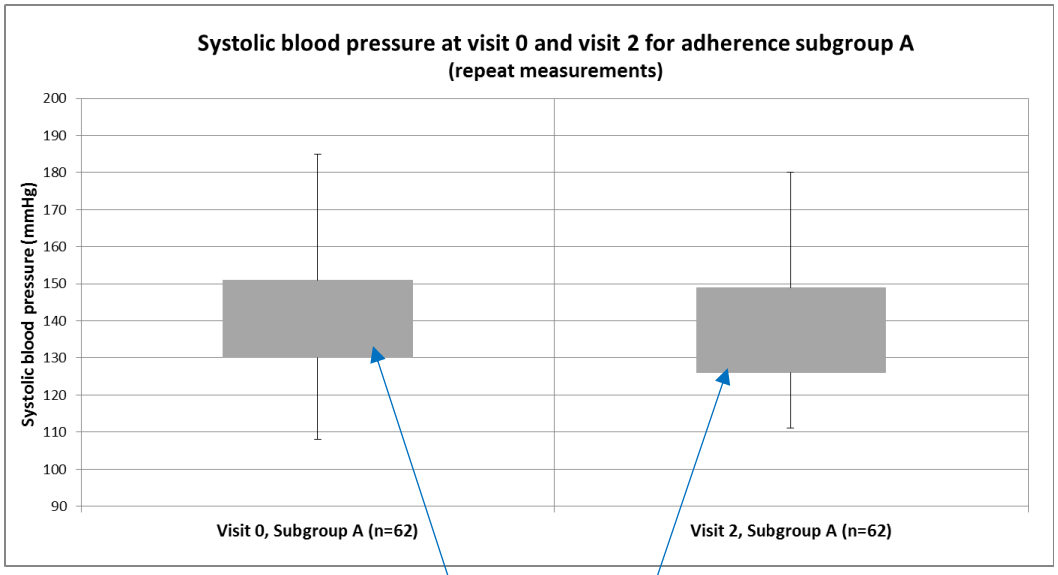


Figure 3.32. Box-and-whisker plot with systolic blood pressure (mmHg) based on repeat measurements at visit 0 and visit 2 for adherence subgroup A.

1. Subgroup A having a higher SBP level at visit 0 and visit 2 relative to subgroup A and IR.

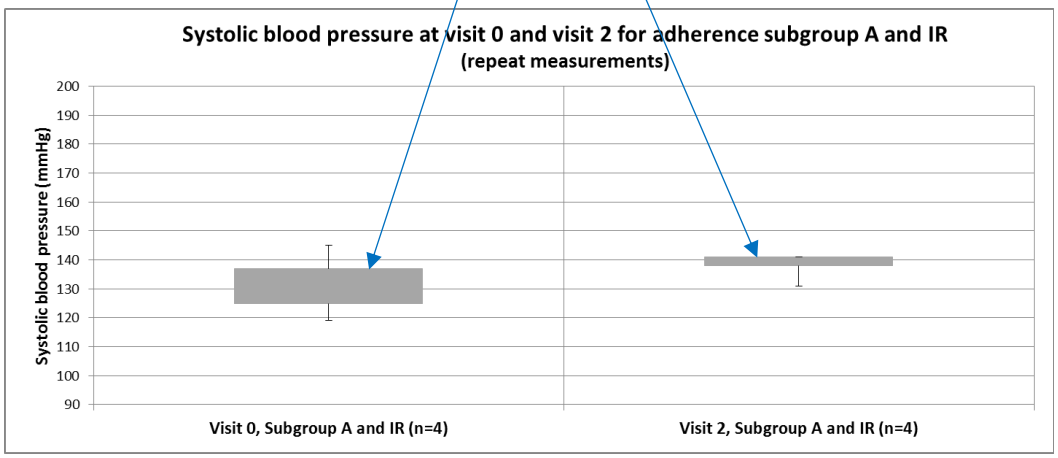


Figure 3.33. Box-and-whisker plot with systolic blood pressure (mmHg) based on repeat measurements at visit 0 and visit 2 for adherence subgroup A and IR.

Figures 3.32 and 3.33 show the SBP levels for A and A and IR subgroups at visit 0 and visit 2 respectively. Arrows initiating from box number 1 point at the SBP levels at visit 0 and visit 2 for each of these two adherence subgroups. It is seen a higher SBP level for A subgroup both at visit 0 and visit 2 in comparison to the SBP levels for subgroup A and IR.

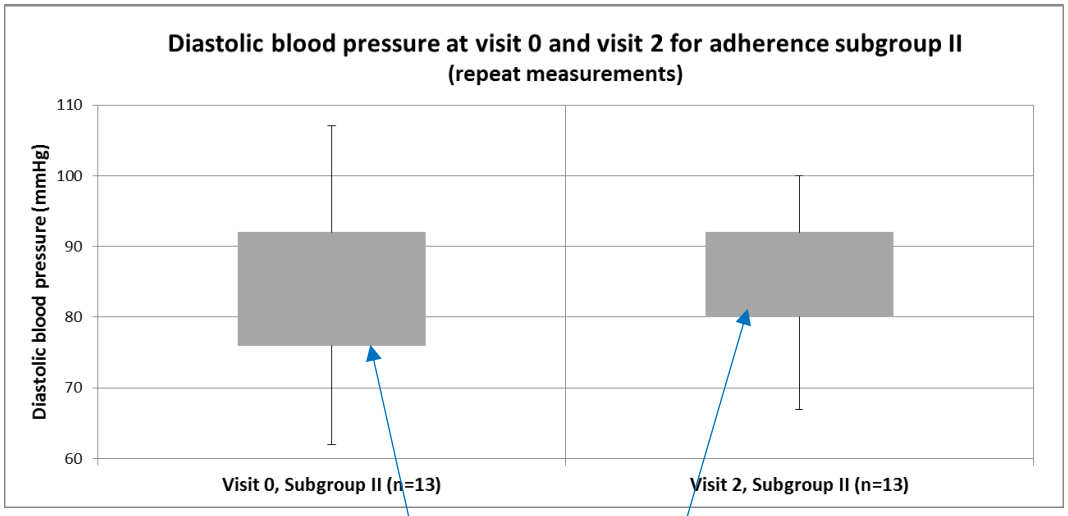


Figure 3.34. Box-and-whisker plot with diastolic blood pressure (mmHg) based on repeat measurements at visit 0 and visit 2 for adherence subgroup II.

2. Subgroup II having a higher DBP level at visit 0 and visit 2 relative to subgroup A and II.

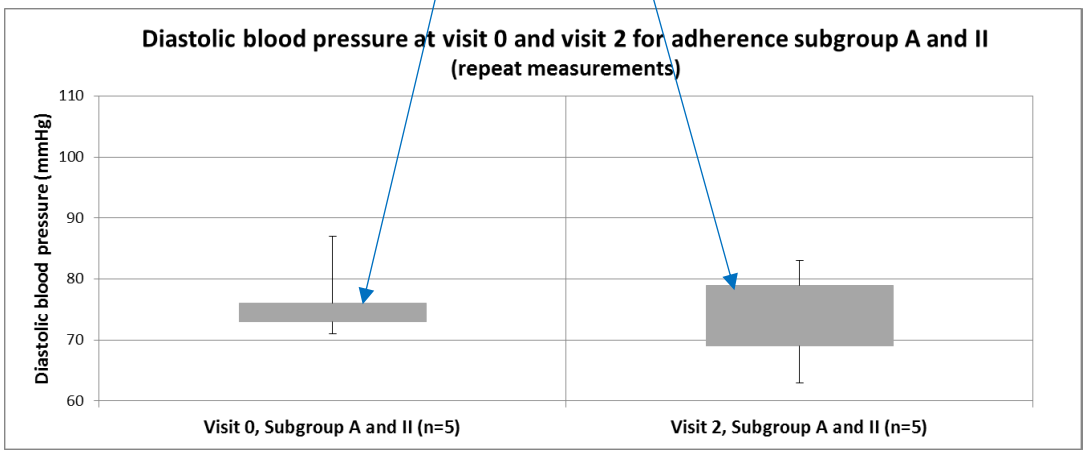


Figure 3.35. Box-and-whisker plot with diastolic blood pressure (mmHg) based on repeat measurements at visit 0 and visit 2 for adherence subgroup A and II.

Figures 3.34 and 3.35 show the DBP levels for II and A and II subgroups at visit 0 and visit 2 respectively. Arrows initiating from box number 1 point at the DBP levels at visit 0 and visit 2 for each of these two adherence subgroups. It is seen a higher DBP level for II subgroup both at visit 0 and visit 2 in comparison to the DBP levels for subgroup A and II.

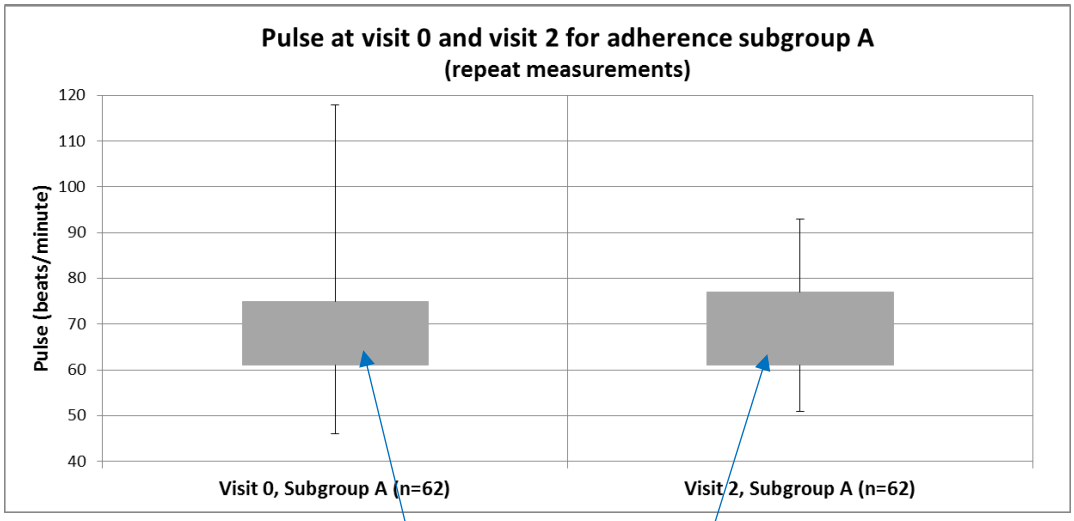


Figure 3.36. Box-and-whisker plot with a pulse (beats/minute) based on repeat measurements at visit 0 and visit 2 for adherence subgroup A.

3. Subgroup II having a higher pulse level at visit 0 and visit 2 relative to subgroup A and II.

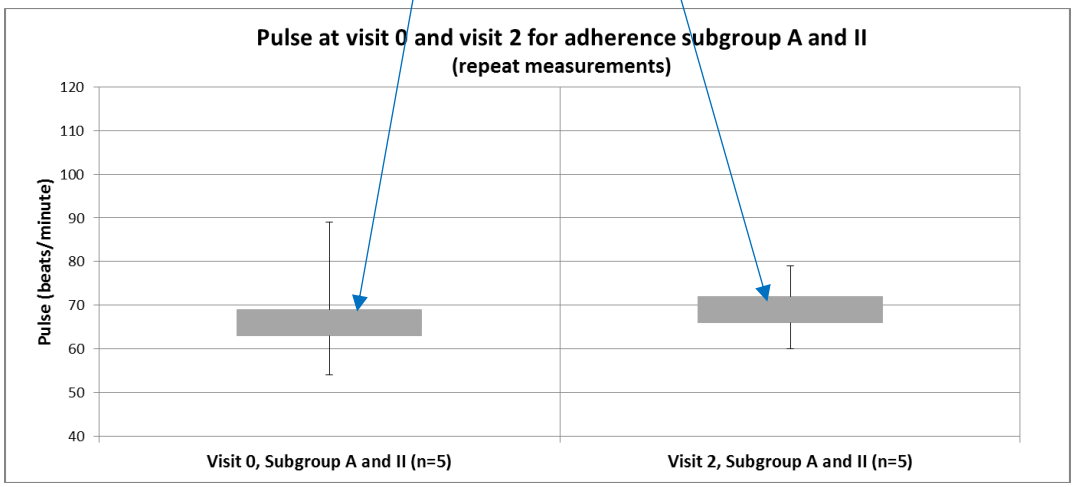


Figure 3.37. Box-and-whisker plot with a pulse (beats/minute) based on repeat measurements at visit 0 and visit 2 for adherence subgroup A and II.

Figures 3.36 and 3.37 show the pulse levels for A and A and II subgroups at visit 0 and visit 2 respectively. Arrows initiating from box number 1 point at the pulse levels at visit 0 and visit 2 for each of these two adherence subgroups. It is seen a higher pulse level for A subgroup at both visit 0 and visit 2 compared to pulse levels for subgroup A and II.

Although a pragmatic statistic approach has been employed, this does not match up to a situation when some subgroups relative to other subgroups at visit 0 would have higher levels of BP and pulse resulting in a larger magnitude of BP and pulse change relative to other subgroups once reaching visit 2 due to all adherence subgroups ending up at the same BP and pulse level at visit 2.

3.4.8 Limitations

First, this pilot study was a relatively modest size study in a single community pharmacy. It was too small to accommodate the constraints of the statistical methods employed. However, evidence from this small study shows that within the constraints of the statistical tests there are some significant findings. In a larger study, this would maybe show some larger issues with adherence and the major cardiovascular parameters. Thus, it is possible that a larger study allowing discrimination of larger numbers of patients in each adherence subgroup would show significant differences in important cardiovascular parameters relevant to hypertension.

Secondly, the questionnaires used for the adherence screens were used outside of their validation, i.e. how they are supposed to be used. Since there was no proper correlation between the questionnaires scores from the adherence screens and the blood pressure outcomes, it is not the fault of the questionnaires. Rather, it must do with the way the

questionnaires were employed in the study. The questionnaires were merely used as tools to categorize patients in adherence subgroups and not used in their strictest sense as adherence screens. There was no validation of the thresholds of questionnaire scores in this study. Each of the questionnaires used in adherence screens in this study has been validated previously, but only for evaluation of adherence to a single agent.

Thirdly, there is a potential limitation in that a patient may respond differently to a general adherence scale when applied to a specific pathological condition. However, it has been assumed that scales developed to be non-specific for disease could be applied to hypertension. Furthermore, the current study design did not restrict to patients receiving antihypertensive monotherapy, rather patients were asked to consider their therapy for hypertension in general. Besides, there was no confirmation of the patient's diagnosis of hypertension with the patient's physician. It was mainly considered that the patient was on oral antihypertensive pharmacotherapy. It is possible that patients' attitudes to adherence might vary between different antihypertensive drugs even though they are prescribed for the same condition.

Finally, the study pharmacist not making a full objective judgement during adherence subgroup categorization could create a potential bias. It is also recognized that the study pharmacist and/or patients were not blinded in the present study creating a possibility for selection bias and a Hawthorne effect. There is a potential flaw that patients may sit between adherence groups, which is a limitation when doing this in practice. Despite this, it informs about the future requirement for a refinement of the allocation process to simplify this process for use in community pharmacy practice.

3.4.9 Restrictions on the use of pharmacy refill data

The intention was to calculate pharmacy refill data from pill count and an electronic dispensing database. It was soon clear that the pill count method did not work due to reasons such as the patient forgetting to bring the medicine/s bottle/s to the study pharmacy during medicine refills etc.

In the Swedish community pharmacy system, the study pharmacist could have collected pharmacy refill data from the Swedish electronic dispensing database *Läkemedelsförteckningen*. If it was done, MPR would have shown or not shown an interesting result. However, the attempt to use MPR was halted due to structural methodological reasons. The electronic dispensing database was not feasible because the study pharmacist's understanding of Swedish law is that it does not permit using the data in the dispensing database for research purposes, despite prior ethical approval and patient consent. Nonetheless, in another healthcare system, MPR might show an interesting result.

3.4.10 Future work

To refine the methods, it would be of importance to confirm with the medical practitioner the number of patients with a hypertension diagnosis and identify the number of patients who visit the physician and then do not even present their prescription. In a future study, when screening medication adherence, the effect of the total drug load of the patient should be considered including therapies for conditions other than hypertension.

To build on this pilot study the first step is to conduct a larger comparative trial to evaluate if targeted community pharmacist-led interventions really work. It would be necessary to test

various combinations of interventions in different sub-types e.g. would IR subgroup benefit from counselling to establish the nature of their rational problem and implement any solutions. This would be done by performing a four-armed parallel randomized trial with subdivision into study groups. There would be measures of adherence in all four study groups. To see if the study groups behave differently the intentional non-adherent patients would be in group A and B. Group A would receive an intervention with reminders, whereas group B would receive an informatics type of intervention. Unintentional non-adherent patients would belong to either group C or D. Group C would receive reminders targeting forgetfulness, whereas group D would receive informatics.

The second step would involve a larger study to confirm the prevalence of the smaller adherence subgroups and identify the measures to which the patients in these subgroups would respond to. In these smaller subgroups, the patients might be really showing significance in pathology and negative outcomes. There is at least one small, but important group of individuals who are resistant to being adherent. However, due to the relatively small patient cohort in the present study, the results should be treated with caution and a larger study should be conducted.

3.5 Conclusions

The pilot study has shown that it is likely to be useful to categorize community pharmacy hypertensive patients into adherence subgroups based on their responses to questionnaire format adherence screens. It is feasible to deliver different intuitively designed community pharmacist-led interventions to each adherence subgroup to optimize antihypertensive medication adherence whilst assessing blood pressure control and changes in attitudes to

adherence. The results from the smaller subgroups form a small, but still an important group of patients who are problematic from an adherence perspective. The present study is suggestive of that there are likely to be exposed significances in a larger comparative trial.

4 General discussion

This chapter will provide a general discussion based on the studies described in chapters 2 and 3.

4.1 The research domain community pharmacy practice, hypertension, and adherence

The current research programme was focused on community pharmacy practice in relation to cardiovascular disease, specifically examining patients with hypertension in a community pharmacy setting. It might be argued the systematic review presented in Chapter 2 solely focused on studies with an outcome to optimize blood pressure, whereas the community pharmacy-based *in vivo* adherence project in Chapter 3 examined the optimisation of patients' antihypertensive adherence with the intent to optimize BP control. Indeed, the overarching theme of the present research was not the specifics of patients' adherence to antihypertensive medication. Rather, the focus was aimed at ensuring that BP was improved in patients, albeit that the participants' primary therapy comprised antihypertensive pharmacotherapy.

Developments in pharmacy practice have promoted disease state management, i.e. not explicitly concentrating on medicines management, as a clear focus for pharmacy practitioners, with the patient and the illness at the centre of care. Patient adherence to medication is often used as an outcome measure for research (Armour *et al*., 2008). Hence, in the present community pharmacy studies a convenient model to use to optimize BP was through assessment of antihypertensive medication adherence with accompanying BP measurement.

4.2 Research findings

4.2.1 A systematic review of pharmacist-led interventions within a community pharmacy setting aimed at optimising blood pressure (BP) in patients undergoing oral antihypertensive medication therapy

A systematic review was conducted (see Chapter 2) to explore the scope of the evidence-base within the research domain of mixed-method studies. The focus was community pharmacist-led interventions within a community pharmacy setting aimed at blood pressure optimisation in patients undergoing oral antihypertensive medication therapy. The overall aim of the systematic review was to explore the research area as a scoping exercise.

4.2.1.1 Findings from the systematic review

Outputs in varying quantity were derived from five selected electronic biomedical databases. Visual interpretation of funnel plots with grey literature revealed publication bias. However, the statistical test for funnel plot asymmetry showed the opposite. These opposing findings highlight the subjective role of visual inspection of funnel plots. In addition, these observations point to the possibility of reasons other than publication bias to explain funnel plot asymmetry such as poor methodological quality, heterogeneity between studies and chance (Higgins and Green, 2011).

4.2.1.1.1 Patients

It is highlighted in the present systematic review that patient screening should be standardized. A standardization process could involve the creation of an algorithm in relation to patient characteristics, screening, and recruitment. Moreover, community pharmacy

working together with GPs has an important function in the framework to optimize adherence (Herborg *et al*., 2008). Collaboration with physicians and other healthcare staff would provide points of referral of patients to the community pharmacy. This would facilitate the foundation on to which to build the community pharmacist's provision of pharmaceutical care to patients. However, it should be noted that this would be a complementary methodological approach to self-referred patients. In addition, in those healthcare systems where clinical data sharing is allowed, such an inter-professional collaboration would enable clinical data sharing.

4.2.1.1.2 Interventions

There is a wide spectrum of pharmaceutical interventions targeted at improving patient adherence: this raises the problem of which interventions are effective (and in which situations). Established interventions are often complex and appear to be delivered to patients without consideration of individual attitudes to pharmacotherapy (Horne *et al*., 2001; Hugtenburg *et al*., 2013; Nieuwlaat *et al*., 2014; Stewart *et al*., 2014; Stewart *et al*., 2015). Currently, the evidence from the present systematic review points to community pharmacy-based, pharmacist-led interventions lead to a positive effect, no effect or a negative effect. Hence, it may even be detrimental to intervene in some patients.

Since the present feasibility study in Chapter 3 appears to indicate that patients could be subgrouped according to their attitudes to adherence, there is a need for well-designed studies which could establish the patient subgroups likely to benefit from particular intervention. In addition, those patients who may not benefit from pharmaceutical intervention should be identified.

4.2.1.1.3 Comparators

In the present systematic review, there is a wide representation of the randomised controlled trial study design with intervention and control groups. From the perspective of the risk of bias, the RCT design provides the lowest risk. However, there are studies in the present systematic review with a before-and-after comparison resulting in increased risk of bias (Khan *et al*., 2011; Wiffen *et al*., 2012). Indeed, there also exist evaluations of outcomes in patient subgroups, which is a starter to recognizing the individual patient approach to pharmaceutical interventions.

4.2.1.1.4 Outcomes

Blood pressure outcome among the studies in the present systematic review is highly variable mirroring the variation in study design among the included studies. The present meta-analysis shows interventions either leading to no effect or a minor positive effect on BP. Consequently, the outcome of the meta-analysis is possible since pharmaceutical interventions with regards to medicines usage are simplistic. As such, these interventions do not work. In the light of this, it should be recognized that manoeuvres which community pharmacists take with a good intention could even be detrimental to patients. In fact, the outcome from the present meta-analysis stands in contrast to the premise of earlier research where it appears that intervention/s produce a positive effect. Another possible explanation relating to the meta-analytic outcome is the low quality of some studies in the present systematic review leading to unsatisfactory results. Among the studies in the present systematic review, there is an array

of outcomes to which researchers investigate, making it difficult to know which outcomes are of relevance for assessing the pharmacy service.

4.2.1.1.5 Study design

Measures of consistency show heterogeneity existing between the included studies in the present systematic review. Different study designs among the studies in the present systematic review make the research unnecessarily complex. Moreover, the barriers on current study designs are not represented in the evidence-base. Thus, all this calls for a requirement of standardization of study design. Standardising the study design would mean to apply a study design which lowers the risk of bias. This would include the study population rigorously being defined. Moreover, it should be considered if the patient is on monotherapy or polytherapy since the total drug load would have an impact on adherence. In addition, the patient's attitudes to different antihypertensive medications may vary. Study duration should set to last at least 6 months, allowing for an optimal data collection period. Adherence assessment would include a triangulative approach of different adherence screening tools considering different adherence models have their own strengths and limitations.

4.2.2 A pilot study evaluating the impact of community pharmacist-led interventions to optimize antihypertensive medicines adherence

The community pharmacy-based *in vivo* adherence study (see Chapter 3) sought to assess the feasibility of screening antihypertensive medicine adherence in community pharmacy hypertensive patients and delivering pharmacist-led interventions targeting adherence status according to adherence subgroups to optimise blood pressure (BP). The pilot study was

performed in a 153-ambulatory hypertensive patient population at a community pharmacy in Uppsala, Sweden with 147 patients completing all study visits.

The study findings indicate that it is possible and beneficial to categorize patients into different adherence subgroups, which supports the concept that generalised adherence interventions might not suit all patients. Furthermore, the pilot study highlights the potential value in screening antihypertensive adherence in community pharmacy. It is feasible to perform this service in a community pharmacy.

In some adherence subgroups identified in the present study, certain targeted interventions appear to optimize BP when compared to other interventions. For example, pharmaceutical interventions involving memory aids or reminders appear to be particularly effective in those patients exhibiting an unintentional attitude towards their non-adherence. By contrast, there was some indication that patients in certain adherence subgroups react negatively to pharmaceutical interventions possibly with detrimental outcomes on adherence and their blood pressure control. Using reminder interventions in those exhibiting intentional, irrational attitudes to non-adherence could well reinforce negative perceptions of medicines usage exacerbating the avoidance of prescribed medication use.

4.2.2.1 Blood pressure (BP) outcomes

4.2.2.1.1 Cohort (n=153)

There was a statistically significant SBP reduction between visit 0 and visit 2 in the cohort. This outcome is of clinical importance since it is highlighted SBP is a marker connected to cardiovascular risk, but it is also shown that an elevated SBP has a larger effect on angina, myocardial infarction, and peripheral arterial disease. By contrast, an elevated DBP has a

stronger connection to abdominal aortic aneurysm (Kaplan *et al*., 2015; Rapsomaniki *et al*., 2014; Warrell, 2010).

4.2.2.1.2 Adherent subgroup (A) (n=62)

Patients in subgroup A had a stable blood pressure control although showing administration of antihypertensive medicines in a stable manner. The results indicate the intervention resulted in additional benefit for this subgroup. There is noise in the BP data, possibly indicating that some patients may not have given accurate indications of their attitudes to adherence, which is a known limitation of self-reported adherence (Wiffen *et al*., 2012). Patients in this subgroup are unlikely to be at risk unless contrary clinical evidence is obtained.

4.2.2.1.3 Intentional non-adherent rational (IR) subgroup (n=0)

There was no IR subgroup existing alone which raises two possible explanations: I) there either may be a flaw in the adherence subgroup categorization and/or II) there is good therapeutics in the entire cohort.

4.2.2.1.4 Intentional non-adherent irrational (II) subgroup (n=13)

The II subgroup had highly variable BP control. In addition, post-hoc analysis from MANOVA at visit 2 showed a significantly higher SBP compared to A and U subgroups. Therefore, it is intuitive that those patients having higher BP are not using their antihypertensive medication optimally. Hence, pharmacists should be aware that delivering interventions to patients with irrational beliefs may strengthen the position of their beliefs, resulting in worsened BP control.

4.2.2.1.5 Mixed subgroups: Adherent and Intentional non-adherent rational (A and IR) (n=4); Adherent and Intentional non-adherent irrational (A and II) (n=5); Intentional non-adherent rational and Unintentional non-adherent (IR and U) (n=2); Intentional non-adherent irrational and Unintentional non-adherent (II and U) (n=2)

There was inconsistency in the allocation process resulting from the application of 8-item MMAS, MARS and BMQ. Thus, patients were categorized in mixed adherence subgroups A and IR; A and II; IR and U; II and U. Patients in the A and IR; A and II subgroups had stable BP control considering these patients were almost fully adherent. Subgroup IR and U showed an improvement in BP possibly showing a beneficial effect of the intervention. Another possible explanation is the scope of IR being low compared to U since there may be good therapeutic control in the cohort. The II and U subgroup showed a worsening in BP control, possibly owing to the II portion of this mixed subgroup. The patient numbers in the IR and U; II and U subgroups were very low. Consequently, the results for these two subgroups should be treated with caution.

4.2.2.1.6 Unintentional non-adherent (U) subgroup (n=59)

BP improvements for the U subgroup was achieved showing the intervention package may be effective in reaching BP reductions for this subgroup.

4.3 Implications for the profession, practice, and policy

Accessibility of the community pharmacy and pharmacist to the public potentially constitutes a positive environment for disease management programmes. Being a complementary function to the general practitioner, the pharmacist can assist in the management of hypertension (WHO, 2005).

The community pharmacy-based *in vivo* project in Chapter 3 has highlighted the feasibility of conducting a pharmacist-led, community pharmacy-based hypertension service.

The findings from the present feasibility study suggest that patients should not receive generic interventions irrespective of their adherence status. Hence, the findings stand in direct contrast to the interventional approach included in the RCT investigating the effectiveness of the New Medicines Service (NMS) in England. The NMS is a community pharmacy service in England provided to patients prescribed a new medication for a chronic condition. To participate in the service, patients can be self-referred, referred by their prescriber or identified by the community pharmacist. The intervention being face-to-face or telephone consultation with the patient one to two weeks after including the patient into the service. A follow-up consultation is held two to three weeks after the initial consultation. During the consultation, drug-related problems the patient is experiencing will be resolved. Referral to the prescriber may done if required (Elliott *et al*., 2014; Elliott *et al*., 2016). However, the intervention in the NMS is generic in nature and does not consider that patients have individual attitudes to adherence.

The systematic review in Chapter 2 has examined the patient screening process, to establish which patients are likely to benefit from the community pharmacy service. The present study has investigated the contribution of the community pharmacist in hypertension management being suggestive of pharmacist-led interventions leading to highly variable outcomes being positive, negative or no effect. Again, this indicates that generic pharmacist-led interventions cannot be delivered to ambulatory hypertensive patients in a community pharmacy. Thus, beginning to look at groups of patients for individual interactions with interventions is the proper way to go forward.

Indeed, the community pharmacy-based *in vivo* adherence project suggests a way forward to categorize patients into adherence subgroups based on their adherence status assessed through a set of adherence screening questionnaires whilst assessing BP and pulse. Consequently, it appears that the community pharmacist could direct the pharmacy service to those patients who are in greatest need of interventions. In addition, there is an indication that some pharmaceutical interventions could be avoided where they might be detrimental to certain patients.

Notwithstanding the above, the research base needs to be expanded to obtain definitive results on which to base practice and policy. This would enhance the possibility of extending the role of the community pharmacist to patient-centred hypertension care and make the community pharmacy a hub for hypertension management being a complementary approach to the physician. A standardization of processes relating to the delivery of community pharmacy services in patients with hypertension is required.

As suggested by Mancia and co-workers, a team-based approach may be the best way forward for hypertension management (Mancia *et al*., 2013). A different perspective has been taken in the present studies. In fact, the system for hypertension management suggested here could be a point were ”at risk” hypertensive patients are referred to by physicians and other healthcare staff. Collaboration with the physician would enable the confirmation of the hypertension diagnosis and other clinical data. However, at present, when a pharmacist needs to obtain clinical data, this is often hampered owing to legal aspects, links between professions and healthcare system factors (Farris *et al*., 2005; Mansoor *et al*., 2015). Efforts should be put into investigating solutions to overcoming these challenges. Information for the pharmacist to

obtain during assessment consist of patient data, disease data and drug data (Cipolle *et al*., 2012).

For the delivery of pharmaceutical care in pharmacy practice, it requires a management system which embraces logistics, evaluation and financial aspects, e.g. adequate number of competent pharmacists and pharmacy staff, private or semi-private space, availability of literature, a management system to schedule appointments and documenting the pharmaceutical care (Cipolle *et al*., 2012; Puspitasari *et al*., 2015). Moreover, the location of the pharmacy, as well as a neighbouring GP practice, increases the likelihood of implementation of the service (Puspitasari *et al*., 2015).

Hence, accommodating special pharmacists on appointment to fully take on the role of patient-centred pharmaceutical care is mandatory. The level of community pharmacist competency is a relevant parameter to ensure delivery of quality pharmaceutical care. In addition, it is of importance to establish the working role of the community pharmacist in order not to cross the professional boundaries of other health care staff.

4.4 Limitations

4.4.1 Systematic review

During the screening process, the databases retrieved some interesting studies (Amariles *et al*., 2012; Blenkinsopp *et al*., 2000). However, these studies did not meet the systematic review inclusion criteria.

A draw-back in some studies is that they did not report data for inclusion in the meta-analysis or assessing publication bias. It was not always successful to reach study authors to obtain data even though the contact information was available.

The application of the EPOC study design criteria was affected by the mixed-methods approach. However, the studies which did not conform to the EPOC study design criteria were marked in the results section in Chapter 2. Even though the systematic review employed a mixed-methods approach, it is considered not to have any impact on the quantitative and qualitative outputs.

4.4.2 Community pharmacy-based *in vivo* adherence project

This was a small-scale study, though a large-scale from the perspective of this pilot study being conducted by an independent single researcher in a single community pharmacy. Thus, there was no expectation to obtain fully definitive results. However, the results are highly suggestive of there being groups of patients who are resistant to therapy/intervention and there being variability within a specific adherence subgroup. Therefore, this pilot study provides an intimation of points were the likely success will be.

For the community pharmacy-based *in vivo* adherence project, a pragmatic approach to the statistical analysis was sought. However, this was not always feasible and the results were interpreted in the light of those constraints.

4.4.2.1 Non-pharmacological interventions

It is recognized that non-pharmacological interventions such as recommending physical activity and restricting sodium in the diet can be valuable and have a pronounced effect on BP

(Mancia *et al*., 2013; Nadar and Lip, 2009; Warrell *et al*., 2010). In the community pharmacy-based *in vivo* adherence project, non-pharmacological interventions were not measured relating to performing or following any of those kinds of interventions. It was not considered if the patient initiated or halted any non-pharmacologic intervention and any potential impact it could have on BP. In addition, there was no measurement included on any change in following non-pharmacologic interventions.

There is no strong evidence in the pilot study to suggest that patients were changing their behaviour relating to non-pharmacologic interventions during the study. Consequently, there is not much reason to believe changes in non-pharmacological behaviour had any impact on BP readings.

4.4.2.2 Challenges encountered during the research endeavor

There was no real issue in recruiting patients for the pilot study. Besides, there was a low amount of patient drop-outs. This shows there is a public interest for community pharmacy-based, pharmacist-led services. Working collaboratively between the UK and Sweden unmasked some unexpected challenges, as community pharmacy regulations and operating systems somewhat differ between these countries. This led to some redesign of the planned research methods and data collection: differences between ethical permissions and patient data management systems were of most significance in necessitating these modifications. Nonetheless, pharmaceutical research such as the community pharmacy-based *in vivo* adherence project has been able to utilize a shared experience and knowledge to promote the advancement of pharmaceutical care to improve BP in patients with hypertension.

As the endorsed definition of pharmaceutical care includes improved quality of life, neither an assessment of the quality of life aspect or a pharmacoeconomic evaluation was conducted in the community pharmacy-based *in vivo* project (Hepler and Strand, 1990). Also, the project did not follow the research proposal on a setup with monotherapy or polypharmacy groups. The reason for this was not being able to frame these outcome measures within the authentic practice situation, considering that all research was carried out by a single researcher in a single community pharmacy. In addition, MPR was not used due to the understanding of the Swedish law that does not permit collection of MPR data in pharmacy practice. Moreover, the adherence screening questionnaires were not used as adherence measurement tools to measure adherence, rather to allocate patients into adherence subgroups. Despite this, the project went along meeting all the other stated aims and objectives.

4.4.2.3 Study design

The gold standard in clinical research is to conduct a blinded randomized controlled trial. However, as the community pharmacy-based *in vivo* adherence project employed a before- and after study design with a single researcher in a single community pharmacy, it is difficult to know how to conduct a blinded trial as there are different elements to different patients by default. In addition, in a community population, there is always the risk of contamination in the study by a patient receiving one type of intervention talking to another patient receiving another type of intervention.

It is acknowledged, in terms of bias, that there are potentially more reliable, less risk methodological approaches. However, since this was a pilot study being conducted by a single researcher in a single community pharmacy with a defined patient population, the

before-and-after design was deemed to be the most robust as each patient was their own control. There is a possibility of risk of bias from the perspective of the single investigator/assessor. However, the psychosocial way to influence the risk on BP readings and questionnaire responses is judged not to have any larger impact on the results.

4.4.2.4 Interventions and persistence in blood pressure (BP) control

The present pilot study did not incorporate a study design which enabled to explore the persistence of effect caused by the interventions. This requires a different study over a longer period to investigate such an effect. It was not feasible to carry out such a long study within the specified time frame. Consequently, it is not known if these types of interventions lead to persistence in effect.

A pharmacist is likely to see a hypertensive patient more often than a general practitioner as they collect refills of their medication. Intuitively, any kind of intervention involving regular reminders and interaction with the community pharmacy is likely to give persistent and beneficial effects. However, providing the patient with education does not cause a persistent effect on behaviours surrounding medicines administration (Lee *et al*., 2006). A systematic review by Conn and co-workers, 2016 provided an assessment of studies with adherence interventions in adult patients with adherence issues. The authors conclude face-to-face interventions being important as well as connecting medication-taking with routines and reminders. The latter is more likely to produce a persistent effect since it is a continuous intervention in comparison to when a patient receives education, which is provided at a single time point or within a set time frame (Conn *et al*., 2016). In contrast, there is an intimation in the present pilot study there being a certain subgroup where it might be detrimental to be

persistent in reminders and such an approach may reinforce the incorrect views in those patients who do not respond well to traditional medications and interventions.

4.5 Future directions

4.5.1 General considerations

As suggested in Chapter 3, a first step is to conduct a larger comparative trial to evaluate if targeted community pharmacist-led interventions really work. It would be necessary to test various combinations of interventions in different adherence subgroups. The systematic review and community pharmacy-based *in vivo* adherence project indicate the possibility of negative outcome arising from pharmacist-led interventions. There is an indication of at least one resistant patient subgroup to pharmacist-led interventions. Thus, caution with pharmacist-led interventions to a certain subset of patients. A future study should establish the prevalence of these patient subgroups and a decision pathway on how to proceed with treating these patients. Some patients may require referral to specialist hypertension care. There is a definite possibility to gear up towards a longer study duration with improved study design such as the application of RCT trials and conducting larger multi-centre studies to provide definite evidence for the community pharmacy-based service. This would possibly throw light on the methodological deviations occurring in the community pharmacy-based *in vivo* adherence project and pave the way for refinement of the methods.

In addition, further future work would include:

- Going forward to evaluate the interventions in each adherence subgroup relating to effect and persistence in effect bearing in mind any subgroup being resistant to pharmaceutical interventions which could reinforce the incorrect views of the patients.

- Antihypertensive medicines adherence would be interesting to investigate as an outcome measure. In those healthcare systems where it is allowed to go forward with MPR, it would be of interest to explore this outcome looking at MPR at different time points.

- Consider a study design with data collection through a triangulated methodological approach which manifests the data collection from different perspectives possibly creating more robust data.

- A collaborative approach with GPs and other healthcare staff should be sought. Not all same health-systems have the same attitudes on physician and community pharmacy interactions. However, there is a huge opportunity for community pharmacists to take on these clinical pharmacy roles in situations where the setting is such not being feasible to provide sufficient physicians or where physicians claim to be underfunded and overworked. Therefore, this study has shown that it is physically and technically possible that patients can be monitored in the community pharmacy. In a future study, it would be interesting to investigate if the methods used in this pilot study could equally be applied to the management of other disease states.

- The working role of the community pharmacist in the light of a changing professional role should be defined, not crossing the borders of the other

healthcare professions which could lead to an acceptance of the extended pharmacist role by other healthcare staff.

- To embrace the concept of pharmaceutical care, quality of life as an outcome measure should be included and assessed.

- Further investigation into the aspect of pharmacist prescribing as an interventional element. In a randomized controlled trial conducted by Tsuyuki and co-workers, 2015, in community pharmacies, hospitals and primary care teams in Alberta, Canada, the impact of pharmacist prescribing on BP control was investigated in patients 18 years and above. The results were a clinically and statistically significant effect of pharmacist prescribing on BP control (Tsuyuki *et al*., 2015).

- Pharmacists, professional pharmacist organizations, other healthcare staff and governments should through communication make the community pharmacy services known to the public.

4.5.2 Financing pharmaceutical care service in community pharmacy

Pharmacy services are moving into being a part of both the professional practice as well as the business model (Moullin *et al*., 2013). Payers of the service will tend to look at the benefit of a safe and rational use of medicines (Cipolle *et al*., 2012). However, payment for service in the community pharmacy has not been taken forward to the larger arena. For example, in

Australia, an agreement between the professional organization for community pharmacists and the government has resulted in remuneration for pharmaceutical services in community pharmacy. However, the community pharmacy is required to meet certain criteria to receive this payment (Puspitasari *et al*., 2015).

In community pharmacy, the cost of dispensing prescription medicines is declining (Cipolle *et al*., 2012; Puspitasari *et al*., 2015). This results in a larger amount of prescriptions required to be filled to gain profit in the pharmacy business. As such, interventions aimed at the time of refill may not produce the best results and distort the prescription-handling process (Cipolle *et al*., 2012).

There is a call for pharmacoeconomic evaluations to provide evidence on the cost-effectiveness of interventions relating to hypertension (Santschi *et al*., 2015). Evaluations such as these would possibly increase the likelihood of securing funding for future studies and reimbursement for community pharmacy implementation of the service. Reimbursement and cost for the service are the responsibilities of the governments, health insurance companies, pharmacists, researchers, pharmacy companies and patients (Hourihan *et al*., 2003; Maher *et al*., 2014). For the pharmacy service to be successful, there should be a minimum requirement of delivering pharmaceutical care to 10-15 patients a day **(**Cipolle *et al*., 2012).

4.6 Conclusion

Tying together the systematic review and the community pharmacy-based *in vivo* project results in a joint effort for an opportunistic role for the community pharmacist to bring together a service intended to optimize patients' BP. There are challenges along the way, though future studies have the possibility to influence the evidence-base which will form the

basis to include the fully developed pharmaceutical care service into practice and policy. Regarding this, this thesis has established:

- It is feasible for ambulatory hypertension patients to attend a community pharmacy-based hypertension management program with pharmacist-led interventions aimed at optimizing BP.

- There is a possibility in a community pharmacy to deliver targeted pharmacist-led interventions tailored to the patient's adherence status, although bearing in mind for certain patients, pharmaceutical interventions may have a detrimental effect. As such, there is a need to establish the subgroups which need or do not need the pharmaceutical intervention package.

- A collaborative approach with GP's and other healthcare staff should be sought as a point of referral of "at risk" patients to benefit from the pharmacy service as well as for clinical data sharing for the benefit of optimizing the hypertension therapy of the patient.

- A multi-centre randomized controlled trial with the utilization of adherence screening tools through a triangulated approach to categorizing patients into adherence subgroups together with an interventional approach individually tailored to the patient's adherence status would be the next step to build upon the research conducted in this thesis.

5 Appendices

5.1 Systematic review protocol

Research question: What is the scope of pharmacist-led interventions within a community pharmacy setting aimed at optimising blood pressure?

Aim: To perform a systematic literature review to identify and evaluate studies aimed at blood pressure optimisation in patients undergoing oral antihypertensive medication therapy.

Process

- **Study population:**

  Patients 18 years and above, undergoing treatment with at least one oral antihypertensive medicine, community pharmacy setting, no language restrictions on obtained papers
- **Study design:** Mixed-methods design
- **Interventions:** Interventions in a community pharmacy aimed at blood pressure optimisation
- **Search terms and key words (MESH):**

1. pharmacists hypertension antihypertensive agents medication adherence pharmacies intervention studies pharmaceutical care
2. pharmacists antihypertensive agents intervention studies medication adherence pharmaceutical care

3. pharmacies hypertension intervention studies medication adherence pharmaceutical care

4. pharmacies antihypertensive agents intervention studies medication adherence pharmaceutical care

5. pharmacists hypertension medication adherence pharmaceutical care
6. pharmacists antihypertensive agents medication adherence pharmaceutical care
7. pharmacies hypertension medication adherence pharmaceutical care
8. pharmacies antihypertensive agents medication adherence pharmaceutical care

- **Appropriate databases**

PubMed, Embase, Medline, Cinahl, Cochrane Database

Grey literature was searched using LexisNexis, Web of Science and Google.

- **Study outcome measures**

  Interventions leading to blood pressure optimisation

5.2 R Code for testing of funnel plot asymmetry based on odds ratio as an effect estimate of systolic blood pressure (SBP) and diastolic blood pressure (DBP) as a combined outcome

```
#loading the meta package
> library(meta)
Loading 'meta' package (version 4.4-1).

#importing data from RevMan 5
> hypertension<-read.rm5("hypertension.csv", numbers.in.labels=FALSE)

#calculating arscine test
> hyper <- metabin(event.e, n.e, event.c, n.c, data=hypertension, sm="ASD")

#testing for funnel plot asymmetry
> metabias(hyper, method.bias="mm")

      Linear regression test of funnel plot asymmetry (methods of moment)

data:  hyper
t = 2.8174, df = 9, p-value = 0.02013
alternative hypothesis: asymmetry in funnel plot
sample estimates:
     bias    se.bias      slope
1.78580484 0.63384252 0.08530217
```

5.3 Risk of bias assessment within studies

Table 5.1. Risk of bias assessment within studies with the Cochrane Collaboration Tool for assessing risk of bias. Risk of bias within the included studies with the dimension of bias (entry), the assessment of risk of bias (judgement) and the evidence for the assessment (support for judgement) with quotes and comments is presented.

McKenney *et al.*, 1973		
Entry	**Judgement**	**Support for judgement**
RSG	HR	Quote: "Male and female patients were listed separately and numbered consecutively. Patients with even numbers were assigned to the control group; patients with odd numbers were assigned to the study group." Comment: Probably not done.
AC	HR	Quotes: "Patients with even numbers were assigned to the control group; patients with odd numbers were assigned to the study group. This division resulted in two groups with similar age, sex, race, and level of hypertension characteristics..." "Study patients were approximately 15 pounds heavier in weight. The total number of patients in the study was reduced from 50 to 49 when one of the study patients moved outside..." Comment: Probably not done.
BPP	UR	Comment: Blinding not reported.
BOA	UR	Comment: Blinding not reported.
IODA	HR	Quotes: "Even though appointments were missed, no study patient was lost to medical or pharmaceutical follow-up during the study period." "Five control patients were lost to medical or pharmaceutical follow-up during the study period." Comment: No information on how missing data was dealt with and reasons for missing data.
SR	LR	Comment: Study protocol not available, but it is clear the published report included all expected outcomes (including those pre-specified)
OB	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".

Hughes *et al.*, 2002		
Entry	**Judgement**	**Support for judgement**
RSG	LR	Quote: "using a table of random numbers." Comment: Probably done.
AC	HR	Quotes: "The groups differed in their composition but this is likely to be due to the small numbers recruited into each." "Some patients expressed disappointment at assignment to the Control group..." Comment: Probably not done.
BPP	UR	Comment: Blinding not reported.
BOA	UR	Comment: Blinding not reported.
IODA	HR	Quote: "Patients lost to follow up are not included in the final analysis as there is no post intervention data for comparison." "...their inclusion in analysis would produce more favourable result towards the disease management model..." "Reasons for withdrawal amongst intervention groups varied." Comment: Probably not done.
SR	LR	Comment: Study protocol available and all of the study's pre-specified (primary and secondary outcomes) have been reported in the pre-specified way.
OB	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".

Garção and Cabrita, 2002		
Entry	**Judgement**	**Support for judgement**
RSG	UR	Quote: "...patients were randomly assigned..." Comment: Support for sequence generation entry not sufficient. Attempt with e-mail correspondence with author to clarify details on randomisation. No response from author.
AC	HR	Quote: "Because the research pharmacist assigned patients to the two groups, the study was only single-blinded. This could have introduced bias." Comment: Probably not done.
BPP	UR	Quote: "Because the research pharmacist assigned patients to the two groups, the study was only single-blinded. This could have introduced bias. In addition, the research pharmacist took all blood pressure readings; measurements made by patients, physicians, or nurses were not part of the study." Comment: Single-blinded.
BOA	HR	Quote: "Because the research pharmacist assigned patients to the two groups, the study was only single-blinded. This could have introduced bias. ." Comment: Probably not done.
IODA	UR	Quotes: "Five patients in the intervention group were dropped from the study. The reasons for discontinuation were missing more than one scheduled interview (n = 2), patient's lack of belief in any health-related added value in the study (n = 2), and patient moved out of the area (n = 1). Seven patients in the control group were dropped -- four for missing the final scheduled interview and three because of repeated difficulties in contacting them. " "We registered no significant differences between the demographic, clinical, therapeutic, and lifestyle variables of those patients excluded from follow-up and those who completed the study. These variables were comparable for the two groups at baseline." Comment: Probably not done. No intention to treat analysis, data collected for drop-outs not reported.
SR	LR	Comment: Study protocol not available, but it is clear the published report included all expected outcomes (including those pre-specified)
OB	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".

Taylor et al., 2003		
Entry	**Judgement**	**Support for judgement**
RSG	HR	Quote: "A pretest-posttest design was used…" Comment: Probably not done.
AC	HR	Comment: Probably not done. Due to the study design used.
BPP	HR	Comment: Blinding not reported.
BOA	HR	Comment: Blinding not reported.
IODA	UR	Quote: "Of the twenty-five patients targeted to participate in the study, eight patients completed the study. Attrition and lack of participation were largely due to patients' unwillingness to participate for the length of the study period." Comment: Not clear if it was only possible to recruit eight patients. Not been able to establish contact with study authors.
SR	LR	Comment: Study protocol not available, but it is clear the published report included all expected outcomes (including those pre-specified).
OB	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".

Chabot *et al.*, 2003		
Entry	**Judgement**	**Support for judgement**
RSG	HR	Quote: "The population was not randomized and the baseline distribution of many variables differed between the control and intervention groups." Comment: Probably not done.
AC	HR	Quote: "screening of each pharmacy database was performed to identify patients aged 18–80 years who had received at least 1 antihypertensive agent during the 30-day period preceding the beginning of the study. Potentially eligible patients were contacted by phone by pharmacists." Comment. Probably not done.
BPP	UR	Quote: "BP values were based on 9 measurements performed by blinded research assistants". Comment: Blinding of patients not reported.
BOA	LR	Quote: "BP values were based on 9 measurements performed by blinded research assistants". Comment: Probably done.
IODA	UR	Quotes: "Drop-outs included 4 patients who refused to pursue the study, 6 patients with whom contact was lost, and 1 deceased patient." "Since 9 patients refused to indicate their family income, the stratified analyses included 91 subjects." Comment: Probably not done. No intention to treat analysis, data collected for drop-outs not reported.
SR	HR	Quotes from full text paper: "In high-income patients, a significantly greater proportion of patients in the intervention group had their BP controlled with an SBP <140 mm Hg and a DBP <90 mm Hg compared with those in the control group after adjustmentfor age and baseline level of BP control (69% vs. 42%; OR 6.2; p = 0.073). Difference between groups was not significant for low-income patients (OR 1.11; p = 0.895)." "...was conducted to assess the impact of a pharmacist intervention program on BP levels, drug treatment adherence, physical activity, alcohol consumption, body mass index, and factors affecting adherence in hypertensive patients." Comment: Proportion patients with controlled BP in the intervention group for low-income patients not reported. BMI and alcohol consumption not reported as results.
OB	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".

Zillich et al., 2005		
Entry	**Judgement**	**Support for judgement**
RSG	HR	Quote: "Last, selection bias may minimize the ability to generalize this study. Recruitment and participation of both pharmacies and patients was voluntary and unblinded." Comment: High risk
AC	HR	Quote: " It is possible that pharmacists in the HI group recruited patients whom they felt would be the best participants in the intervention.". Comment: High risk
BPP	HR	Quote: "Recruitment and participation of both pharmacies". Comment: High risk and patients was voluntary and unblinded."
BOA	HR	Quotes: "Recruitment and participation of both pharmacies and patients was voluntary and unblinded." "Therefore, reductions in BP may be attributed to several factors including the LI intervention. Additional factors such as regression to the mean, Hawthorne effect, and secular effects may contribute to the findings." Comment: High risk
IODA	LR	Quote: "Missing data were minimal and statistical imputation methods were employed but did not affect analysis results." Quote from email correspondence with author: "As the study was completed more than 10 years ago, I am afraid I no longer have the details about the specific approach we used for the missing data. As the missing data did not affect the overall analyses, we likely reported the intent-to-treat in the paper." (Zillich, 2015) Comment: Low risk
SR	HR	Quotes: "From baseline, SBP declined 13.4 mmHg in the HI group and 9.0mmHg in the LI group (P<.01 for within-group comparison from baseline to final visit). Similarly, DBP declined significantly from baseline in each group (P<.01 for within-group comparisons)." "During the study, 38 patients in the HI group had antihypertensive medication added or increased. Conversely, 16 patients in the LI group had antihypertensive medication added or increased. Twenty-nine separate antihypertensive medications were added in the HI group compared with 14 in the LI group." Comment: DBP change within-group comparison not mentioned in narrative, only in figure. Comparison of changes in antihypertensive pharmacotherapy reported for both High-intensity and low-intensity intervention groups even though pharmacist recommendations/treatment recommendations was not part of the intervention for Low-intensity intervention group.
OB	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".

Carvalho and Nagavi, 2007		
Entry	**Judgement**	**Support for judgement**
RSG	UR	Quote: "...patients were then block randomized into test or control group." Comment: Process of selecting blocks not clear.
AC	UR	Comment: Method of concealment is not described
BPP	HR	Quotes: "This was a prospective, open label, block randomized, study." "During each follow-up, the research pharmacist, educated patients belonging to the test group, regarding their disease,..." Comment: Researcher meeting patients. Blinding not reported.
BOA	HR	Quote: "This was a prospective, open label, block randomized, study." "During each follow-up, the research pharmacist, educated patients belonging to the test group, regarding their disease,..."Comment: Researcher delivering intervention. Blinding not reported.
IODA	UR	Quote: "A total of 58 patients were enrolled into the study. Eleven patients (18.96 %) were lost to follow up. Of the seven patients lost to follow up in the control group, one patient had a stroke and could not return for follow up, three patients expressed a lack of interest to continue with the study (despite motivation form the research pharmacist), two patients were out of station and therefore missed their follow-ups and one patient" "Of the 47 patients who completed all follow-ups,..." Comment: Probably not done. No intention to treat analysis mentioned in full text paper, not clear from full text paper if data collected for drop-outs is reported.
SR	LR	Comment: Study protocol available and all of the study's pre-specified (primary and secondary outcomes) have been reported in the pre-specified way.
OB	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".

Lai, 2007		
Entry	**Judgement**	**Support for judgement**
RSG	RSG	Quote: "Quasi-Experimental Time Series Design". Comment: Probably not done.
AC	HR	Comment: Probably not done. Due to the study design used.
BPP	HR	Comment: Blinding not reported.
BOA	HR	Comment: Blinding not reported.
IODA	HR	Quote:"A total of 103 patients were enrolled in the study. Fifty-three patients (50.5%) completed the entire hypertension disease-management program provided by community pharmacists during the nine-month study period. The high attrition rate was because some patients did not complete the QOL survey at the end of the program." Comment: Attempt with e-mail correspondence with author to clarify details on incomplete data. No response from author.
SR	LR	Comment: Study protocol not available, but it is clear the published report included all expected outcomes (including those pre-specified).
OB	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".

Aguwa et al., 2008		
Entry	**Judgement**	**Support for judgement**
RSG	HR	Quote: "A non-randomised, crossover design was used. Patients served as their own control. Forty hypertensive patients were registered for the study after oral consent was obtained." Comment: Probably not done.
AC	HR	Comment: Probably not done. Due to the study design used.
BPP	UR	Comment: Blinding not reported.
BOA	UR	Comment: Blinding not reported.
IODA	HR	Quote: "Forty patients were recruited for the study. Twenty-four patients (60%) completed the study." Quote from author by e-mail correspondence: "Most of the participants dropped because they relocated from Port Harcourt (work reasons, visits etc). Others did not continue because they refill their medications in different pharmacies. Analysis was "per protocol" basis." (Ekwunife, 2014) Comment: No information is stated about reasons for attrition/exclusions in full paper. Missing outcome data for 16 patients not completing study is not reported in the full paper. Analysis done "per protocol".
SR	HR	Quote: "Main outcome measure Blood pressure and quality of life measured before implementation of pharmaceutical care and at the end served as main outcome measures. Other end-points assessed at baseline and at the end of investigation included smoking cessation, adherence to therapy, exercise, salt restriction, alcohol moderation and self blood pressure measurement." Comment: Body Mass Index (BMI) and drug-related problems (DRP:s) not pre-specified.
OB	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".

Júnior et al., 2008		
Entry	**Judgement**	**Support for judgement**
RSG	HR	Quote: "A longitudinal, prospective study (semi-experimental) was conducted at a primary health care unit (PHCU)" Quote: "During a week period, all hypertensive outpatients who came to the ambulatory care pharmacy of PHCU to receive their medication were identified as potential candidates for the study. Patients were eligible to participate if they met three or more of the following criteria..." Comment: Probably not done.
AC	HR	Comment: Probably not done. Due to study design used.
BPP	UR	Comment: Blinding not reported.
BOA	UR	Comment: Blinding not reported.
IODA	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".
SR	LR	Comment: Study protocol not available, but it is clear the published report included all expected outcomes (including those pre-specified).
OB	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".

Planas *et al*., 2009		
Entry	**Judgement**	**Support for judgement**
RSG	LR	Quote: "Using a generated random number list..." Comment: Probably done.
AC	HR	Quotes: "Eligible individuals meeting the study criteria were referred to the patient scheduler, who randomly assigned them to either the intervention or the control group based on a previously generated random number list." "because of potential selection bias among program participants. These individuals may have been more highly motivated than the average patient." Comment: Probably done.
BPP	UR	Comment: Blinding not reported.
BOA	UR	Comment: Blinding not reported.
IODA	HR	Quote: "Intention-to-treat analyses were conducted. If a participant did not complete the study, his or her last blood pressure level was carried forward to represent the 9-month level. Participants who dropped out of the study before the 3-month visit were excluded from analyses." Comment: Probably not done. Not a complete intention to treat analysis.
SR	LR	Comment: Study protocol not available, but it is clear the published report included all expected outcomes (including those pre-specified).
OB	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".

Robinson *et al.*, 2010		
Entry	**Judgement**	**Support for judgement**
RSG	HR	Quotes: "PC pharmacies were selected based on the number of hypertension prescriptions dispensed in the stores, store location, and input from the district managers." "Seven additional pharmacies from the same corporate chain in the same geographic region were selected by their district manager to serve as a concurrent UC control group." "To identify patients who may benefit from the PC program, each pharmacy's automated prescription database was queried to identify patients..." Comment: Probably not done.
AC	HR	"To identify patients who may benefit from the PC program, each pharmacy's automated prescription database was queried to identify patients..." "Initial contact with each patient receiving care in a PC or UC pharmacy occurred either by a telephone call from his or her pharmacist or while the patient was present in the pharmacy." "It may be possible that patients enrolled in the study may have visited both pharmacy groups without realizing it." "First, with the selection of PC versus UC pharmacists by the chain district managers, there is inherent bias in the populations being served by the pharmacies. Although the pharmacies are within the same geographic area, it is possible that they serve people with varying socioeconomic backgrounds. These possible differences in socioeconomics may have also played a role in regard to medication adherence, including losses to follow-up." Comment: Probably not done.
BPP	HR	Comment: Blinding not reported.
BOA	HR	Comment: Blinding not reported.
IODA	HR	Quote: "We omitted data from the analyses for subjects who received prescription services during the 12-month study related to their hypertension from a pharmacy other than the PC or UC pharmacy where they were enrolled. We also omitted data from subjects who did not complete a final visit at the end of the study since a BP measurement was needed to assess BP control and the survey was needed to assess QOL." "Rather than using an intent-to-treat analysis, we decided to include only patients for whom we had clinical endpoints in the analysis..." Comment: Probably not done.
SR	HR	Quote: "We omitted data from the analyses for subjects who received prescription services during the 12-month study related to their hypertension from a pharmacy other than the PC or UC pharmacy where they were enrolled. We also omitted data from subjects who did not complete a final visit at the end of the study since a BP measurement was needed to assess BP control and the survey was needed to assess QOL." Comment: Probably done.
OB	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".

Octavia and Florica, 2011		
Entry	**Judgement**	**Support for judgement**
RSG	UR	Quotes: "...randomised, controlled research..." "Between the two batches there were no significant statistic differences linked to age, antihypertensive prescribed medication or comorbidities." Comment: Attempt with e-mail correspondence with author to clarify details on randomisation procedure. No response from author. Insufficient information to permit judgement of "Low risk" or "High risk".
AC	HR	Quote:"For the introduction into the research, I received the patients' written agreement as per the international standards of clinical researches. Initially, we interviewed each and every patient for at least 30 minutes with regard to patient's socio-demographic issues..." Comment: Probably not done.
BPP	UR	Quotes: "For the introduction into the research, I received the patients' written agreement as per the international standards of clinical researches. Initially, we interviewed each and every patient for at least 30 minutes with regard to patient's socio-demographic issues..." "...I have instructed the patients regarding the treatment righteousness, the need for a continual administration, the risk of side effects, the proper keeping of medication administrated..." Comment: Researcher meeting patients. Blinding not reported.
BOA	UR	Quotes: "For the introduction into the research, I received the patients' written agreement as per the international standards of clinical researches. Initially, we interviewed each and every patient for at least 30 minutes with regard to patient's socio-demographic issues..." "...I have instructed the patients regarding the treatment righteousness, the need for a continual administration, the risk of side effects, the proper keeping of medication administrated..." Comment: Researcher delivering the intervention. Blinding not reported.
IODA	UR	Comment: Attempt with e-mail correspondence with author to clarify details on incomplete data. No response from author. There is no reference for what an improvement would be. "...but using my own query I could notice an improvement of the physical activity, of the psychic behaviour (unrest, irritability, insomnia, lack of active life mood), but I did not quantify these improvements." However, in general there is insufficient information to permit judgement of "Low risk" or "High risk".
SR	HR	Comment: Table 3: Table with variations in blood pressure average ±SD before and after the pharmaceutical care program by age groups not described further in the discussion. Just stating "...but using my own query I could notice an improvement of the physical activity, of the psychic behaviour (unrest, irritability, insomnia, lack of active life mood), but I did not quantify these improvements." There is no reference for what an improvement would be.
OB	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".

Skowron *et al.*, 2011		
Entry	**Judgement**	**Support for judgement**
RSG	LR	Quote: "Randomization of community pharmacies to control and study group was done by generation of random numbers by computer software." Comment: Probably done.
AC	LR	Quote: "Randomization of community pharmacies to control and study group was done by generation of random numbers by computer software." Comment: Probably done.
BPP	UR	Quotes: "The researchers' team responsible for coordination of this project did not interfere in any way with the pharmacists' actions during this program; however, the website was prepared, its role was to facilitate exchange of information between pharmacists. Pharmacists were also informed about the possibility of consulting with the researchers team by e-mail, phone or personally during the entire period of project duration." "Assignment to the study group could be the reason for resignation from the study of a large part of community pharmacies." Comment: Blinding not reported.
BOA	UR	Quote: "The researchers' team responsible for coordination of this project did not interfere in any way with the pharmacists' actions during this program; however, the website was prepared, its role was to facilitate exchange of information between pharmacists. Pharmacists were also informed about the possibility of consulting with the researchers team by e-mail, phone or personally during the entire period of project duration." Comment: Blinding not reported.
IODA	HR	Quote: "The analysis of results was conducted according to Intention of treat (ITT) and Per Protocol (PP) methods. Data of all patients who had at least two visits and filled out at the first and last meeting the knowledge questionnaires were included to the ITT analysis. In addition, pharmacists that took care of those patients filled out one of the questionnaires were evaluated. Data of patients who had planned number of visits (≥12 in the study group and 2 in the control group) were evaluated in PP analysis only if their pharmacists fulfilled two times the knowledge and satisfaction questionnaire." Comment: Potentially inappropriate application of intention to treat analysis.
SR	HR	Quotes: "At the last visit it was observed that patients from the study group have been taken one antihypertensive and two cardiovascular diseases medications more than they declared at the initial visit. The number of dispensed medications did not change in the control group." "Increased number of dispensed medications did not have any effect on therapy efficacy..." "The analysis of results was conducted according to Intention of treat (ITT) and Per Protocol (PP) methods. Data of all patients who had at least two visits and filled out at the first and last meeting the knowledge questionnaires were included to the ITT analysis. In addition, pharmacists that took care of those patients filled out one of the questionnaires were evaluated. Data of patients who had planned number of visits (≥12 in the study group and 2 in the control group) were evaluated in PP analysis only if their pharmacists fulfilled two times the knowledge and satisfaction questionnaire." Comment: No justification for reporting number of medications. No reasoning/justification for the modified intention to treat and per protocol analysis making the validity of the results to be questioned.

Continuation of Skowron *et al*., 2011, OB		
Entry	**Judgement**	**Support for judgement**
RB	UR	Quotes: "The randomization of community pharmacies to the study and control group were done due to avoid unintended increase in quality of standard pharmaceutical services, but it might have influenced the number and characteristic of patients enrolled into the study and control group." "Despite this limitation we did not observe the differences in characteristic of patients included in study and control group." Comment: Insufficient information to permit judgement of "Low risk" or "High risk".
BI	HR	Quotes: "The control and study group differed in terms of education, age and place of residence." "Six community pharmacies (15 pharmacists) from study group and three (10 pharmacists) from control group resigned before the first meeting with patients. Therefore the first meeting was carried on for 34 patient and 84 in study and control group, respectively." Comment: High risk.
LOC	HR	"Six community pharmacies (15 pharmacists) from study group and three (10 pharmacists) from control group resigned before the first meeting with patients. Therefore the first meeting was carried on for 34 patient and 84 in study and control group, respectively." Comment: High risk
IA	HR	Comment: Analysis not taking clustering into account.
CWIRT	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".

Aguiar et al., 2012		
Entry	**Judgement**	**Support for judgement**
RSG	HR	Quote: "...a nonrandomized..." Comment: Probably not done.
AC	HR	Quotes: "...a nonrandomized..." "During a 1-month period, all elderly patients (aged 60–75 years) who visited the pharmacy to receive antihypertensive medications were identified as potential candidates for the study." Comment: Probably not done.
BPP	UR	Quote: "...the research pharmacist took all blood pressure readings; measurements made by patients, physicians, or nurses were not part of the study." Comment: Quote provides provides indication that staff were not blinded. Blinding of patients not reported.
BOA	HR	Quote: "...the research pharmacist took all blood pressure readings; measurements made by patients, physicians, or nurses were not part of the study." Comment: Probably not done.
IODA	HR	"Only data for patients completing the study were included." Comment: Probably not done.
SR	HR	Comment: Probably done. Reporting of drug related problems in the results section.
OB	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".

Fikri-Benbrahim *et al.*, 2012		
Entry	**Judgement**	**Support for judgement**
RSG	HR	Quote: "A coin toss was used to determine the group assignment of the first recruited patient, and subsequent patients were assigned on an alternating basis to the two groups." Comment: Probably not done.
AC	HR	Quote: "A coin toss was used to determine the group assignment of the first recruited patient, and subsequent patients were assigned on an alternating basis to the two groups. The assignment method was known only to the study coordinator. After visits 1, 2, and 3 (initial phase), the participating pharmacist contacted the study coordinator to determine the assignment of each patient to the control or intervention group. Comment: Probably not done.
BPP	HR	Quotes: "...the pharmacists who provided the intervention in this study were not blinded." "Also, there may have been contamination between the intervention and the control group (i.e., the control group may have received more attention than usual)." "Both scenarios could explain the baseline-to-endpoint reduction in SBP observed in the control group." Comment: Probably not done. No information if patients were blinded.
BOA	HR	Quotes: "...the pharmacists who provided the intervention in this study were not blinded." "Also, there may have been contamination between the intervention and the control group (i.e., the control group may have received more attention than usual)." "Both scenarios could explain the baseline-to-end point reduction in SBP observed in the control group." Comment: Probably not done.
IODA	LR	Quotes: "Additional analyses were conducted according to the intent-to-treat principle." "Assuming that all patients dropping out during the follow-up had the same BP value at the endpoint as at baseline, the intent-to-treat analysis demonstrated that the results for the intervention group remained better than those for the control group..." "Assuming that all patients who dropped out during the follow-up period had uncontrolled BP (≥140/90 mm Hg), the intent-to treat analysis showed a higher rate of BP control in the intervention group versus the control group..." Comment: Probably done.
SR	LR	Comment: Study protocol not available, but it is clear the published report included all expected outcomes (including those pre-specified).
OB	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".

Nemerovski et al., 2013		
Entry	**Judgement**	**Support for judgement**
RSG	HR	Quotes: "This pharmacy hypertension service was offered to employees participating in the Wayne State Wellness Warriors Program." "Self-declared hypertensive patients met with the pharmacist..." "High baseline rates and maintenance of commitment to the goals over the 6-month program may be due to participant selection from patients already engaged in the Wellness Warriors Program, in which lifestyle and wellness are key topics." Comment: Probably not done.
AC	HR	Comment: Probably not done. Due to the study design used.
BPP	UR	Comment: Blinding not reported.
BOA	UR	Comment: Blinding not reported.
IODA	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".
SR	HR	Quote: "A subgroup of patients who were not at their blood pressure goal at baseline (n=62) was evaluated post hoc." Comment: Probably done. Reporting of baseline characteristics in table with "all participants" and "not at goal at baseline" as separate groups. Comment: Subgroup analysis not mentioned in methods section/among main outcome measures.
OB	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".

Svarstad *et al.*, 2013		
Entry	**Judgement**	**Support for judgement**
RSG	LR	Quote from study protocol: "The study statistician used computer software to randomize the 28 sites...". Comment: Probably done.
AC	LR	Quote from study protocol: "The study statistician used computer software to randomize the 28 sites into an intervention group (TC) and a control group..." Quote from full text paper: "All screenings were conducted by project assistants, who were hired and supervised by investigators, blinded to pharmacy allocation, and trained to obtain consents and three blood pressure readings with 30-second intervals between readings. " "Study groups were similar on demographics, blood pressure, number of drugs, missed doses, and barriers to adherence (Table 1). Physical activity level varied by group and was entered into all models." Comment: Probably done.
BPP	HR	Quotes from full text paper: "Pharmacy allocation was concealed from patients until investigators verified that enrollment goals were met at their pharmacy." "All screenings were conducted by project assistants, who were hired and supervised by investigators, blinded to pharmacy allocation, and trained to obtain consents and three blood pressure readings with 30-second intervals between readings." Comment: Patients not blinded. Risk of patients knowing pharmacy allocation.
BOA	LR	Quote from full text paper: "All screenings were conducted by project assistants, who were hired and supervised by investigators, blinded to pharmacy allocation, and trained to obtain consents and three blood pressure readings with 30-second intervals between readings. " "Blinded interviewers reassessed 94.8% of all patients at 6 months and 85.6% at 12 months." Quote from study protol: "The primary outcomes (BP control and reductions in BP) were measured 6 and 12 months after enrollment by data collectors blinded to the patient's assigned group..." Comment: Probably done.
IODA	LR	Quote from full text paper: "The primary analysis included all patients based on the intent-to-treat concept." Comment: Probably done.
SR	HR	Quote from study protocol: "Secondary end points were changes in adherence monitoring and intervention, patient adherence and barriers to adherence, prescribing, and cost-effectiveness." Quote from full text paper: "Fourth, research is needed to evaluate the optimal duration of intervention for different subgroups, validity of items for measuring patient perceptions of pharmacist performance, and cost effectiveness of different strategies." Comment: Probably done. Cost-effectiveness not reported in full-text paper.

Continuation of Svarstad *et al.*, 2013, OB		
Entry	**Judgement**	**Support for judgement**
RB	LR	Quote: "Black patients who took at least one blood pressure prescription were encouraged to attend one of the screenings using study posters, flyers, gift card incentives, and interest forms distributed at study pharmacies and several churches.9 All screenings were conducted by project assistants, who were hired and supervised by investigators, blinded to pharmacy allocation, and trained to obtain consents and three blood pressure readings with 30-second intervals between readings."
BI	LR	Quote: Study groups were similar on demographics, blood pressure, number of drugs, missed doses, and barriers to adherence (Table 1). Physical activity level varied by group and was entered into all models." Comment: Low risk.
LOC	LR	Quote from full text paper: "The primary analysis included all patients based on the intent-to-treat concept." Comment: Low risk. 28 clusters reported for in total. No loss of clusters among these 28.
IA	LR	Quotes: "...between-group comparison adjusting for cluster randomization..." "...controlling for cluster randomization and covariates."Comment: Low risk
CWIRT	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".

Pojskic *et al.*, 2014 (Pojskic, 2014a)		
Entry	**Judgement**	**Support for judgement**
RSG	LR	Quote from the final paper: "Pharmacies from each region were randomly assigned..." Quote from author by e-mail correspondence: "We used a random number table to assign the pharmacies to either the intervention or control group." (Pojskic, 2014b) Comment: Probably done.
AC	LR	Quote: "The randomization was conducted at the pharmacy level, in order to avoid contamination at the patient level" Comment: Probably done.
BPP	HR	Quote: "Neither the patients nor the pharmacists were blinded with respect to their group assignment." Comment: Probably not done.
BOA	HR	Quote: "Neither the patients nor the pharmacists were blinded with respect to their group assignment. Given the transparent nature of pharmacist intervention, blinding was not feasible." Comment: Probably not done.
IODA	HR	Quote from author by email correspondence: "The final report (as posted on our website) reflects only the patients who completed the entire study (all 7 appointments) - there was a total of 118 patients. We originally recruited 154 but some dropped out due to various reasons. We did perform an intention to treat analysis though it's not reported in the final paper." (Pojskic, 2014b) Comment: Figure explaining 35 patients dropping out and reasons for drop-out, but not stating within which groups this occurs. Imbalance in numbers in both control and intervention groups. No report/analysis of missing outcome data in final paper.
SR	HR	Quotes: "While the difference between the two groups was not statistically significant (p=0.125), the trend was clearly favourable for the intervention group. This improvement in BMI in the intervention group is likely due to a number of factors, including changes in diet and frequency of physical exercise (report below). In particular, all study pharmacists reported that the enrolled patients had greater awareness of the sodium levels in products and made healthier dietary choices as a result of pharmacist counselling." "Patient is doing well with maintaining his exercise program. He is also reading labels to check sodium level before purchasing foods at the grocery store. He is dealing with stress at work and is trying to find a way to minimize these stressors." Comment: Indicating positive outcomes which are not statistically significant in a positive light with narratives.

Continuation of Pojskic *et al.*, 2014 (Pojskic, 2014a), OB		
Entry	**Judgement**	**Support for judgement**
RB	HR	Quote: "Neither the patients nor the pharmacists were blinded with respect to their group assignment.". Comment: Probably likely with recruitment bias since the pharmacists were not blinded to their group assignment.
BI	LR	"Table 4. Pharmacy characteristics by group" "Pharmacy level descriptive characteristics, including mean and standard deviation for the number of patients were reported." "Adjustment was made in these models for the intra-cluster correlation within pharmacies by allowing pharmacies to be modeled as a random effect." Comment: Reporting of base-line characteristics of clusters done and statistical adjustment done.
LOC	HR	Quotes: "Out of the 38 pharmacies originally recruited for this study, 11 dropped out due to their inability to recruit any patients and/or staffing issues." Comment: High risk.
IA	LR	Quotes: "Pharmacy level descriptive characteristics, including mean and standard deviation for the number of patients were reported." "Adjustment was made in these models for the intra-cluster correlation within pharmacies by allowing pharmacies to be modeled as a random effect." "Because this study utilized a cluster sampling technique (with each cluster being a pharmacy), the above sample size was then adjusted for the variance inflation factor, using the following formula:..." Comment: Clustering has been taken into account.
CWIRT	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".

Stewart *et al.*, 2014		
Entry	**Judgement**	**Support for judgement**
RSG	LR	Quote: "Randomization was performed at the pharmacy level to avoid any contamination likely to result from the same pharmacy recruiting and following up both intervention and control group patients. The randomization process was carried out by one of the investigators using the 'sealed envelope technique'." Comment: Probably done.
AC	LR	Quote: "The randomization process was carried out by one of the investigators using the 'sealed envelope technique'." Comment: Probably done.
BPP	HR	Quote: "…non-blinded…" Comment: Probably not done.
BOA	HR	Quote: "…non-blinded…" Comment: Probably not done.
IODA	LR	Quote: "Analysis was performed under the intention-to-treat principle...". Comment: Probably done.
SR	HR	Quotes from study protocol: "The primary outcomes of the HAPPY trial are changes in patient adherence and persistence at the end of six months. These will be measured subjectively using the self-reported Morisky scale [16] and the Tool for Adherence Behaviour Screening (TABS) [17] and objectively using the medication refill data (e.g. MedsIndex score)..." "Secondary outcomes include changes in patients' BP control, satisfaction with and willingness to pay for the service and economic benefits." "The Beliefs and Behaviour Questionnaire [17] will be used to assess patient experiences, attitudes and beliefs regarding their health and treatment and the 8-item short Assessment of Quality of Life (AQoL) [25] will be used to measure health-related quality of life." Quotes from full text paper: "The primary outcome was change in the proportion of patients self-reporting adherence on the Morisky scale at the end of 6 months. Patient non-adherence was defined by a Morisky score of greater than zero. Secondary outcomes were changes in patients' systolic and/or diastolic BP and the proportion selfreporting adherence on the TABS. A differential of 15 or more between the TABS subscales (adherence and non-adherence) was regarded as good adherence." "As improvements in the outcomes were dependent upon each patient's baseline levels, to target populations of specific interest, exploratory analyses were planned for the following subgroups..." Comment: Probably done. Subgroup analysis not mentioned in study protocol.

Continuation of Stewart *et al.*, 2014, OB		
Entry	**Judgement**	**Support for judgement**
RB	UR	Comment: Insufficient information to permit judgement.
BI	LR	Quote: "There were no significant differences between groups." Quote: "Baseline characteristics between groups were compared using chi-square tests for equal proportion and reported as numbers (percentages)." Quote: "To control for the effects of cluster randomization, group changes were compared using mixed linear and nonlinear modelling for normally and non-normally distributed data, respectively, with individual pharmacies treated as a random effect." Comment: Low risk of baseline imbalance.
LOC	LR	Loss of clusters from PCG: No longer interested = 1; Loss of clusters from UCG: No longer interested = 3 Did not meet inclusion criteria = 1. Comment: Missing data have been dealt with using appropriate methods.
IA	LR	Quote: "To control for the effects of cluster randomization, group changes were compared using mixed linear and nonlinear modelling for normally and non-normally distributed data, respectively, with individual pharmacies treated as a random effect..." Comment: Low risk of incorrect analysis.
CWIRT	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".

Sharma et al., 2014		
Entry	**Judgement**	**Support for judgement**
RSG	HR	Quotes: "single-cohort pre-/post-intervention study" "The participants included in the study were patients diagnosed with hypertension attending “a pharmacist-led hypertension clinic” Sunday, Thursday, and Friday every week at Sankalpa pharmacy". Comment: Probably not done.
AC	HR	Quotes: "single-cohort pre-/post-intervention study" "The participants included in the study were patients diagnosed with hypertension attending “a pharmacist-led hypertension clinic” Sunday, Thursday, and Friday every week at Sankalpa pharmacy" "Initially, patients meeting the inclusion criteria were recruited to the study following their verbal informed consent." Comment: Probably not done.
BPP	HR	Quotes: "A team of healthcare professionals, including two community pharmacists, a nurse, and a physician, was involved in the intervention programme. The educational intervention was individualised (i.e., one-to-one counselling) and consisted of three counselling sessions." "The intervention programme consisted of face-to-face counselling sessions." Comment: Probably not done.
BOA	HR	Quote: "In the first visit to the pharmacy, all the socio-demographic variables and initial BP were recorded, and their baseline level of knowledge and lifestyle practices were also recorded. At the end of nine months, patients’ levels of knowledge and lifestyle modification practices were reassessed and their blood pressure was recorded." "The intervention programme consisted of face-to-face counselling sessions." Comment: Probably not done.
IODA	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".
SR	HR	Quotes: "To control for the educational level, as there was a statistically significant difference between the literate and illiterate patients in terms of KP score before the intervention, a comparison between these two subgroups after the intervention was conducted. However, as shown in Table 6, there were no statistically significant differences between these two subgroups in terms of their knowledge, practice, and blood pressure control." "However, the educational status of the patients was found to affect awareness and practice. Literate patients had significantly higher scores compared to illiterate patients. This emphasises the need to consider the educational status of the patients for their treatment strategy." "Most patients were aware of the role of salt intake in the management of hypertension, but their practice regarding it was poor. Additionally, their medication compliance was poor, as was the habit of doing physical exercise. The answer to the question, “How often you do physical exercise?”, and “How often do you avoid fatty food intake?” was “Never” in most cases. However, overall knowledge and practice significantly improved after the intervention, as revealed by the change in knowledge and practice scores shown in Table 5." Comment: Conflicting reporting of subgroup analysis and selective reporting of positive outcomes as narratives.
OB	UR	Comment: Insufficient information to permit judgement of "Low risk" or "High risk".

Abbreviations for Table 5.1:

AC=Allocation concealment (selection bias); BI= Baseline imbalance; BOA=Blinding of outcome assessment (detection bias); BPP=Blinding of participants and personnel (performance bias); CWIRT=Comparability with individually randomized trials; HR=High risk; IA=Incorrect analysis; IODA=Incomplete outcome data addressed (attrition bias); LOC=Loss of clusters; LR=Low risk; OB=Other bias; RB=Recruitment bias; RSG=Random sequence generation (selection bias); SR=Selective reporting (reporting bias); UR=Unclear risk

5.4 Research Proposal

Abstract

The aim of this research is to evaluate pharmacist-led intervention among patients in a single-community pharmacy to improve antihypertensive medicines adherence. This investigation will consist of a longitudinal before-and-after study, undertaken at a single-community pharmacy in Uppsala, Sweden. Ethics approval will be sought for at ethics board in Sweden. Patients recruited should be at least 18 years old or above, having minimum one prescription on an antihypertensive medicine, been using the medicine/s for the past 3 months and should get the medicine refill done at the study pharmacy while the study is ongoing. The participants will be serving as their own controls. The study duration is set to 6 months. Data will be collected at baseline and after a 6-month follow-up: adherence (8-item Morisky Medication Adherence Scale, Medication Adherence Report Scale, Medication Possession Ratio), a questionnaire on patient perception on medicines (Belief about Medicines Questionnaire) and a pharmacoeconomic evaluation of the pharmacist-led intervention. The intervention will be implemented after 3 months from baseline.

Research question

Can pharmacist-led adherence intervention/s in a single-community pharmacy contribute to improved antihypertensive medication adherence?

Aims and Objectives

Aim: to evaluate pharmacist-led intervention/s among patients in a single-community pharmacy to improve antihypertensive medication adherence.

Objectives:

- measure the change in blood pressure, pulse and antihypertensive medicine adherence
- establish the cost-effectiveness of a pharmacist intervention in improving antihypertensive medicines adherence

Research design

- Longitudinal before-and-after study
- Single community pharmacy in Uppsala, Sweden
- Six-month study duration
- Two study groups run in parallel: monotherapy and polypharmacy
- Patients serve as their own control
- Quantitative measurement at baseline (first visit) and after 6 months (last visit): blood pressure and pulse, 8-item Morisky scale (8-item MMAS), Medication Adherence Report Scale (MARS) Medication Possession Ratio (MPR), Belief about Medicines Questionnaire (BMQ)
- Intervention implemented after 3 months from baseline
- Pharmacoeconomic evaluation of the implemented pharmacist-led intervention

This study uses a triangulated research approach which revolves around:

1. Personal contact and review of elements
2. Self-reported scale devices: 8-item MMAS, MARS, and BMQ
3. The long-term chronic historical record of the usage of medication

The project will be undertaken as a longitudinal before-and-after study in a single-community pharmacy in Uppsala, Sweden. There will be two study groups run in parallel: one group with patients having one antihypertensive agent (monotherapy) and the other group in which each participant has two or more antihypertensive medicines (polypharmacy). Patients will serve as their own control. A significant reduction in blood pressure is in this project set out to be 10 mmHg systolic pressure and 5 mmHg in diastolic pressure.

The research procedure is as follows:

1. Participant recruitment

   Participants being dispensed antihypertensive medicines at the dispensing counter at the pharmacy will be approached by the dispensing pharmacist (researcher) and will be informed about the study with the following information: “There will be an ongoing study here at this pharmacy for patients undergoing treatment with blood pressure lowering medicines. This study is aimed at evaluating if a pharmacist can contribute to improving patient blood lowering medicines taking. Does this sound interesting to you?”. The participant will also be asked by the researcher for how long they have been taking antihypertensive medicine/medicines. If they inform that they are interested to participate, they will be handed the participant information leaflet which they should carefully read through. They will then be given at least 24 hours to decide whether they would like to participate. If they decide to participate, they should contact the researcher either by phone/e-mail and a date is mutually agreed upon when the patient can return to the pharmacy to meet the researcher and opportunity will be given to ask questions and discuss the study. If the eligible participant then after this decides that he/she wants to participate,

an informed consent will be handed the eligible participant and this consent sheet should be carefully read through and then signed by both the participant and the researcher. Informed consents will be stored in a locked safe at the pharmacy, accessible only to the researcher, two pharmacy managers, and pharmacy managers' assistant.

1.1. After signing the informed consent, the participant will be assigned a participant code (number). They will be asked by the researcher for how long they have been taking antihypertensive medicine/medicines and which antihypertensive medicine/s they are currently taking. The researcher will ask the participants permission to approach their GP/prescriber. The researcher will then go and approach the prescriber with the full details of this project. It will be explained to the them that under Swedish law the researcher is not allowed to download prescription data from the pharmacy dispensing computer system in front of the researcher, so, therefore, the researcher is requesting their assistance which is legal on how many prescriptions they wrote and what for and if the researcher can have permission to ask your practice manager to give the researcher that data when a patient has given the researcher ethical consent to do so. The GP/prescriber/practice manager can be provided with copies of the ethical consent and the researcher will not trouble the GP/prescriber each time if the practice manager could provide the researcher this data off the prescribing system. This information will be registered electronically linking it with the participant code. The participant will be assigned to a monotherapy or poly pharmacy study arm depending if they are taking one or more antihypertensive medicines.

1.2. The participant will be handed a protocol sheet where the participant must record when they begin to take the first pill in the medicine/s bottle/s. Participant names will not appear on any of these data collection papers, only the assigned participant code. Patient name, demographic details, assigned participant codes and which medicines they are taking will be stored in a master computer file in two USB memory sticks (one backup) which both will be protected by encryption using the encryption software TrueCrypt. These two USB memory sticks will be stored in a locked safe in the pharmacy only accessible to the researcher, 2 pharmacy managers, and one pharmacy managers' assistant.

2. Data collection questionnaires

The participant will be handed the questionnaires containing the 8-item MMAS, MARS, and BMQ which the participant will be partially facilitated by the pharmacist to answer in a quiet room in the pharmacy building. After the participant has filled out the questionnaires these will be handed back to the researcher.

3. Blood pressure and pulse measurement

The participant will then be asked to be seated on a chair in a quiet room in the pharmacy and rest for 5 minutes (Mancia *et al*., 2007; O'Brien *et al*., 2005; The British Hypertension Society, 2012). Blood pressure and pulse of the participant will then be measured using the clinically validated electronic blood pressure monitor Omron 705-IT and take up to 3 readings to check for continuity (The British Hypertension Society, 2012). Step 1.1, 1.2, 2 and 3 is set to take maximum 1 hour. Blood pressure data will be recorded on a separate

paper sheet for each participant containing only the participant code. The participant will also be informed about the result of the blood pressure and pulse measurement.

4. Pill count

The participant will be asked to bring their medication bottles to the pharmacy to enable the researcher to perform pill counts. This will be done each time the participant comes to the pharmacy for medicines refill (usually after 3 months or depending on the prescribed amount). Now the participant would have to bring in the pill count protocol to show it to the researcher.

5. Intervention

After 3 months from baseline, the intervention will be implemented for each participant based on their individual results received on the 8-item MMAS and MARS. Participants will be contacted preferably by telephone and informed about the intervention and should visit the pharmacy. Depending on the individual 8-item MMAS and MARS results participants receive the following intervention separately or in combination/s will be implemented:

(a) Targeted counselling from the pharmacist – explaining the disease state, medication mechanism and importance, outcomes and importance of adherence (this targeted counselling will take place in a separate, calm and quiet room in the pharmacy building). The time duration for this counselling is maximum 30 minutes per participant.

(b) A patient medication explanation leaflet (titrated to the individual patient's drugs regime/condition

(c) A reminder sheet (to be put up at home in a convenient, prominent position) that is titrated to the individual patient and has tick boxes to show when and if a dose was taken.

6. After 6 months from the first blood pressure measurement visit, the participant should make their last study visit to the pharmacy. The participant will be handed the questionnaires containing the 8-item MMAS, MARS, and BMQ which the participant will be partially facilitated by the pharmacist to answer in a quiet room in the pharmacy building. After the participant has filled out the questionnaires these will be handed back to the researcher in the pharmacy.

7. For blood pressure measurement, the participant will be asked to be seated on a chair in a separate, quiet room in the pharmacy and rest for 5 minutes (Mancia *et al*., 2007; O'Brien *et al*., 2005; The British Hypertension Society, 2012). Blood pressure and pulse of the participant will then be measured using the clinically validated electronic blood pressure monitor Omron 705-IT and take up to 3 readings to check for continuity (The British Hypertension Society, 2012). Step 1.1 and 1.2 is set to take around 1 hour. Blood pressure data will be recorded on a separate paper sheet for each participant containing only the participant code. The participant will after this also be informed about the result of the blood pressure measurement. Step 4 and 5 should take maximum 45 minutes per participant.

A pharmacoeconomic evaluation of delivering a pharmacist-led intervention will be done throughout the duration of the study:

- Cost per increment: How much it costs to deliver 1 mmHg in blood pressure reduction (cost per unit change in clinical outcome) – Following data will be considered: The measured change in systolic, diastolic and mean arterial pressure.

Capital cost will be calculated during the study duration addressing questions such as:

- How much time does it take to administer various counselling as a pharmacist?
- How much does the pharmacist cost per minute and per hour?
- If a special counselling area does not exist – how much will this cost?
- Cost of paper?
- Waste cost of the medication is calculated: Physical pill count provides information how much is wasted or not. Level of adherence data obtained from 8-item MMAS and MARS will also provide data on waste cost. Drug cost is available through The Dental and Pharmaceutical Benefits Agency, TLV website (Tandvård- och Läkemedelsförmånsverket, 2012).

Population and sample

Inclusion criteria: age at least 18 and above, must be having at least one active prescription on an antihypertensive medicine or fixed combinations of antihypertensive medicine, been using the medicine within the past 3 months, medicine refill done only at the study pharmacy throughout the duration of the study, can understand, write and speak Swedish.

Exclusion criteria: Not self-administering medicine, participating in another clinical study

Research instruments

Blood pressure and pulse measurement using a clinically validated blood pressure monitor accordingly to The British Hypertension Society (The British Hypertension Society, 2012). Adherence: (8-item Morisky Medication Adherence Scale, Medication Adherence Report Scale, Medication Possession Ratio), a questionnaire on patient perception on medicines (Belief about Medicines Questionnaire) and a pharmacoeconomic evaluation of the pharmacist-led intervention.

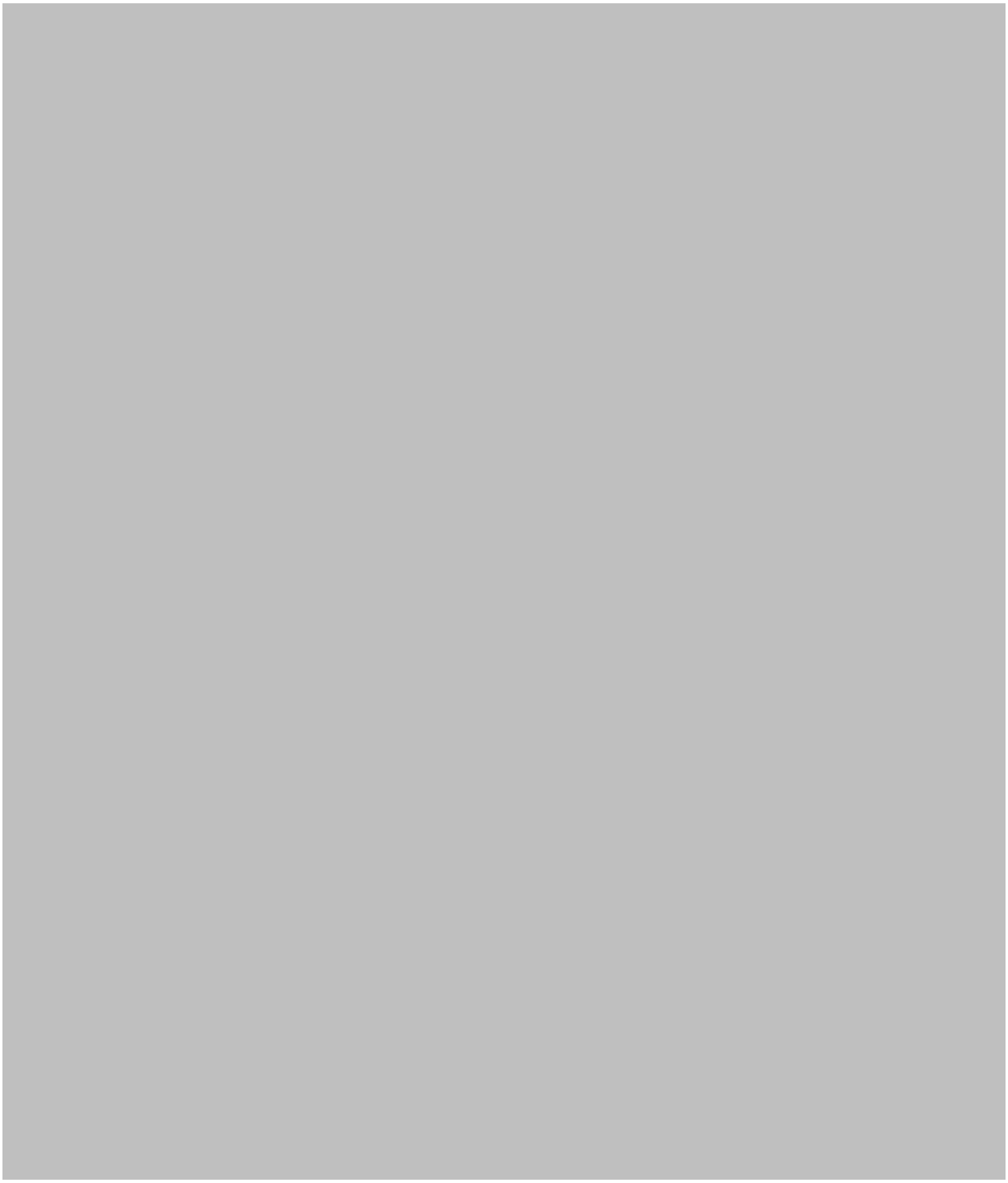
Ethics

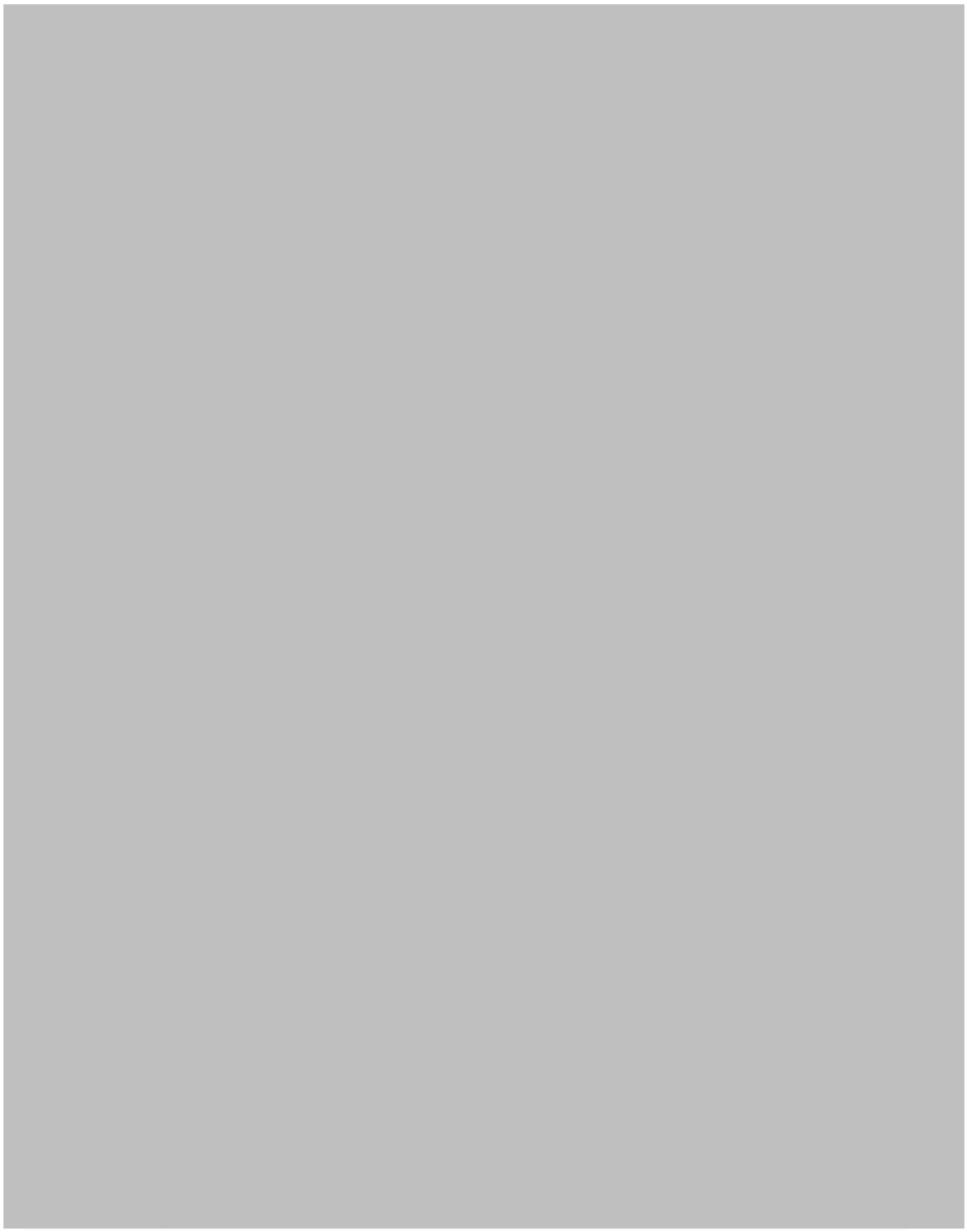
The researcher will apply for ethics approval through the Central Ethical Review Board, Sweden. Ethical issues will involve dealing with human subjects and dealing/gathering personal/confidential data. No identity of any participant will be disclosed in the dissemination of the results. The participant is free to withdraw from the study at any time without giving a reason and no penalty is involved at any stage.

Impact

The impact of this research is to show the significance of antihypertensive medicines adherence check in a pharmacy by a pharmacist is beneficial to contribute to the best pharmacist-led intervention which not only shows to increase antihypertensive medicines adherence, but also results in a decrease in blood pressure and pulse, an increase of quality in life and simultaneously is a cost-effective approach.

5.5 Approval by Regional Ethical Review Board





5.6 Information for research participants

Evaluation of pharmacist-led intervention for improving adherence to treatment with antihypertensive medicines

Background and Purpose The purpose of this research project is to evaluate the efforts made by a pharmacist at a community pharmacy to improve adherence to antihypertensive medication therapy.

Inquiry concerning participation You are asked to participate in this project because you have in the last three months undergone treatment with antihypertensive medicines. We have gained access to this information because you have collected your medications at Apoteksamariten AB. To participate, you are at least 18 years of age, have at least one active prescription on antihypertensive medicine, you are not participating in another clinical trial, you can self-administer the medicine, and that you can understand, speak and write Swedish unhindered.

How will the study be conducted? The study will be conducted at Apoteksamariten AB in Uppsala for 6 months and you are asked to visit Apoteksamariten AB at regular intervals.

- Your blood pressure and your pulse will be measured by the researcher (the pharmacist) during your visit to Apoteksamariten AB at the beginning and end of the study. You will also at each of these two occasions get to answer three different questionnaires which show your adherence to your antihypertensive medication

therapy as well as your beliefs about medications. Every visit were blood pressure and pulse measurement is carried out as well as answering the three questionnaires is expected to take up to 40 minutes.

- You will get a paper protocol and if you been dispensed a refill of your antihypertensive medications from the pharmacy, you should make a note of the date on which you started taking your medications. During the 6-month study period, you should always pick up your medication at Apoteksamariten AB.
- Every time you pick up a refill of your antihypertensive medication you should bring your recently used medicine's package. The researcher will count the remaining pills in the medicine's package. If for any reason you would pick up your medicine at another pharmacy, you should inform the researcher of this to take account of this in the research results/analysis.
- The researcher will with your permission contact the doctor who has prescribed your anti-hypertensive medicine. The researcher will also explain what this project is about. The researcher will then ask for your doctor's help to provide the researcher with information on the number of prescriptions written for you, and for what purpose and date the prescription/s were written.
- Three months after the beginning of the study it will be conducted an intervention aimed at increasing your adherence to your antihypertensive medicines treatment. The intervention is one of the following or a combination of the following:

(a) Targeted counselling from the pharmacist – explaining the disease state, medication mechanism, outcomes and importance of adherence. Counselling will take place in the pharmacy. This counselling will take a maximum of 30 minutes.

(b) An information leaflet about antihypertensive medication/s which is titrated to your medication therapy.

(c) A reminder sheet (to be put up at home in a prominent position) that is titrated to you with tick boxes to show when and if a dose was taken.

What are the risks? The possible risks in this project are that you can feel anxious over your antihypertensive medication therapy, any issues about privacy (to talk about your medications in an open pharmacy environment) and feel embarrassed/singled out to participate in a study. Another potential risk is if the automatic blood pressure monitor used provides incorrect results during blood pressure and pulse measurement. If any problem occurs during the study which puts the safety of the participant and/or the researcher at risk, the project will immediately be stopped until the problem has been investigated and resolved.

Are there any advantages? The project's effects are unknown.

Dealing with data and confidentiality

- All personal data collected in this project are stored and handled in accordance with the Swedish Personal Data Act (1998:204). Responsible for the personal data is Apoteksamariten AB. According to the Personal Data Act, you have the right to once a year at no cost receive all the details about you which are handled and, where

necessary, to have any errors corrected. Contact person is researcher Amirthan Amirthalingam (see contact information under the heading Responsibility).

- Your answers and results will be dealt with to avoid unauthorized access to them. The researcher is a licensed pharmacist and covered by the obligation of professional secrecy applying within health care. You will be assigned an individual participant code. Data will be handled both in paper and electronic form. All material in paper form will only contain your participant code except the consent form which will include your name and personal identity number. The consent form is securely stored at Apoteksamariten AB. Participant code along with your name and your contact information is stored electronically protected by encryption technology.
- Anonymous data will be shared with the University of Birmingham in the United Kingdom which is the academic institution that supervises the study. Personal information is retained until the researcher's doctoral thesis is approved. If the study is being published and presented to the public your identity will not be revealed. If you want to take part of your results in the study or the full study results, we will make sure you do so.

Insurance, compensation Insurance for participation in this study is provided through Länsförsäkringar which is the insurance company Apoteksamariten AB is connected to. No compensation is provided for participation in this study, nor travel expenses, loss of income etc.

Voluntariness Participation in the project is voluntary. You may, at any time and without specific explanation withdraw your study participation without any impact on your usual care.

What happens if something goes wrong or if you have complaints? You should then immediately contact either the researcher or the independent contact person listed below.

Responsibility

Researcher:	***Independent contact person:***
Amirthan Amirthalingam,	Kristina Fritjofsson

Principal Researcher: (communicates in English)

John Marriott, Professor of Clinical Pharmacy

Pharmacy, Pharmacology and Therapeutics Section,

School of Clinical and Experimental Medicine,

College of Medical and Dental Sciences (CMDS),

Medical School Building, University of Birmingham,

Edgbaston, B15 2TT, United Kingdom

5.7 Consent form

Project title: Evaluation of pharmacist-led intervention for improving adherence to treatment with antihypertensive medicines

I have read the information sheet (information for research participants) and I have also been given an oral explanation of the research project by the researcher. I have had the opportunity to ask questions and discuss participation in the study and the study in general, and received at least 24 hours for me to decide whether I want to participate in the study or not. I give my consent to the treatment of my personal data as described in the information for research participants. I give the researcher permission to contact my doctor who prescribed my antihypertensive medicines to get information on how many prescriptions on antihypertensive medications has been written to me and for what purpose and what date the prescription/s are written. I also give permission for the researcher to give my doctor a copy of this consent form, if my doctor requires this. I am aware that my participation in the study is voluntary and that I may at any time cancel my participation without providing an explanation, and that this will not affect my treatment or continuing care. I agree to participate in the study.

Study participant

Place and date:

_____

Study participant's signature: **Study participant's personal identity number:**

_____ _____

Study participant's name:

_____

Researcher

Place and date: **The researcher's signature:**

_____ _____

The researcher's name

_____

5.8 Information leaflet for improving your blood pressure medicine's adherence

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In the year 2000, hypertension existed in 26% of the adult population. It is estimated to be responsible for 4% of the global disease burden. It is a world-wide public health problem. Lowered blood pressure can lead to a reduction in the incidence of stroke and cardiovascular heart disease. According to WHO, treatment of hypertension has shown to prevent cardiovascular diseases, extend and enhance life. Despite this, hypertension is everywhere still inadequately managed. The lack of adherence to blood pressure lowering medicines plays a major role. The concept adherence can be defined as to which extent the patient follows instructions to the treatment which has been prescribed. It is a concept which is non-judgmental and is not thought to be used to blame the treatment, patient or prescriber.

Non-adherence can exist due to many reasons, for example, due to adverse effects, poor instructions, and poor memory. Low adherence is very common: adherence rates to prescribed medicines are about 50% (on a 0-100% scale). This is particularly critical when the treatment response relates to the dose and therapy schedule. In turn, this leads to reduced treatment benefits. The adherence rate to blood pressure lowering medicines depends on the population being studied but is in the range between 50-70 percent. The purpose of this information sheet is to improve your blood pressure medicine's adherence.

- Consult your doctor to make sure that you have understood the disease state.
- Consult your doctor and/or pharmacist to make sure that you have understood the benefit of your treatment.
- Take your medicine only as instructed on your medication label and instructed by your doctor. Ask your doctor or pharmacist if you do not know and/or understand how to take your medicine.
- Never by yourself decide to alter the dose or stop taking the medicine before consulting with your doctor.
- Consult your doctor or pharmacist if you are concerned about possible side-effects or the risks of the treatment.
- Consult your doctor or pharmacist if you experience unpleasant side effects from your treatment.
- Consult your doctor and/or pharmacist if you encounter issues with tablet form, medicines combination, the timing of the dose/s, the cost of the treatment and insurance coverage of the medicine.
- Store your medicine bottle in an environment accordingly to the instructions on your medicine bottle. Make this storage environment will be easily accessible for you.
- Visit your local pharmacy and ask the pharmacy staff to help you with dose aids that will help you remember to take your medicine as prescribed by your doctor.
- When travelling remember to bring your medicine with you and take it as instructed on the label and instructed by your doctor.

- Find a pharmacy which is easily accessible to you. Ask somebody you trust for help when you are not able to visit the pharmacy and make your medicine refill by yourself.
- Make sure to have your blood pressure checked at regular intervals and that there will be a continuous follow-up of your treatment by your doctor.

5.9 Reminder sheet

Participant code________

Reminder sheet

Year:________ Month:____________

On this reminder sheet we kindly ask you to add a check mark when you have taken the dose/s of your blood pressure lowering medicine accordingly to your doctor's prescribed dosage.

Drug name:		**Strength:**	
1		**16**	
2		**17**	
3		**18**	
4		**19**	
5		**20**	
6		**21**	
7		**22**	
8		**23**	
9		**24**	
10		**25**	
11		**26**	
12		**27**	
13		**28**	
14		**29**	
15		**30**	
		31	

Drug name:		**Strength:**	
1		**16**	
2		**17**	
3		**18**	
4		**19**	
5		**20**	
6		**21**	
7		**22**	
8		**23**	
9		**24**	
10		**25**	
11		**26**	
12		**27**	
13		**28**	
14		**29**	
15		**30**	
		31	

Drug name:		**Strength:**	
1		**16**	
2		**17**	
3		**18**	
4		**19**	
5		**20**	
6		**21**	
7		**22**	
8		**23**	
9		**24**	
10		**25**	
11		**26**	
12		**27**	
13		**28**	
14		**29**	
15		**30**	
		31	

Drug name:		**Strength:**	
1		**16**	
2		**17**	
3		**18**	
4		**19**	
5		**20**	
6		**21**	
7		**22**	
8		**23**	
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15		**30**	
		31	

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