To compare the efficacy of blood pressure reduction with or without the biochemical profile.

A thesis submitted to the University of Salford for the degree of Professional Doctorate in the Faculty of Health and Social Care 2010

by

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DECLARATION

No portion of the work referred to in the thesis has been submitted in support of an application for another degree of qualification of this or any other university.
GLOSSARY

ACEI:
Angiotensin converting enzyme inhibitors. A group of drugs used in the treatment of hypertension.

Addison's Disease:
Bronze-like pigmentation of the skin, severe prostration, progressive anaemia, low blood pressure, diarrhoea, and digestive disturbance, due to adrenal hypo function.

Afterload:
The myocardial wall tension developed during systolic ejection.

Agonist:
(Pharmacology) A drug that has an affinity for and stimulates physiologic activity at cell receptors normally stimulated by naturally occurring substances.

Angiotensin:
A decapeptide hormone formed from the plasma glycoprotein angiotensinogen by renin secreted by the juxtaglomerular apparatus.

Atheroma:
A mass or plaque of degenerated thickened arterial intima, occurring in arterial disease.

Atherosclerosis:
A form of arteriosclerosis in which atheromas containing cholesterol, lipoid material, and lipophages are formed within the intima and inner media of large and medium-sized arteries.

Athrogenesis:
Formation of atheromatous lesions in arterial walls.

Bradykinin:
A nonapeptide kinin formed from Kallindin 11 by the action of Kallikrein; it is a very powerful vasodilator and increases capillary permeability; in addition, it constricts smooth muscle and stimulates pain receptors.
Cardiac output:
Cardiac output is the product of heart rate and stroke volume.

Chronotropic:
Interference with regularity of a periodical movement, such as the heart's action.

Collagen:
The protein substance of the white fibers of skin, tendon, bone, cartilage and all other connective tissue; composed of molecules of tropocollagen.

Conn's Syndrome:
Primary aldosteronism; this rare condition is caused by excess aldosterone production leading to sodium retention, potassium loss and the combination of hypokalaemia and hypertension.

Diastole:
The phase of the heartbeat when the heart muscle relaxes and allows the chambers to fill with blood.

Diastolic BP:
Pressure in the arteries during ventricular dilatation.

Diuretic:
An agent that promotes urine secretion.

Efferent:
Conveying away from a centre, as an efferent nerve.

Endothelial dysfunction:
Endothelial dysfunction or injury is caused by mechanical sheer stresses, biochemical abnormalities, immunological factors, inflammation and genetic alteration, and is believed to trigger atherogenesis.

Endothelium:
The layer of epithelial cells that lines the cavities of the heart and of the blood and lymph vessels, and the serous cavities of the body.
Fibroblasts:
An immature fiber-producing cell of connective tissue capable of differentiating into chondroblast, collagenoblast, or osteoblast.

Fibronectin:
An adhesive glycoprotein: one form circulates in plasma, acting as an opsonin; another is a cell-surface protein, which mediates cellular adhesive interaction.

Homocysteine:
A transmethylation product of methionine; it is an intermediate in the synthesis of cystine.

Humoral mechanism:
Relating to the body fluids, especially with regard to immune responses involving antibodies in body fluids as distinct from cells.

Hyalinised:
Made glassy and transparent due to amyloid degeneration.

Hyponatremia:
A deficiency of salt in the blood; salt depletion.

Infarct:
A localised area of ischaemic necrosis produced by occlusion of the arterial supply or venous drainage of the part.

Inotropic:
Affecting the force of muscular contractions.

Liddle's Syndrome:
Early onset hypertension and hypokalaemia, associated with low circulating renin and aldosterone concentrations (Liddle et al 1966). It is due to a mutation of the mineralocorticoid-dependent epithelial sodium channel, which results in constitutive channel activation, even in the absence of mineralocorticoid. Liddle's syndrome is inherited in an autosomal dominant manner, and fails to respond to spironolactone (aldosterone antagonist), but does respond to triamterene (epithelial sodium-channel blocker).
Lumbar sympathectomy:
Transection, resection or other interruption of the lumbar sympathetic nervous pathway.

Myocardium:
The middle and thickest layer of the heart wall composed of cardiac muscle.

Myocyte:
A muscle cell.

Opsonin:
An antibody, which renders bacteria susceptible to phagocytosis.

Peripheral resistance:
Vascular resistance is a term used to define the resistance to flow that must be overcome to push blood through the circulatory system.

Primary aldosteronism:
Arising from an over secretion of aldosterone by an adrenal adenoma, characterised typically by hypokalaemia, alkalosis, muscular weakness, polyuria, polydipsia, and hypertension.

Renin:
A proteolytic enzyme synthesised, stored, and secreted by the juxtaglomerular cells of the kidney; it plays a role in regulation of blood pressure by catalysing the conversion of angiotensinogen to angiotensin I.

Renin angiotensin system:
The juxtaglomerular apparatus in the kidney secretes renin, which converts angiotensinogen in blood to angiotensin I. This is in turn converted to angiotensin II, which is both a vasoconstrictor and the most important stimulus for the release of aldosterone by the renal cortex. It also modifies intrarenal blood flow.

Sarcomere:
The contractile unit of a muscle fiber.
**Stroke volume:**
The amount of blood passed into the aorta with each contraction of the left ventricle.

**Sulphonomides:**
Bacteriostatic agents, i.e. a substance that prevents bacteria from multiplying, active against a wide variety of bacteria. Largely supplanted by more effective and less toxic antibiotics.

**Sympathetic nervous system:**
One of the two parts of the autonomic nervous system, which is concerned with maintaining a stable internal environment. It governs functions, which are normally carried out below the level of consciousness.

**Systolic BP:**
Pressure in the arteries during ventricular contraction.

**Vascular tone:**
The degree of resistance to passive elongation or stretch in blood vessels.

**Vasodilatation:**
A state of increased calibre of the blood vessels.
**Abbreviations Key**

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<td>ARB</td>
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<td>ARR</td>
<td>Aldosterone Renin Ratio</td>
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<td>ASCOT</td>
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<td>BB</td>
<td>Beta blocker</td>
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<td>BHS</td>
<td>British Hypertension Society</td>
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<td>BNF</td>
<td>British National Formulary</td>
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<td>BP</td>
<td>Blood Pressure</td>
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<td>BPLTTC</td>
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<td>CAD</td>
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<td>CCB</td>
<td>Calcium Channel Blocker</td>
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<td>CHD</td>
<td>Coronary Heart Disease</td>
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<td>CHARM</td>
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<td>CONVINCENCE</td>
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<td>CVD</td>
<td>Cardio vascular disease</td>
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<td>DASH</td>
<td>Dietary Approaches to Stop Hypertension</td>
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<td>DBP</td>
<td>Diastolic blood pressure</td>
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<td>EUROPA</td>
<td>European Trial on Reduction of Cardiac Events with Perindopril in Stable heart disease</td>
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<td>HOPE</td>
<td>Heart Outcomes Prevention Evaluation</td>
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<td>HOT</td>
<td>Hypertension Optimal Treatment</td>
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<td>JBS</td>
<td>Joint British Society</td>
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<td>LIFE</td>
<td>Losartan Intervention for End Point Reduction in Hypertension Study</td>
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<td>LV</td>
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<td>LVH</td>
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<td>MRI</td>
<td>Manchester Royal Infirmary</td>
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<td>NHS</td>
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<td>NICE</td>
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<td>NORDIL</td>
<td>Nordic Diltiazem</td>
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<td>National Service Framework</td>
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<td>OP</td>
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<td>PA</td>
<td>Primary Aldosteronism</td>
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<td>PROGRESS</td>
<td>Perindopril Protection Against Recurrent Stroke Study</td>
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<td>RAS</td>
<td>Renin Angiotensin System</td>
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<td>RH</td>
<td>Resistant Hypertension</td>
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<td>RCT</td>
<td>Random Controlled Trials</td>
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<td>SBP</td>
<td>Systolic blood pressure</td>
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<td>SCOPE</td>
<td>Study on Cognition and Prognosis in the Elderly</td>
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<td>SHH</td>
<td>Stepping Hill Hospital</td>
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<td>UKPDS</td>
<td>United Kingdom Prospective Diabetes Study</td>
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<td>VALUE</td>
<td>Valsartan Antihypertensive Long-term Use Evaluation</td>
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<td>WCC</td>
<td>White Cell Count</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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ABSTRACT

**Background** - Resistant hypertension (RH) is common among adults with hypertension affecting up to 30% of patients on treatment for blood pressure (BP) control. It is predicted to increase, as old age and obesity are considered major risk factors for RH. Effective treatment of RH still remains an unmet goal of antihypertensive treatment. This thesis compared two methods of treating RH in two hospital settings, with or without the use of a biochemical blood test.

**Methods and Results** - This was a prospective, quantitative cohort study conducted over 20 months. A total of 213 patients were recruited; 109 (100%) from site 1 (S1) and 111 (100%) from site 2 (S2). The mean age was 53.6 for S1 and 55.1 for S2 and there were 58 male patients from both sites (S1, 53% v S2, 52%). There were 12.9% v 18.21% smokers, 6.8% v 15.3% diabetics, 54.1% v 79.3% hypercholesterolaemia and a family history of coronary heart disease 61.1% v 83.3% in S1 and S2 respectively. The comparison of BP control between the two groups for the study period showed 30.5% from S1 and 32.5% from S2 achieved BP control. A comparison at fixed time of three, six, and nine months S1 v S2 (10.5% v 16.2%, 20.0% v 22.2%, 26.3% v 23.2%) showed no statistically significant difference in BP control. Among those aged <55yrs, 29.5% at S1 v 36.4% at S2 achieved BP control. Among those aged >55yrs, 22.5% at S1 v 34.5% at S2 achieved BP control,

**Conclusion** - There was no statistically significant difference in BP control between those treated on the basis of a biochemical profile or on the nationally agreed algorithm. It can be proposed that health care professionals such as specialist nurses in cardiology could play a significant role in addressing this growing problem.
Resistant hypertension (RH) is defined as (patients with) uncontrolled hypertension despite receiving optimal pharmacological treatment (Markis, Seferou & Papadopoulos 2011). High blood pressure is one of the leading health risk factors for global mortality, being a higher risk factor than tobacco use, high cholesterol and under-nutrition in both developed and developing regions (Ezzati et al, 2002). Hypertension is a very complex disease, where systolic and diastolic BP levels remain elevated which increases the risk of developing major adverse renal and cardiovascular complications (Volp & Tocci 2010). Hypertension is a major global economic burden. It is a common disorder and a powerful risk factor for death and disability from heart disease and kidney failure (Mensah, 2002). BP management remains one of the most cost-effective methods of cardiovascular risk factor reduction. However, at present hypertension management remains suboptimal and BP remains poorly controlled in a high number of patients (Ambrosioni, 2001). The high BP readings commonly found in treated hypertensive individuals reveal that inadequate BP control is a global problem and cannot be solely ascribed to a lack of access to medical care or poor compliance with therapy. Hypertension remains a major public health problem, affecting up to 20% - 30% of the adult population in western societies (Ong et al, 2007).

In the UK the improved awareness is due to the encouragement of the National Institute of Excellence (NICE), British Hypertension Society guidelines. But this still needs to be improved. Much remains to be learned to understand the obstacles for adequate BP control in the population and efforts need to be intensified to improve BP control (Erdine & Aran, 2004). BP control improved dramatically in the latter part of the twentieth century, resulting in a reduction in cardiovascular mortality in the western world. However, despite the increased awareness of physicians and patients of the need to reduce BP, many patients are still inadequately treated and reductions in cardiovascular mortality are beginning to plateau.
In spite of advances in antihypertensive therapy, it remains an unfortunate fact that only about half of patients with hypertension are correctly identified, half of whom are actually treated, and only half of those treated have adequate BP control – the "rule of halves" (Lip & Chung, 2002). Hypertension is amenable to treatment; hence combining treatment with monitoring may prevent fatal and non-fatal complications.

The purpose of this investigation was to compare the two methods that informed the option of treating hypertension between two hospitals in the North West of England. In the author's practice an aldosterone renin ratio (ARR) test is used to decide the type of medication patients are to be prescribed, whereas in a neighbouring hospital the biochemical test is not in use and treatment is based on a nationally recognised algorithm. This study is a quantitative clinical outcome orientated study, which is projected in the choice of the study design. Although this could be considered to be medically orientated the researcher discusses how nurses can lead this management to enhance continuous timely care to this population. This study focused on the BP reduction and length of time taken to achieve target BP in hypertensive patients, using two different methods of decision making. A comparison was made between the two hospitals, where one centre utilised a blood test as an indicator to identify the appropriate antihypertensive drug of choice, whereas the second centre followed an algorithm to control BP.

This thesis provides an insight into the history of hypertension and RH, the pathophysiology and its treatment. The rationale for treating RH is explained to emphasise the need for conducting this study. The management guideline is explained along with current evidence. The impact of the chosen method of treating hypertension and its impact on the NHS is explained, with the aim of developing the specialist nurse role in this area. More reliable BP assessment may benefit from nurse-led clinics. Nurses have proved to be more user friendly,
accessible and less hurried, and to improve patients' understanding of their condition, encouraging healthy living and forming an alliance with patients (Oakshott et al, 2003). Nurses are known to lead services based on a protocol, and as the study outcome suggested, the possible role development has been explored.

Data collection was started in December 2006. The data were entered on a database using SPSS statistics 17.0 software package. A number of confounding variables were identified, hence inclusion and exclusion criteria were utilised to control them. But for the purpose of this study the percentage of BP reduction and the time taken to achieve this were the primary outcomes of this study. Comparisons between the two settings were made.

The literature review provides the reader with an insight into the subject area. A range of electronic healthcare databases was searched for relevant literature. An enormous amount of literature that focused on hypertension was discovered; therefore only the major studies, which focused on BP reduction with antihypertensive agents and which brought a change to practice, were included. In this first section of the literature review an overview of the disease burden, physiology, and pathophysiology are provided. In the latter part, barriers to achieving BP control, Meta analysis and critical review of BP trials are explored. Chapter 4 explains the methodology adopted for this study. Chapter 5 gives a detailed account of the analysis of the study, and the sixth chapter discusses the outcome and its impact on education, policy, practice and research, along with strengths and limitations of this thesis and recommendations.
CHAPTER 1
OVERVIEW OF HYPERTENSION

Introduction

This chapter provides the reader with an overview of hypertension management, the global burden of hypertension and the effects this has on the individual, which in turn gives emphasis to this study. The history of hypertension and the pathology, pathophysiology as a disease process, is explored in detail. Although the main intention of this study was to compare the two methods of tools that informed the treatment option in treating RH, the focus was to identify if the biochemical blood test aided in achieving BP control earlier than the nationally agreed algorithm. This is considered necessary to provide the reader with an understanding of the illness process and the evidence to support the management strategies. The common risk factors and the need for the treatment are also discussed in this chapter. It is vital to understand what hypertension is, to enable the reader to understand RH.

1.1 Current view of hypertension management

As one of the earliest recorded medical conditions, hypertension and its consequences contribute significantly to worldwide morbidity and mortality (Kakar & Lip, 2006). The term “rule of halves” was coined in the 1960s to describe the management of hypertension, because, for a given population of people with hypertension, about half were diagnosed, about half of these were treated and about half of the treated hypertensives were controlled.

Though this phrase was coined in the 1960s it is as true today as it was then. The British Heart Foundation (2011) suggests that nearly half of those who have high BP are not being treated for it. In the UK, 30% of the adult population have been identified as hypertensive, with a BP >140/90mmHg, or are on antihypertensive therapy; and the rule of halves continues to apply.
(Mant & McManus 2006). Sawicki & McGauran (2006) suggest that the focus had been towards identifying the best antihypertensive agents and the strengths and weaknesses of megatrials, though little has been done to improve the overall quality of control in the population. Hypertension is still uncontrolled, and the quality of control in those who need it most, such as patients with diabetes, is by no means better. In the US in 2003-2004, the treatment rate among hypertensive patients was only 53.7% thus approximately half of the hypertensive patients were not being treated (Ong et al, 2007). In Ireland, the inevitable consequence of increased longevity and the accompanying rise in the prevalence of hypertension is that despite remarkable therapeutic advances, complications related to hypertension are expected to increase. It has been known for more than two decades how important it is to have good BP control to prevent complications, yet despite having drugs available to effectively treat hypertension the rule of halves is still applicable in most European countries (O'Brien, 2011). To address the rule of halves a lot remains to be done to improve BP control.

It has been suggested that 31% of men and 28% of women in England had hypertension or were being treated for hypertension. Around three fifths (58%) of men and nearly half of women with hypertension were not receiving treatment, of those that were treated around half remained hypertensive (Alder, Peto & Scarborough, 2008).

Hypertension is the leading cause of stroke, a major catastrophe from a human, financial and societal point of view (Schiffrin, 2005). Clinical trials provide clear evidence that reducing BP with antihypertensive drugs significantly reduces cardiovascular disease (CVD) mortality and morbidity. International studies such as Systolic Hypertension in Europe showed that control of high BP was followed by a significantly reduced incidence of stroke and by a decrease in development of dementia of almost 50% (Waldstein et al, 2005. Forette et al, 1998). Against
the backdrop of the increasing CVD burden worldwide, the gap between what we know and do in hypertension prevention and management is a major cause for concern (Mohan & Campbell, 2009). It is also a contributory factor in over 90% of patients who develop heart failure. Stroke and coronary heart disease (CHD) accounts for six of every ten deaths in developed countries (MacGregor & Kaplan, 2001).

1.2 Global burden

Although BP lowering treatment reduces the hypertension-related burden of disease, BP control continues to be poorly achieved worldwide (Volp & Tocci, 2010). Hypertension has a high prevalence and is associated with high mortality and morbidity. The effective treatment of hypertension still remains an unmet goal of antihypertensive drug treatment (Grassi, 2011). Hypertension is one of the most common causes of the global disease burden. This situation is likely to worsen rather than improve given an aging population. (Brown et al, 2003). An analysis of pooled data from various regions of the world estimated that overall 26.4% of the adult population had hypertension in 2000 and this would increase to 29.2% by 2025. Thus the number of patients with hypertension in 2025 is predicted to increase by about 60% of a total of 1.56 billion (Beevers, Lip & O'Brien, 2007).

Unfortunately, despite the availability of effective pharmacological and non-pharmacological treatments for hypertension, and the widespread dissemination of management guidelines and treatment goals, BP control rates are very poor across the world. In the United States where levels of public awareness and access to health care are comparatively high, whilst control rates are improving, only a minority of patients are adequately treated to goal (Ong et al, 2007).
The gap between the ability to prevent and treat hypertension and the actual levels of control achieved constitutes a significant failing of public health management and health care worldwide (Bakris et al, 2008). During the past century, such disease has changed from a minor cause of death and disability to one of the major contributors to the global disease burden (Levenson, Skerrett & Gaziano, 2002). Hypertension is a greater population burden in economically developing rather than developed countries. Hypertension is more common in economically developed countries (37.3%) than in economically developing ones (22.9%). The much larger population of developing countries results in a considerably larger absolute number of individuals affected (Kearney et al, 2005).

1.3 Burden of hypertension in the United Kingdom

The Health Survey for England in 2009 showed the prevalence of high BP in 2009 was 32.0% among men and 28 % among women. The hypertension control in 2009 increased among men to 8.3% compared to 5.4% in 2003. Among women the difference was not significant, 6.0% in 2003; 7.2% in 2009 (The NHS information centre 2010). Brown et al, (2003) highlighted that it is a tragic fact that 90% of patients with high BP in the UK do not have their BP adequately controlled to current targets, and hence many preventable strokes, heart attacks and cases of heart failure occur unnecessarily: there is a gap between recommendations and practice. In 2009, data shows a slight improvement in BP control, but the BHF data suggests that the BP control in the UK is not adequate.

Concerns over national health issues and implication of hypertension have led to the development of the British Hypertension Society (BHS) guidelines and the National Service Framework (DOH 2000) for Coronary Heart Disease. Falaschetti et al, (2009) in their evaluation of improvement in BP management in England between 2003 and 2006 using cross–sectional representative random samples of 8,834 participants (in 2003) and 7,478 (in
2006) showed, overall mean BP levels in 2006 were 130.8/74.2 mmHg in men and 124.0/72.4 mmHg in women. Awareness of hypertension assessment involved an interview where a cardiovascular module of questions was asked and followed by a visit by a specialist nurse to measure their BP. This study showed that the awareness, treatment and control increased significantly in the overall population (from 62% in 2003 to 66% in 2006; p<0.001), the increase being significant in women (from 64% to 71% in 2006; p>0.001) but not in men (from 60% to 62%; p>0.26). Similarly, the proportion treated had risen significantly overall (from 48% to 54%; p<0.001) in women (from 52% to 62%; p<0.001) but not in men (from 43% to 47%; p= 0.05). Among those on treatment, control rates increased from 46% to 52% (p<0.001; from 44% to 53% in women, p<0.001; and from 48% to 52% in men p=0.18), but despite this improvement, control rates of those deemed hypertensive were only 22% in 2003. Awareness, treatment and control of hypertension increased between 2003 and 2006, particularly in women, but opportunities for further improvement remain.

1.4 Prevalence of RH

Clinical trials suggest that RH is not uncommon and 20% to 30% of study patients are known to have RH (Calhoun et al, 2008). It is important to learn about the prevalence of RH to understand the nature of the problem. Cross-sectional studies suggest that RH is not uncommon. Small studies demonstrate a prevalence of RH that ranges from ≈5% in general medical practice to >50% in nephrology clinics (Kaplan, 2005). Based on data from the National Health and Nutrition Examination Survey, 2003 to 2004, 58% of people being treated for hypertension achieve BP levels <140/90 mmHg (Ong et al, 2007). However, control rates among those with diabetes mellitus or chronic kidney disease are <40% (Ong et al, 2007). In Europe, the situation is worse, with control rates among treated hypertensive patients between 19% and 40% in five large countries (Wolf-Maier et al, 2004). Such data
suggests that RH is more common than appreciated; however, accurate estimates are not possible as control rates under treatment are affected by many factors.

To accurately determine the prevalence of RH, a forced titration study of a large diverse hypertensive cohort would be required. Such a study has not been undertaken, but recent hypertension outcome studies offer an alternative as medications in these studies were provided at no charge; adherence was closely monitored and titration was dictated per protocol. In this regard, the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) may be the most relevant, as it included a large number of ethnically diverse participants (>33,000): 47% female, 35% African American, 19% Hispanic and 36% with diabetes (ALLHAT Research Group, 2002). At the study’s completion after five years, 27% of participants were on three or more medications. Overall, 49% of ALLHAT participants were controlled on one or two medications, meaning that approximately 50% of participants would have needed three or more BP medications. This percentage, however, may underestimate the degree of treatment resistance relative to the general hypertensive population, as patients with a history of difficult-to-treat HT needing more than two medications to achieve BP control were precluded from enrolling in ALLHAT (Calhoun et al, 2008).

Lim & MacDonald (2003) assert that there are many potential reasons why BP control is poor in those diagnosed with the disease. This is not due to the lack of antihypertensive agents, as we now have an ever-expanding armamentarium of drugs that are better tolerated. It is believed that one problem with the current practice in hypertension management is that hypertension treatment is empirical, that the choice of drugs is dictated more by large drug trials based on populations rather than based on the individuals. There is thus disassociation between the underlying pathophysiology and drug therapy.
1.5 Definition of hypertension and RH

BP is a continuous variable in any population with a normal distribution along a bell shaped curve. The difference between “normotensive” and “hypertensive” BP value is therefore somewhat arbitrary, but since CV risk increases with BP, various operational definitions have been developed (Rosendorff 2006). In the past several decades, the levels at which definite hypertension is defined as beginning, have changed from >160/95 mmHg to >140/90 mmHg. Although there is still some disagreement most authorities now agree on several important principles (Black, Bakris & Elliott, 2008). Both systolic and diastolic BP levels should define hypertension. Simply defining and consequently categorising individuals as hypertensive or not only on the basis of their BP levels neglects the value of using the presence or absence of other risk factors, co-morbidity and target organ damage to assess prognosis and ultimately to guide therapy.

The pragmatic definition of hypertension is – the level of BP at which there is evidence that BP reduction does more good (in terms of reducing CVD risk) than harm (JBS 2, 2005). Hypertension based on clinical BP readings is defined in adults (aged >18 years) as a systolic BP >140 mmHg and/or a diastolic BP >90 mmHg, whereas RH is defined as BP that remains above goal in spite of the concurrent use of three antihypertensive agents of different classes. This also includes patients whose BP is controlled but require three or more medications considered to be resistant to treatment (Calhoun et al, 2008). In some patients, achieving goal BP proved to be difficult despite the use of several antihypertensives; and this non-responsive condition was called ‘refractory hypertension’, ‘difficult to treat hypertension’ or ‘difficult to control hypertension’ but this condition is grouped under RH (Faselis, Doumas & Papademetriou, 2011). RH is currently defined as uncontrolled BP despite the use of optimal doses of three antihypertensive medications of which one is a diuretic (Calhoun et al, 2008).
Makris, Saferou & Papadopoulos (2011) highlight that a sizeable percentage of the hypertensive population do not manage to achieve adequate control in spite of receiving 3 or more antihypertensive medications and they are said to have RH. It is necessary for the reader to understand what hypertension is. This is needed to underpin the progression of the disease process and the associated complication profile. This will also help the reader to understand the need for an early diagnosis and treatment within the established guidelines to address the associated morbidity, mortality and the economic cost to society.

The Joint British Societies 2 (JBS2, 2005) guidelines state that the results of clinical trials have determined the pragmatic definition of hypertension as the level of BP at which there is evidence that reduction does more good in terms of reducing cardiovascular disease risk than harm. The JBS2 (2005), BHS and British Cardiac Society guidelines recommend that hypertension treatment should be aimed to achieve goal BP. That is, <140 mmHg systolic BP (SBP) and <85 mmHg diastolic BP (DBP). In high risk patients i.e. people with established atherosclerotic disease, diabetes or chronic renal failure, a lower BP target of <130 mmHg SBP and <80 mmHg DBP may be more appropriate. These targets can usually be achieved with antihypertensive drugs prescribed at doses and in combinations whose efficacy and safety have been shown in trials (JBS2, 2005). In this thesis a comparison of two methods of treating RH between two neighbouring hospitals were studied; the following were the aims and objectives

- To discuss the general characteristics of the patients attending the specialist hypertension clinics.
- To establish whether there was any difference in BP reduction with or without a biochemical profile.
- To identify if there were differences in BP reduction at different points, i.e. three, six and nine months.
In the next section the background to the disease process will be explored to help the reader to understand the complex nature of hypertension.

1.6 History of hypertension

Historically, hypertension has been subdivided into “essential” and “secondary” forms. Essential hypertension (cause unknown) accounts for 95% to 99% of cases and traditionally has been viewed as a consequence of interaction between environmental factors such as salt intake, and genetic background. However, the identity of the genes that predispose to hypertension in the great majority of patients remains unknown. A smaller proportion of patients are identified as having secondary hypertension, as a consequence of an underlying biochemical or mechanical problem or impairment that is potentially reversible, e.g. renal artery narrowing which can be treated by stenting the narrowed artery (Freel & Connell, 2004).

The notion that secondary hypertension is rare has been challenged by the suggestion that primary aldosteronism (PA), which was thought to be present in only 1% of individuals with hypertension, is present in up to 12% of unselected individuals with hypertension (Lim et al, 2000). PA is characterised by excessive aldosterone production beyond that required for maintaining electrolyte balance. The most common underlying cause is an aldosterone-producing tumour known as an adrenal adenoma. The best pointer toward underlying primary hyperaldosteronism is a low potassium level (hypokalaemia) (Wilkinson, Waring & Cockcroft, 2003). Aldosterone is a hormone secreted by the adrenal gland, which is located on the upper pole of the kidney. The position of the adrenal glands depicted below “See Figure 1.1: Position of adrenal glands (http://www.daviddarling.info/web-books.com)”
The principle biological activity of aldosterone is the regulation of electrolyte and water balance by promoting the retention of sodium and excretion of potassium (Dorland's Medical Dictionary, 1989). The renin-angiotensin-aldosterone system (RAAS) is a hormone system that regulates BP and water (fluid) balance. The RAAS plays an important role in the pathophysiology of hypertension such that it affects the regulation of fluid and blood volume, electrolyte balance, and regulates vascular tone (Nadar & Lip, 2009).

One of the most important physiologic mediators in regulating BP is the RAAS. Primarily angiotensinogen is released from the liver. The angiotensinogen is acted upon by renin from the kidneys to produce angiotensin I (Black, Bakris & Elliott, 2008). This in turn is further cleaved by angiotensin-converting enzyme (ACE) to form angiotensin II, which is a powerful stimulator of aldosterone and has a major influence on the adrenal cortex controlling the production and release of this hormone (Kumar & Clark 2004,). Aldosterone stimulates the production of proteins that function as sodium channels in the kidneys to retain sodium and water. This increases the volume of fluid in the body and therefore increases BP (Atlas, 2007).
In the early 1970s, considerable progress was made in the understanding of the pathogenesis of arterial hypertension, especially in the field of the regulation of the renin-angiotensin system (Brunner et al, 1972). Since then the focus has been on a simple diagnostic test, the angiotensin to renin ratio (ARR) as a guide to identify patients with a history of RH. In such individuals this test will allow tailoring of effective treatment targeted at the neurohormal abnormality. Mulatero et al, (2002) insist that ARR is the most reliable method of screening for secondary hypertension and must be performed in hypertension clinics.

1.7 Physiology of hypertension

At its simplest level, the circulatory system consists of a pump, an array of outgoing and returning vessels, and regulatory mechanisms to modify flow and pressure. These components constitute the haemodynamic core BP as the product of cardiac output and systemic vascular resistance (Rudd & Hagar, 1998). Cardiac output refers to the outcome of stroke volume and heart rate. The stroke volume is the amount of blood squeezed out of the heart per contraction, which is multiplied by the number of times the heart beats in one minute.

\[ \text{Cardiac output} = \text{Stroke volume} \times \text{heart rate}. \]

The pathogenesis of essential hypertension remains unclear. In some young hypertensive patients, there is an early increase in cardiac output, in association with increased pulse rate and circulating catecholamines. This could result in changes in baroreceptor sensitivity, which would then operate at a higher BP level. In chronic hypertension, the cardiac output is normal and it is an increased peripheral resistance that maintains the elevated BP. The resistance vessels (the small arteries and arterioles) show structural changes in hypertension. There is an increase in wall thickness with a reduction in the vessel lumen diameter. There is also some evidence for rarefaction (decreased density) of these vessels. These mechanisms would result in an increased overall peripheral vascular resistance.
1.8 Pathophysiology – the disease process

Genetic factors: a strong family history predicts a future occurrence of hypertension with a relative risk. The hereditary determinants of BP elevations remain unknown. The search for genetic determinants is handicapped by the absence of a marker to identify pre-hypertensive individuals before the pressure rises since, thereafter, the initiating factor may be rendered unrecognisable (Rudd & Hagar, 1998).

1.9 Hypertension causes

The gene

To date, three gene mutations have been implicated in human hypertension, (a) glucocorticoid-remediable aldosteronism, (b) Liddle’s Syndrome, (c) Primary hypertension in some Caucasians (Rudd & Hagar, 1998). The gene for angiotensinogen has been associated with essential hypertension in pregnancy, although the clinical significance remains unclear (Wilkinson, Waring & Cockcroft, 2003).

Nature of the blood vessel lumen

In hypertensive subjects, a reduction in lumen and an increase in tunica media (tunica media – the middle layer of the vessel) to lumen ratio are found, without increase in its media cross-section, as a result of rearrangement of smooth muscle cells and collagen and fibronectin. Approximately 60% of hypertensive patients exhibit endothelial dysfunction already in stage 1 hypertension (Schiffrin & Touyz, 2004). A small number of patients (between 2% and 5%) have underlying renal or adrenal disease as the cause of their raised blood pressure. In the rest no clear single identifiable cause is found and their condition is labelled “essential hypertension” (Beever, Lip & O’Brien, 2006).
Hypertension is the product of dynamic interaction between various diverse genetic, physiologic, environmental and psychological factors. However, the extent to which each of these factors contributes to hypertension is not yet clear. As yet there is no strong evidence to support Barker’s hypothesis relating foetal origins and low birth weight to high BP in later life (Kakar & Lip, 2006). Hypertension and socio-economic levels have long been recognised to be inversely associated. However, some inconsistencies exist in the available studies that assess the role of socio-economic status and hypertension in developing countries due to a number of factors, such as obesity, salt intake, diet, exercise, education and alcohol consumption, which may have a significant interaction with low socio-economic status and also with hypertension (Geleijnse, Grobbee & Kok, 2005).

**Inflammation**

Boos & Lip (2006) have explained an interesting disease process in which a relationship between hypertension and inflammation has been recognised. The possibility of an inflammatory state leading to the initiation and sustenance of hypertension raises relevant questions and has implications for novel therapeutic strategies. The modulation of inflammation in cardiovascular disease may be a potential mechanism for the benefits of statins and drugs affecting the renin angiotensin-aldosterone system (Kakar & Lip, 2006). There is a linear relationship between hypertension and white cell count (WCC) explained by Orakzai, Orakzai, Nasir et al (2005) in a Brazilian population. What is not certain is whether elevated WCC contributes to hypertension by translating into increased adherence, capillary leukocytes and increased vascular resistance, or whether increased cytokines secondary to a high WCC result in endothelellial damage/dysfunction leading to the development of hypertension (Kakar & Lip, 2006).
Homocysteine

Another interesting pathophysiological risk factor is plasma total homocysteine. The mechanism is thought to be related to smooth muscle proliferation, collagen synthesis, increased oxidation stress and endothelial dysfunction, all of which contribute to increased arterial stiffness (Kakar & Lip, 2006). Vascular endothelial cells play a key role in cardiovascular regulation by producing a number of potential local vasodilator molecular agents, including the vasodilator molecular nitric oxide and the vasoconstrictor peptide endothelin (Beever, Lip & O’Brien, 2006).

Dysfunction of endothelium has been implicated in human essential hypertension. Modulation of endothelial function is an attractive therapeutic option in attempting to minimise some of the important complications of hypertension. Clinically effective antihypertensive therapy appears to restore impaired production of nitric oxide, but does not seem to restore the impaired endothelium dependent vascular relaxation or vascular response to endothelial agonists (Beever, Lip & O’Brien, 2006). Endothelial damage/dysfunction is closely associated to abnormal thrombosis and atherogenesis in cardiovascular disease; another related pathological process, abnormal atherogenesis. It is also linked to many cardiovascular disorders including hypertension (Kakar & Lip, 2006). The known factors such as cardiac output, peripheral vascular resistance, renin angiotensin system, sympathetic nervous system, renal sodium handling and nitric oxide bioavailability have an important role in maintaining normal BP. Any dysfunction to any part of this equilibrium contributes to high BP. It was important to discuss the ARR mechanism and the rationale for its use. This was considered necessary to help the reader to understand the background for utilising this biochemical test. The next section is focused to underpin the background to ARR and the rationale for its use in clinical practice.
1.10 The renin – aldosterone - angiotensin system

The RAAS has been the predominant pathophysiologic paradigm explaining derangements in BP in patients with kidney disease. More recently, other paradigms have emerged along with its relationship with hypertension management in individuals with no kidney impairment. The RAAS represents the best-known regulator of systemic BP and plays an important role in the pathogenesis of hypertension (Campese & Park, 2006). Along with its role of eliminating waste and maintaining fluid and electrolyte balance, the kidney serves as an endocrine organ to control BP through the secretion of renin, a special protein (Laragh, 2001).

Biosynthesis of aldosterone

Aldosterone, the principle human mineralocorticoid, is produced in the zona glomerulosa of the adrenal gland depicted below “see Figure 1.2: The renin-angiotensin-aldosterone cascade (Nadar & Lip, 2009)” The hormone is a product of a series of biosynthetic reactions. The final key steps in aldosterone synthesis are sequential ii – hydroxylation, 18 – hydroxylation, and 18 – oxidation of the precursor steroid deoxycorticosterone in the zona gromerulosa cells (Kumar & Clark 2004).
Aldosterone regulation mechanism

The principal regulators of aldosterone production are angiotensin ii and plasma potassium. Angiotensin ii stimulates aldosterone secretion from the zona glomerulosa of the adrenal gland in response to sodium depletion and reduced extracellular fluid volume. Aldosterone is known to cause sodium and water retention, which leads to further increase in hypertension (Beevers, Lip & O'Brian 2007).

Initially the principal target organ for aldosterone was said to be the kidney. Mineralocorticoid receptors are found in high concentration in the renal distal nephron as well as other epithelial sites, such as the colon and the ducts of sweat and salivary glands (Orth, Kovacs & Debold, 1992). Mineralocorticoids have been found in non-epithelial sites such as...
heart, brain, vascular smooth muscle, liver and peripheral blood leucocytes (Orth, Kovacs & Debold, 1992). The major sites of aldosterone-induced sodium and potassium transport are luminal cells of the cortical collecting tubules and the distal convoluted tubule. The apically located epithelial sodium channel is the major determinant of renal sodium reabsorption (Horisberger, 1998).

Hypertension and the kidney are inextricably linked. The kidney being the cause of hypertension, renal failure may also be its consequence. Several lines of evidence suggest that the kidneys contribute to the development of essential hypertension (Padmanabhan & Brady, 2004). Renal impairment is associated with huge increases in the risk of CVD, which accounts for up to 50% of all deaths in patients with chronic renal failure. The major structural cardiovascular abnormality found in patients with end stage renal failure is left ventricular hypertrophy (LVH), which is found in 75% of patients commencing dialysis (Padmanabhan & Brady, 2004).

Aldosterone enhances potassium secretion by increasing sodium and potassium ATPase activity and sodium and potassium channel activities. Sodium absorption in the collecting tubule operates a lumen negative potential, which enhances potassium secretion. Aldosterone antagonists interfere with this process. Unlike other diuretics these agents can cause mild, moderate or even severe hyperkalemia. In primary aldosterone (PA), hypertension, hypokalaemia, a condition where there is low blood potassium, suppressed renin activity and increased aldosterone are the characteristics first explained in 1955 (Conn, 1955). When patients presented with hypokalaemia, antihypertensives were discontinued for two weeks to predict PA. It has now been recognised that most patients with PA are not hypokalaemic and that screening can be completed with a simple blood test, whilst continuing to take anti-hypertensives (Young, 2003).
Renin

Renin is a proteolytic enzyme that is produced by the juxtaglomerular cells of the kidney. In conditions in which the blood flow or salt concentration going through the kidney is decreased, the kidney releases renin into the bloodstream. Renin secretion can also occur as the direct result of kidney stimulation by the sympathetic nervous system. Blood renin catalyses the formation of the peptide angiotensin 1 from the larger peptide angiotensinogen. The inactive angiotensin 1 is, in turn, cleaved by angiotensin converting enzyme (ACE) to form the biologically active octapeptide, angiotensin 2. In effect, the secretion of a small amount of renin quickly results in an exponential increase in angiotensin 2 in the blood. Angiotensin 2 causes BP to increase by two distinct mechanisms. It acts as a potent vasoconstrictor to increase the peripheral resistance to blood flow. It also acts on the adrenal gland to stimulate the release of aldosterone, which in turn causes the kidney to retain water (Valcour, 2008).

Need for using Aldosterone Renin Ratio (ARR)

This is a simple diagnostic test, which is used as a marker of inappropriate activity in hypertensive patients. In theory, dividing the plasma aldosterone level by the plasma renin activity derives the ratio. This ratio capitalises on the divergence between the two neurohormones. In patients with PA the plasma aldosterone level is high and this is a negative feedback system, which suppresses renin production, the level of which provides the denominator of the ratio (Lim & McDonald, 2003). Hence in PA the ratio puts into context any given aldosterone level. Thus the importance of a “high normal” aldosterone is amplified by a low renin status. In contrast, subjects with a “high normal” aldosterone and high renin are less likely to have the changes in plasma aldosterone, mirroring that of renin and producing a low ratio (Lim & McDonald, 2003). “See Figure 1.3: Steps in the renin/angiotensin/aldosterone system (Hinchliff & Montague 1998)”
Figure 1.3 – Steps in the renin/angiotensin/aldosterone system

- Decreased renal blood flow → Increased renin release

- Angiotensinogen

- Angiotensin I
  - Angiotensin I converting enzyme

- Angiotensin II
  - Angiotensin II antagonists
  - ↑ Aldosterone:
    - Salt and water retention

- Vasoconstriction
  - ↑ Blood Pressure

During an 18-month prospective study designed to examine the validity of the ARR as a screening test for PA, 90 hypertensive patients with poor BP control were studied. 15 patients (17%) had elevated ARRs greater than 100%. Ten of the 15 patients were found to have adrenal adenoma (tumour) on diagnosis workup and the adenomas were removed. Five patients were found to have adrenal hyperplasia, all of who responded to anti aldosterone treatment. This again suggests that ARR is a valid screening assay for primary aldosteronism.
(PA) in patients with poorly controlled BP (Gallay et al., 2001). If hypertension is not treated it can lead to serious risks. Goodfriend & Calhoun (2004) highlight that in RH, the renin-angiotensin-aldosterone axis is subject to reasonably accurate laboratory testing. Another advantage is that this can be useful even when drawn during therapy with antihypertensive medication. The most useful test of renin-angiotensin-aldosterone status is measurement of both plasma aldosterone concentration and plasma renin activity. The ratio of ARR is useful in uncovering patients in whom aldosterone is inappropriately high, which is over the range needed to maintain adequate plasma volume and renal perfusion with a normal potassium level, and the renin activity below 1.0 ng/ml. Seiler & Reincke (2008) state that the ARR can be used as a screening test in patients with RH.

This study’s intention is to provide evidence for using the ARR as a tool to select the treatment in RH. In the microcosm of practices relating to the treatment of hypertension there are national guidelines, but there is only a suggestion to use the ARR in the clinical situation. Hence, in this thesis, the two methods of treating hypertension were compared to provide the evidence for using the ARR. The aims and objectives were to describe the characteristics of patients, to establish if there was any difference in BP reduction with or without the ARR biochemical test and to identify if there were differences in BP reduction at different times i.e. 3, 6 and 9 months.

1.11 Hypertension and risks

An increased CVD risk associated with mortality and morbidity seems to be higher in patients with RH. There is an increased incidence of target organ damage and thereby, an increase in CVD risk (Faselis, Doumas, & Papademetriou 2011). The relative risk reduction of 25% does not inform about the chance of an individual benefiting from treatment by avoiding a cardiovascular complication; hence, absolute risk reduction is considered to be the best
possible way to predict CVD complications. Absolute risk reduction is the product of the relative risk reduction and the absolute risk of developing a cardiovascular complication (Wallis, Ramsay & Jackson, 2002). In any given patient, the decision to begin treatment is governed by the risk of CVD, which is determined by the magnitude of the BP elevation and the presence or absence of target organ disease and/or additional CVD risk factors.

Hypertension and left ventricular hypertrophy (LVH)

LVH is a common finding in patients with fixed or borderline hypertension and can be diagnosed either by ECG or echocardiography. To understand the relationship between LVH and hypertension, we have to look at the process involved in the development of LVH. The myocardium has three morphological compartments (1) the muscular compartment consisting of myocytes, the dominant cell type of the normal heart ~ 30% of the myocardial cells and ~ 70% of cardiac tissue volume; (2) the interstitial compartment formed by fibroblasts and collagen; (3) The vascular compartment with smooth muscle and endothelial cells.

LVH is defined as an increase in the mass of the left ventricle, which can be secondary to an increase in wall thickness, an increase in cavity size, or both. LVH as a consequence of hypertension usually presents with an increase in wall thickness, with or without an increase in cavity size. This increase in mass predominantly results from a chronic increase in afterload of the LV caused by the hypertension, although there is also a genetic component. A significant increase in the number and/or size of the sarcomeres within each myocardial cell is the pathologic mechanism (Schlaich et al, 2003)

An increase in LV wall stress is the principle mechanical factor in the development of LVH, and BP the most powerful determinant of LV mass. Hypertrophy of the arterial resistance vessels with an increased peripheral vascular resistance is present in established hypertension
LVH is a robust independent risk factor for CVD and premature mortality. It appears that all antihypertensive agents are recommended for initial therapy to reduce LV mass (Black, Bakris & Elliott, 2008). The time has come to revisit the current management of hypertensive heart disease such as LVH. Simply focusing on detecting LVH and reducing the left ventricular mass is not adequate. Early identification and accurate measurement of LV anatomy and aiming to correct them would be associated with risk reduction (Diez & Frohlich 2010).

Heart Failure (HF)

In recent trials in hypertension, development of HF was comparable with stroke (Tocci, Sciaretta & Volpe 2008). Thus one must be aware that HF still represents a frequent deleterious consequence of hypertension. People with blood pressure >160/95 mmHg have a six fold higher incidence of heart failure than those with pressures <140/90 mmHg. Hypertension as a cause of heart failure, however, is confounded by the underlying predisposition to coronary artery disease. Most cases of heart failure are the result of left ventricular systolic dysfunction that results from damage to the ventricle after myocardial infarction (Beevers, Lip & O’Brien 2007). In hypertensive LVH, the ventricle cannot relax normally in diastole. Thus, to produce the necessary increase in ventricular input, especially during exercise, there is an increase in left atrial pressure rather than the normal reduction in ventricular pressure, which produces a suction effect (Beevers, Lip & O’Brien, 2001). This demonstrates that hypertension is a contributory factor in developing HF. Appropriate strategies to effectively fight the development of HF during its asymptomatic stages when early structural and functional cardiac abnormalities are identified should be applied to hypertensive patients with a high – risk profile (Lee et al, 2009).
Renal dysfunction

There is a link between antihypertensive agents and renal impairment. The kidney is both a cause and a victim of hypertension. High BP is a key pathogenic factor that contributes to deterioration of kidney function (Sarafidis & Bakris, 2008). It is often difficult to differentiate between the two on clinical grounds. Therefore, treatment of hypertension has become the most important intervention in the management of all forms of chronic kidney disease (Bakris & Ritz, 2009).

To achieve target BP any class of hypertensive can be used, but to preserve renal function, certain principles must be followed: they are – BP will never be controlled adequately in patients with significant renal insufficiency by the use of a diuretic, usually a loop diuretic. An ACEI must be used in combination with other antihypertensives. Where an ACEI cannot be used, i.e. due to side effects, then an angiotensin receptor blocker should be used to protect the renal function. (Black, Bakris & Elliott, 2008).

Coronary artery disease (CAD)

RH remains the most important modifiable risk factor for CAD (Makris, Seferou & Papadopoulos 2011). There is no doubt that the magnitude of hypertension does have an impact in the incidence of CAD. There are important pathophysiological links between atrial BP and CAD. There is endothelial dysfunction remodelling of coronary arteries and increased resistance at microvascular level all contributing to decrease of coronary reserve (Escobar 2002). Mitsutake et al. (2011) suggest that adiponectin and leptin are produced by adipose tissue and are known to play an important role in the development of metabolic syndromes. Therefore there is a strange correlation between leptin plasma concentration and renal sympathetic activation, as shown in men with widely differing degrees of adiposity. (Eikelis et al, 2003). Patients with hypertension appear to have significantly lower plasma adiponectin
levels than normotensive patients. So the plasma level of leptin may be associated with hypertension.

**Stroke**

Sub optimal BP control is responsible for 62% of cerebrovascular disease (WHO, 2002). In the UK about 40% of all strokes are attributable to a systolic BP $\geq 140$ mmHg. Men aged 40 – 59 years with an SBP of 160-180 mmHg are at about a four fold higher risk of stroke in the next eight years than men with an SBP of 140-159 mmHg (Beevers, Lip & O’Brien 2007).

Needless to say, accurate BP measurement is important. The consequences of poor BP control are huge. Despite the clear guidelines on BP measurement technique, there seems to be large inter-observer variations, both among nursing staff and physicians, as well as between the two groups (Pater, 2005). The issues surrounding BP measurement, attitudes and equipment are discussed in a later chapter.

1.12 History of Antihypertensives

Treatment of hypertension has evolved greatly over the past century, moving from difficult to tolerate and often ineffective low salt dietary regimens to an arsenal of modern pharmaceuticals. It was more than two centuries following the first measurement of BP before the first trenchant treatment of hypertension was developed. Sodium restriction was advocated after the role of sodium was elucidated in 1904 and the rice diet of Kempner was popularised in the early 1940s. Sodium thiocynate was the first chemical substance to be used in the treatment of hypertension by Treupel and Edinger in 1900, and Hines in the Mayo clinic: it was potentially toxic and had many side effects and so became unpopular (Esunge, 1991). The only alternative to the Kempner diet was a bilateral lumbar sympathectomy, a major
procedure at that time and one that was limited to only the relatively young and fit (Hamdy, 2007).

1.13 Treatment for hypertension

The biggest step in treating hypertension came with the introduction of the first orally effective diuretic, to increase urine output with Chlorthiazide by Fries, Wanko and Schnaper in 1960 (Freis, 1995). The discovery of diuretics is interesting. The sulphonomides, another group of chemical agents that were discovered in the 1930s, were used for bacterial infections. Karl Bayer modified the formula of the sulphonomide and developed chlorothiazide, a relatively safe but effective diuretic (i.e. Bendroflumethiazide, Bumetanide, Amiloride etc.).

In 1960 beta-blockers (BBs), which act on beta-receptors, were introduced. Although originally marketed as a treatment for angina, it was soon observed to decrease BP. Subsequently, calcium channel blockers (CCBs) became available, and then angiotensin converting enzyme inhibitors (ACEIs). In 1980 the toxic effects of venom from a Brazilian viper were found to cause a massive drop in BP; this led to the discovery of Captopril, the first ACEI. Captopril was a breakthrough not only in the management of BP but also as an early example of structure-based drug design, a revolutionary new approach to pharmacy. This in turn led to the development of angiotensin receptor blockers (ARBs), which are markedly efficacious at lowering BP (Ferrario, 2005). Hypertension management has become increasingly complex. The number of available drugs requires difficult management decisions, especially in the patient with long-standing disease and co-morbidities (Ferrario, 2005). In the latter part of the thesis, each individual drug group will be explored in detail to give the reader an understanding of the types of drugs used, and how they act to control hypertension.
Rationale for RH management

Calhoun, Jones, & Textor (2008) assert that the importance of RH lies in the identification of patients who are at high risk of suffering complications from the reversible cause of hypertension and who may benefit from a particular diagnosis or therapeutic approach. The prevalence of RH is unknown, in part because of its arbitrary definition (Makris, Seferou, & Papadopulos 2011). Kaplan (2005) highlights small studies, which estimate the prevalence to be from 5% in general practice and up to 50% in nephrology clinics. The Framingham data showed a higher baseline SBP, older age, presence of left ventricular hypertrophy, and obesity to be the strongest predictors of lack of blood pressure control (Lloyd-Jones, Evans & Larson 2000 & 2002). The management of RH represents a challenge for the clinician but it is the rationale for patients with RH to be referred to specialised hypertension clinics.

Protogerou et al, (2009) have described large artery stiffening as a common factor contributing to treatment resistance in hypertensive patients. This suggests that there are many factors associated with the development of RH, such as the aging process and associated arterial stiffening as a key characteristic (Williams, 2009). Williams (2010) suggests that in the treatment of RH the evidence base is thin, and this could be a fruitful avenue for therapeutic development, particularly in view of an aging population, as the number of RH cases will be expected to rise. Gaddam et al, (2008) evaluated the characteristics of 279 consecutive patients with RH on 3 hypertensive agents and uncontrolled blood pressure, and 53 patients with normotensive or hypertension controlled with 2 agents. Biochemical evaluation was performed. In this study 60% of patients with RH had suppressed plasma renin activity compared to 40% of controls. 35% of the patients with RH had an elevated aldosterone to renin ratio and 29% had elevated 24-hour urine aldosterone and suppressed plasma renin activity. This multifactorial disorder needs timely evaluation and treatment to reduce the associated complications. Treatment of RH is aimed at reversing life style factors
contributing to treatment resistance. Accurately diagnosing and appropriately treating secondary causes, and effectively using multidrug regimens are necessary. Lifestyle changes, pharmacological therapy and non-pharmacological therapies have all shown benefits in patients with RH, though much additional knowledge is needed to better identify and treat these patients (Segura, de la Sierra & Ruilope 2010). The prevalence of RH continues to increase and the standard approaches of therapeutic lifestyle changes and drug therapy are ineffective in bringing many of these patients to goal BP (Joshi, Taylor & Bisognano 2009). A holistic programme for controlling cardiovascular risk should be fully discussed with the patient, including evaluation to exclude underlying causes of secondary hypertension, and implementation of lifestyle measures (Wang & Zhou 2010). The data from this thesis suggests there was a lack of holistic assessment. Nurses would be ideal to promote holistic care, as they have proved themselves competent in identifying and addressing lifestyle changes in chronic disease management (Boville et al, 2007).

Summary

Hypertension is a major risk factor for cardiovascular and renal diseases and early data indicate that untreated hypertension shortens life expectancy by approximately five years. The prevalence of hypertension continues to increase worldwide. It is paradoxical that despite the enormous advances in hypertensive drug therapy the number of people with uncontrolled hypertension has continued to rise. Timely identification and initiation of antihypertensive therapy is important to prevent organ damage. In this chapter the author has explored the disease process with its historical prospects. An attempt has been made to help the reader to understand the background history, and link it with the present clinical practice and associated risks. In the current thesis the author has explored the patients characteristics, as there is a suggestion that > 65 years old is associated with a higher prevalence of RH (Calhoun, Zaman & Nishizaka, 2008). The length of time taken to achieve the target BP was also explored.
along with justifying the rationale for using the ARR in treating RH. Having explored the disease process in detail, in the next chapter the author will discuss methods of treating hypertension and how clinical trials have affected present practice.
CHAPTER 2
TREATMENT METHODS AND AGENTS

Introduction

In this chapter methods of treating hypertension and commonly used pharmacological agents are discussed. The reader is provided with an insight into different drug groups, their actions and side effects and the controversies associated with the treatment process are explained. A number of national and international studies are explored in relation to this study. This discussion is considered to be important to aid in evidence-based practice and to demonstrate the complexity involved in treating patients with hypertension.

2.1 Indications for treatment

The British Hypertension Society (BHS, 2004) recommends that patients who do not have clinical CVD, target organ damage or other CVD risk factors, fall into stage 1 (BP 140/159 – 90/99 mmHg) and are candidates for a trial of vigorous life style modification with BP monitoring. If the target BP is not achieved in four to six months, then pharmacological treatment is recommended whereas for individuals with a BP of ≥ 160/ ≥ 100 mmHg, immediate drug treatment is recommended. Systolic BP is recognised as an important target for treatment, particularly in older people, where it is an even more important determinant of CVD risk than diastolic BP (Carretero & Oparil, 2000). More aggressive BP targets are in place for hypertensive patients with co-morbid conditions such as diabetes mellitus or renal insufficiency. The importance of tailoring the choice of antihypertensive drug treatment to the patient’s individual profile of concomitant CVD risk factors/co-morbid conditions is emphasised. The need for simultaneous reduction of multiple CVD risk factors in improving prognosis in hypertensive patients is stressed and in particular the need for home and ambulatory BP monitoring are recommended because of its value in guiding therapy and
enhancing adherence to treatment. It is vital that the treatment decisions are made on the basis of evidence from randomised controlled trials (Carretero & Oparil, 2000).

2.2 Treatment target

The aim of antihypertensive therapy for most patients is to lower diastolic BP to <85 mmHg and systolic BP to <140 mmHg. In patients with diabetes mellitus and renal insufficiency, a more aggressive BP goal is recommended, which is ≥130/80 mmHg. When compared to people without diabetes, hypertension is twice as common in people with diabetes. In type 1 diabetes, the excess prevalence of hypertension is strongly related to the presence of incipient or overt nephropathy. In type 2 diabetes, hypertension is very common with prevalence rates nearing 80% in many European countries (Williams, 2003). Hypertension greatly increases the already elevated CVD risk in people with diabetes. BP reduction provides proportional reduction in risks that are largely independent of the starting BP and provides new impetus for a greater use of BP lowering therapies in high-risk individuals (Czernichow et al, 2011).

Diabetes increases the risk of CVD twofold in men and fourfold in women (Zanchetti et al. 2001). The combination of hypertension and diabetes doubles the risk of developing microvascular and macrovascular complications and doubles their risk of mortality when compared to non-diabetic people with hypertension (Zanchetti et al. 2001). The clinical trial evidence shows that more intensive BP lowering is beneficial in reducing cardiovascular and diabetes-specific events in people with diabetes. This has led to the recommendation that BP treatment targets should be lower in people with diabetes (Williams, 2004). There can be no doubt that the aggressive control of BP in diabetes reduces both the rate of progression of nephropathy and the risk of cardiovascular complications (Andrew, 2004).
2.3 Hypertension treatment

In treating hypertension non-pharmacological and pharmacological methods are used. In the former method strict lifestyle modification is used and the individual is kept under strict surveillance to assess the implications. These are discussed below. Patients with borderline elevation of BP, or individuals who are reluctant to take medication and would prefer a natural method of reducing BP, consider this method. In the latter method, as the name suggests, various antihypertensive agents are used to achieve target BP.

2.3a Non-pharmacological treatment

Life style modification

Weight reduction:

Obesity can contribute to treatment resistance. Evidence indicates that there is a graded positive correlation between body mass index and BP levels; whilst weight loss results in BP reduction (Pisoni, Ahmed & Colhoun 2009). Weight reduction results in a lower BP (Neter et al, 2003). A weight loss of 10kg or 10% (of current weight – whichever is greater) will reduce their systolic BP by 10 mmHg. Patients who are overweight may need additional encouragement (McCormack, 2006). Weight loss is closely correlated with reduction in BP and appears to be the most effective of all non-pharmacological measures used to treat hypertension (Carretero & Oparil, 2000).

Exercise:

At least 30 minutes of moderately intense physical activity, such as brisk walking, swimming, or yard work, at least three times per week (preferably once per day) can lower BP by ≈4 to 8 mmHg and is more effective than more strenuous forms of exercise such as running and jogging (Puddey & Cox, 1995). Although this was recommended 15 years ago, it is still being advocated in current practice. Additional benefits of regular physical activity include weight
loss, an enhanced sense of well-being, improved functional health status and reduced risk of CVD and mortality from all causes. Accordingly regular aerobic physical activity is recommended for all hypertensive individuals, including those with target organ damage (Carretero & Oparil, 2000).

**Alcohol:**

Alcohol consumption is an important factor. A large alcohol intake (>3 units a day) has been shown to result in BP elevation (Faselis, Doumas & Papademetriou 2011). Although modest alcohol consumption does not generally increase BP, larger amounts (three or more drinks a day) have a dose related effect on BP, both in hypertensive and normo-tensive persons (Chobanion, Bakris, Black et al, 2003). Alcohol intake in all hypertensive patients should be limited to no more than 1 oz of ethanol a day in most men (the equivalent of three units) and 0.5 oz of ethanol a day in women and lower weight persons (Chobanion et al, 2003). In cross-sectional and prospective studies involving all kinds of populations the relationship between alcohol consumption, BP levels, and the prevalence of hypertension has been remarkably consistent (Carretero & Oparil, 2000).

**Dietary modification:**

In the Dietary Approaches to Stop Hypertension (DASH) trial, a diet rich in fruit, vegetables and low fat dairy products with reduced content of both total and low fat dairy products with reduced content of both total and saturated fat, reduced BP (Sacks, Svetkey, Vollmer et al, 2001). The DASH diet lowered BP independently of peripheral mechanisms (Hodson, Harnden & Roberts 2010). The DASH "combination diet" also produced reductions in BP of 3.5/2.1 mmHg in subjects without hypertension. Translation of the results of the DASH trial to advice for the general public, or the universe of hypertensive patients, is more easily accomplished by recommending four servings of fruit, four servings of vegetables, and three
servings of low fat dairy products per day, than by prescribing a specific daily intake of calcium, potassium and magnesium. This type of advice has shifted the paradigm towards recognition of the powerful role of total diet in the prevention and treatment of hypertension in particular and CVD in general (Carretero & Oparil, 2000).

**Smoking:**
Although cessation of smoking does not alter BP, it is important for the prevention of CVD (Carretero & Oparil, 2000). Smoking is a modest but important risk factor for the development of hypertension (Halperin, Gaziano & Sesso 2008). A Meta analysis of smoking cessation after myocardial infarction showed a relative odds of 0.54 (95% confidence interval 0.46 to 0.62) for coronary mortality in those who stopped smoking compared to those who continued to smoke (Wilson, Gibson & Willan, 2000). It is known that sustaining lifestyle modification is difficult in the real life situation and has not been shown to reduce CVD mortality rates in controlled trials, but this may contribute towards lowering BP, obviate the need for drug treatment or reduce the dosage of antihypertensive drugs needed to control BP (Carretero & Oparil, 2000).

2.3b - Pharmacological therapy
Pharmacological treatment should be based on the most common cause of RH and focused on blocking all physiological pathways to BP elevation (Garg et al, 2005). Many clinical trial outcome data prove that lowering BP with several classes of drugs, including angiotensin converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), calcium channel blockers (CCBs) and thiazide-type diuretics will all reduce the complications of hypertension (Neal, McMahon & Chapman, 2000). In most patients with hypertension, drug therapy is required to achieve target BP levels. It is worth exploring individual classes of drug
to gain a deeper understanding of hypertension treatment along with the clinical trials that underpin the evidence for using these medications in our daily clinical practice.

2.4 Pharmacological agents in the management of hypertension

The NICE, JBS 2 and BHS have developed the A or B or C or D algorithm for selecting individual antihypertensive agents and their combination (NICE, 2006). The BHS suggests the AB/CD algorithm to advise and to assist practitioners on the logical sequence and combination of treatment of hypertension (Williams et al, 2004). In this algorithm each letter refers to a BP lowering drug class. This is a pragmatic template only, although randomised controlled trials have yet to validate this specific algorithm (Brown et al, 2003).

The main classes of BP lowering drugs can be grouped into two categories. The first comprises drugs that inhibit or block the renin-angiotensin system, namely ACE inhibitors, ARBS and BBs. The second category comprises drugs that lower BP independent of the renin-angiotensin system, and indeed causes reflex. The A or B/C or D algorithm is designed to improve BP. In this algorithm, A stands for Angiotensin converting enzyme inhibitor/Angiotensin receptor blocker; B stands for a Beta-blocker; C for a Calcium channel blocker and D for a Diuretic. It incorporates all classes of antihypertensive drugs. Although not specifically validated by a clinical trial, the recommended drug combinations and sequencing are similar to those used in many clinical trials of BP lowering drugs (JBS 2, 2005). In RH antihypertensive agents should be titrated until BP is controlled to the maximum recommended dose is reached, unless patients experience dose related adverse effects. It is then appropriate to add a drug from another class that has additive or synergistic effects with the first drug (Makris, Seferou & Papadopoulos 2011). The AB/CD algorithm has four steps. Step 1 is a single drug: A or B or C or D, depending on the age and ethnic group, titrated up to the highest recommended dose if tolerated. When the first drug is well tolerated but the
response is small and insufficient, the next drug of choice is added. Treatment can be stepped down later if BP falls substantially below the target level. Step 2 involves combining A or B with C or D. Step 3 usually combines A with C and D. Step 4 involves the addition of an alpha blocker or additional diuretic (JBS 2, 2005).

This stepwise approach suggests the initial use of a CCB or an ACE inhibitor with additional classes of drugs being added if BP reduction is not achieved. Although the grouping is based on the capacity of the drugs (A or B) to inhibit, or (C or D) not to inhibit components of the renin-angiotensin system (RAS), in general, A or B drugs are more effective initial therapy in younger patients (<55 years) in whom RAS is generally more active. C and D drugs are generally more effective as initial therapy in older patients (≥55 years) and black adults of any age, in whom the RAS is usually less active (Williams, Poulter & Brown 2004). Currently, in this algorithm B is bracketed. This is because combining a beta-blocker with a thiazide diuretic revealed an increased risk of diabetes. For each major class of antihypertensive drug, there are compelling and possible indications for use in each specific group, and also cautions and compelling contraindications. When none of these special considerations apply then the recommendation is to follow the A or B/C or D algorithm (JBS2, 2005). In the current study the author is comparing the above-discussed algorithm with the biochemical profile, which has been in use (in the author’s current practice) to select treatment for hypertensive patients.

In the next section the author will be discussing each group of medications with evidence for its use. In order to do that the literature search was done using the database MEDLINE, EMBASE, CINAHL, Cochrane Review from 1980 to 2011 to identify trials of BP lowering medication. Search terms such as, antihypertensive agents, adrenergic beta-blockers, angiotensin converting enzyme inhibitors, diuretics, calcium channel blockers, vasodilators and the names of all BP lowering medications were used as keywords or text words. RCTs,
Meta analyses, systematic reviews were the limits. The Cochrane collaboration and citations in trials and previous Meta analysis and review articles were searched. The trials that are cited in this discussion are listed in appendices (appendix 1) for ease of reference.

In this thesis trials included were critically analysed using the Cochrane review criteria. They were: studies aims, justification, methodology used, i.e. single or double blinded, how the sample was selected, what were the outcome measures, how the data was analysed, any bias to the study, validity, and did the outcome reflect the stated aims and objectives (Clark & Oxman 2003). Those studies that met these criteria were included. This was necessary because accessing knowledge is not enough. Appraisal of such information is necessary to discern the salient knowledge and information (Lee, 2009) to be used in this thesis.

2.4a Angiotensin-converting enzyme inhibitors (ACEI)/Angiotensin-II receptor antagonists (ARB)

The development of ACEIs came from studies of the venom of a Brazilian viper – Bothrops Jararaca. This venom potentiates the effect of the vasodilator peptide, bradykinen, strongly enhancing its hypotensive effect to cause shock in the snake’s prey. Further work on this led to the understanding that the bradykinen effect was caused by inhibition of its breakdown. It was then realised that this metabolising enzyme also catalysed the conversion of angiotensinogen to active angiotensin ii. From this work ACE drugs were born (Brady, 2005). The first clinical trials of the active peptide extracted from the snake venom were carried out in the UK and subsequently in the USA. After successfully reducing BP in 14 of the 17 patients tested, an orally active formulation of the peptide was developed, which eventually was marketed as Captopril and was launched in the US in 1981 (Smith & Vane, 2003). Since then many ACEIs have been developed and are in use. Commonly used ACEIs are listed on Table No 2.1.
**Mode of action:**

ACE inhibitors work by blocking the renin-angiotensin system, inhibiting the conversion of inactive angiotensin 1 to active angiotensin 2. Angiotensin 2 is a powerful vasoconstrictor and stimulator of aldosterone release. Inhibition of angiotensin leads to a fall in BP through a decreased pressor response (MIMS, 2004). ACE inhibitors also reduce the breakdown of the vasodilator, bradykinin, which is thought to enhance the antihypertensive effect of ACE inhibitors. ACEIs decrease sympathetic activation. ACEIs suppress aldosterone release. As a result serum potassium levels rise and there is increased elimination of sodium and water. ACEIs also increase the production of renal prostaglandins, which contribute to the diuretic effect. The mode of action is depicted below. “See Figure 2.1: The effects of ACE inhibitors and angiotensinII antagonist on the renin – angiotensin – aldosterone system (Lip & Chung, 2002)”
Evidence for ACEIs:

The Heart Outcomes Prevention Evaluation (HOPE) trial was the second key study to assess Ramipril. In the HOPE trial, Ramipril was given to patients >55 years of age at high risk of
CVD. The HOPE investigators concluded that Ramipril offered numerous benefits to these high-risk patients, perhaps beyond the effect of a small reduction in BP. (Yusuf et al, 2003). The European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) investigated patients at lower risk of developing CHD, regardless of their age or other risk factors (Fox, 2003). EUROPA assessed the effects of Perindopril, a long-acting ACE inhibitor that regulates hypertension over a 24-hour period, in patients with stable coronary artery disease but without heart failure. The investigators of the EUROPA trial concluded that Perindopril was of benefit to all patients regardless of their baseline BP. Is it possible that the reduction in CVD resulted purely from overall improvement in BP control? The results of EUROPA would appear to suggest that the benefits observed with ACE inhibitors are attributable to mechanisms of action other than BP reduction. When a sub-study explored the mechanisms by which ACE inhibitors reduce cardiovascular events, the effect of Perindopril on various markers of inflammation and endothelial dysfunction was measured. Treatment with Perindopril for one year resulted in improvements in endothelial nitric oxide synthase activity, reduction in TNF α and reduction in endothelial apoptosis. This combination of effects seen with Perindopril treatment would be expected to attenuate the atherosclerotic process and offers a possible explanation for the beneficial cardiovascular effects seen. (Baily & Hall, 2006)

ACE is present in both a plasma form and a tissue form. Different ACE inhibitors have varying affinities for plasma and tissue ACE. It is postulated that the short term effects of ACE inhibitors, i.e. BP lowering, are achieved by inhibition of plasma ACE, whereas the long-term cardiovascular benefits arise from inhibition of tissue ACE. The degree of affinity for tissue ACE is dependent on the lipophilicity of the individual drug. Perindopril is highly lipophilic and therefore has a greater affinity for tissue ACE than less lipophilic ACE inhibitors (Fox, 2004). This lipophilicity offers a possible explanation for the greater
cardioprotective effects observed in the EUROPA trial. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was designed to determine the effects of a BP lowering regimen in hypertensive and non-hypertensive patients with a history of stroke or transient ischaemic attack (TIA). The combination therapy was with Perindopril plus Indapamide, which showed a reduction in cardiac events (Progress Collaborative Group, 2001).

Contraindications and side effects:

There are significant contraindications for using an ACEI. In renal artery stenosis circulation is critically dependent on high levels of angiotensin ii. A sharp decrease in angiotensin ii concentration causes dilatation of the glomerular efferent arteriole resulting in a marked fall in renal blood flow, which may cause the loss of a kidney. This catastrophic event is heralded by a sharp rise in serum creatinine concentration (Khan, 2000). In pregnancy it crosses the placenta and causes teratogenic effects on the foetus, hence it is contraindicated. As its main action is exerted on the kidney it is not advisable to use in clients with immune-related kidney disease.

Side effects

Commonly experienced side effects are:

Cough

A dry, ticklish, irritating, non-productive cough, which affects ~ 10% of subjects. A number of suggestions have been put forward as to the aetiology of the cough, including potentiation of bradykinen levels by ACEIs, increased sensitivity of the normal cough reflex, and finally increased levels of circulating prostaglandins. However the cough is definitely due to inhibition of ACE, rather than blockade of the renin-angiotensin system, as angiotensin ii receptor antagonists do not exhibit this side effect. (Wilkinson, Waring & Cockcroft, 2003).
Angioedema

This is a rare but potentially life-threatening side effect of an ACEI. It commonly occurs within several days or a week after initiation of therapy (Wilkinson, Waring & Cockcroft, 2003).

Skin rash

A macular rash is occasionally seen in 3-5% of cases; loss of taste and appetite is also an uncommon side effect but it can occur especially in the elderly, leading to weight loss if the condition is not recognised. It may take up to two weeks for the symptoms to resolve completely (Wilkinson, Waring & Cockcroft, 2003). Commonly used ACEIs are listed in table No 2.1

Table 2.1 – Commonly Used Angiotensin – Converting Enzyme Inhibitors

<table>
<thead>
<tr>
<th>Name</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum</td>
<td>Maximum</td>
</tr>
<tr>
<td>Captopril</td>
<td>12.5mg twice a day</td>
<td>25mg twice a day</td>
</tr>
<tr>
<td>Cilazapril</td>
<td>2.5mg od</td>
<td>5mg od</td>
</tr>
<tr>
<td>Enalapril</td>
<td>5mg od</td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td>10mg od</td>
<td>20mg od</td>
</tr>
<tr>
<td>Perindopril</td>
<td>4mg od</td>
<td>8mg od</td>
</tr>
<tr>
<td>Quinapril</td>
<td>10mg od</td>
<td>20-40mg od</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25mg od</td>
<td>10mg od</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>500mic od</td>
<td>4mg od</td>
</tr>
</tbody>
</table>

BNF March 2010
2.4b Angiotensin ii receptor blockers (ARBII)

Angiotensin ii receptor blockers prevent access of angiotensin ii to its principal receptor AT1. Thus preventing the vasoconstrictor action of angiotensin ii, and thereby blocking the last step in the renin-angiotensin aldosterone cascade. ARBs also block angiotensin ii induced promotion of sodium retention and stimulation of aldosterone secretion. As angiotensin ii is involved in the pathogenesis of end-organ damage, ARBs may help to prevent hypertrophy of the kidney, heart and blood vessels. Unlike ACEIs, angiotensin ii antagonists do not affect kinins and are therefore unlikely to cause cough or angioedema (Khan, 2000). The mode of action of ARB ii is outlined in Figure 2. Commonly used ARB ii are listed in Table 2.2.
### Table 2.2 – Commonly used Angiotensin – II receptor Antagonists

<table>
<thead>
<tr>
<th>Name</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum</td>
<td>Maximum</td>
</tr>
<tr>
<td>Candesartan</td>
<td>2mg od</td>
<td>8mg od</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>600mg od</td>
<td>800mg od</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>150mg od</td>
<td>300mg od</td>
</tr>
<tr>
<td>Losartan</td>
<td>50mg od</td>
<td>100mg od</td>
</tr>
<tr>
<td>Potassium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olmesartan</td>
<td>10mg od</td>
<td>40mg od</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>40mg od</td>
<td>80mg od</td>
</tr>
<tr>
<td>Valsartan</td>
<td>80mg od</td>
<td>160mg od</td>
</tr>
</tbody>
</table>

BNF March 2010

There are two main types of angiotensin ii receptor: AT1. and AT2. AT1 receptors are found in the brain, kidney and lung. The AT2 receptor has been found in the brain, reproductive organs and foetal tissue. Most actions of ARBs are mediated through the AT1 receptor.
Overall differences between ARBs and ACEIs have been noticed in clinical trials (Khan, 2000).

Evidence for ARB use: two trials are available for ARBs. The Losartan Intervention For Endpoint reduction in hypertension study (LIFE) demonstrated a greater reduction in hypertensive target organ damage with Losartan compared to Atenolol, particularly LVH regression (Dahlöf et al, 2002). The study on cognition and prognosis in the elderly (SCOPE) assessed if candesartan in elderly patients showed a reduction in CVD events and cognitive decline, and dementia. Candesartan-based therapy resulted in a slightly greater BP reduction vs control therapy producing a modest, non-significant reduction in major CVD events and marked reduction in non-fatal stroke. It was not clear if the stroke reduction was related to BP reduction or other effects of the properties of ARBs (Lithell, Hansson & Skoog, 2003).

2.4c Beta-blockers

The antihypertensive effect of beta-blockers is not fully understood, but it is thought to be a combination of beta receptors in the heart leads to an increase in the rate and force of contraction (MIMS, 2004). In the kidney, beta-receptor stimulation promotes the release of renin, thereby activating the renin-angiotensin-aldosterone cascade. In the nervous system, central beta-receptor stimulation increases sympathetic nervous activity, while stimulation of the pre-synaptic receptors in the periphery promotes the release of vasoconstrictor neurotransmitters. Treatment with a beta-blocker is able to antagonise all these effects leading to a decrease in the force and rate of contraction, a reduction in renin output and a reduction in the peripheral vascular resistance (MIMS, 2004).
Side effects and contraindications

BBs can produce profound bradycardia, tiredness, dry skin and erectile dysfunction. They are contraindicated in conduction defects.

Evidence for use of Beta-blockers

The ESC and BHS have included BBs among their list of drugs recommended for initial therapy in hypertension. Although BBs have been in use from 1960, the publication of the Losartan Intervention For End point reduction in hypertension study (LIFE) a randomised trial against Atenolol (Dahlof, Devereux & Kjeldsen 2002) threw doubt on the usefulness of BBs in the treatment of arterial hypertension, since this trial revealed superiority of an ARB Losartan, over a BB - Atenolol, in terms of the composed primary end point of the study consisting of death, myocardial infarction or stroke. Although this study was also criticised, particularly because only elderly patients with left ventricular hypertrophy were excluded (Bloch 2007).

In the new 2007 review in the Joint American College of Cardiology, authors concluded that for patients with uncomplicated hypertension, there is a paucity of data or an absence of evidence to support the use of BBs as monotherapy or as first line agents. The NICE and the BHS have updated the guidelines and suggest BBs are no longer preferred as a routine initial therapy. They can still be considered for some patients with uncontrolled or complicated hypertension (NICE, 2004). Commonly used BBs are listed in Table 2.3.
Table 2.3 – Commonly used Beta Blockers

<table>
<thead>
<tr>
<th>Name</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum</td>
<td>Maximum</td>
</tr>
<tr>
<td>Atenolol</td>
<td>25mg od</td>
<td>50mg od</td>
</tr>
<tr>
<td>Acebutalol</td>
<td>200mg od</td>
<td>400mg od</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25mg od</td>
<td>10mg od</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>2.5mg od</td>
<td>5mg od</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>80mg od</td>
<td>160mg od</td>
</tr>
</tbody>
</table>

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2.4d Calcium Channel Blockers (CCBs)

Calcium channel blockers are a heterogeneous group of drugs that can be chemically classified into dihydropyridines and the non-dihydropyridines. The main difference between the two groups relate to their different binding sites on the calcium channels and to the greater vascular selectivity of dihydropyridines. Non-dihydropyridines have negative inotropic and negative chronotropic effects greater than those of the dihydropyridines. They also reduce the force of contraction and heart rate (Girvin & Johnston, 2007).

Mechanism of action

All CCBs selectively inhibit the inward flow of charged calcium ions when the channel becomes permeable or “open”. There are two types of calcium channels: the “L” channel and the “L’” channel. The function of the “L” type channel is to allow the entry of calcium ions into the cell for initiation of contraction via calcium induced calcium release from the

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sarcoplasmic reticulum. All CCBs selectively block the “L” channel in vascular smooth muscle and in the myocardium (Johnston, 1999).

The mechanism of action of CCBs in hypertension is mainly due to vasodilator properties. There is no evidence that any one CCB is more effective than another in the treatment of hypertension. But comparative studies have shown that Amlodipine has a longer duration of antihypertensive action than other CCBs. (Elliott, Edward, Wilkinson et al, 2002). In the ASCOT trial – BP lowering arm, an Amlodipine-based regimen was more effective than one based on Atenolol in terms of secondary cardiovascular end-point in hypertensive patients (Dahlof, Sever, Poulter, 2005). The outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on Valsartan or Amlodipine (The VALUE) trial, demonstrated that both treatments reduced BP, but the effect in the amlodipine group was more pronounced (Lithell, Hansson & Skoog, 2003). A list of commonly used CCBs is listed in Table 2.4.
Table 2.4 – Commonly used Calcium –Channel Blockers

<table>
<thead>
<tr>
<th>Name</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum</td>
<td>Maximum</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>5mg od</td>
<td>10mg od</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>60mg</td>
<td>360mg</td>
</tr>
<tr>
<td></td>
<td>3 times a day</td>
<td></td>
</tr>
<tr>
<td>Felodipine</td>
<td>5mg od</td>
<td>10mg od</td>
</tr>
<tr>
<td>Lercanidipine</td>
<td>10mg od</td>
<td>20mg od</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>20mg</td>
<td>30mg</td>
</tr>
<tr>
<td></td>
<td>3 times a day</td>
<td>3 times a day</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>5mg od</td>
<td>20mg od</td>
</tr>
<tr>
<td>Adalat</td>
<td>3 times a day</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>240mg daily (2 or 3 a day)</td>
<td>480mg daily</td>
</tr>
</tbody>
</table>

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2.4e Diuretics:

Diuretics can be broadly divided into thiazides, loop diuretics, potassium-sparing diuretics, osmotic diuretics and carbonic anhydrase inhibitors. Below “see figure 2.2: the mechanism of diuretics on the kidney (Wilkinson, Waring & Cockcroft, 2003)”

Thiazide diuretics

Thiazide diuretics have been available for over thirty years and remain first line therapy. They increase sodium excretion by the kidney, and have been the backbone of hypertension management for many years. They are useful alone or in combination with vasodilators
(which can otherwise cause fluid retention) and with agents, which inhibit the renin-angiotensin system (Khan, 2000).

Loop diuretics

This group of diuretics inhibit the sodium potassium and chloride transport system of the ascending loops of Henley, and thus block chloride reabsorption at the site where approximately 40% of filtered sodium is normally reabsorbed.

Potassium-sparing diuretics

Potassium-sparing diuretics play a vital role in conserving potassium and magnesium in patients treated with thiazides or loop diuretics. These diuretics block aldosterone, or act at the site in the kidney to cause a small amount of sodium excretion, and prevent exchange of potassium (Khan, 2000).

Caution

All of the thiazide group of drugs cause a rise in the plasma uric acid level and may cause gout, and can make glucose intolerance worse (Lip & Chung, 2002). The huge ALLHAT study (2002) showed that thiazide-like diuretics are still a vital and important class of drugs for the treatment of hypertension and remain first line therapy for many patients (Brady & Petrie, 2004). Commonly used diuretics are listed in Table 2.5.
<table>
<thead>
<tr>
<th>Name</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thiazides</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bendroflumethiazide</td>
<td>2.5mg od</td>
<td>Hypokalaemia, dizziness, gout</td>
</tr>
<tr>
<td>Chlortalidone</td>
<td>25mg od</td>
<td>Hypokalaemia, dizziness, gout</td>
</tr>
<tr>
<td>Indapamide</td>
<td>2.5mg od</td>
<td>Hypokalaemia, dizziness, gout</td>
</tr>
<tr>
<td><strong>Loop diuretics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bumetanide</td>
<td>1mg od</td>
<td>Headaches, dizziness</td>
</tr>
<tr>
<td>Torasemide</td>
<td>2.5mg od</td>
<td>Dry mouth, rarely limb parasthesia</td>
</tr>
<tr>
<td><strong>Potassium-sparing diuretics - Aldosterone antagonists</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiloride</td>
<td>5mg od</td>
<td>Dry mouth, rashes</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25mg od</td>
<td>Diarrhoea, nausea, dizziness</td>
</tr>
<tr>
<td>Spirionolactone</td>
<td>25mg od</td>
<td>Renal impairment</td>
</tr>
<tr>
<td></td>
<td>100mg od</td>
<td></td>
</tr>
</tbody>
</table>

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Figure 2.2 – Mechanism of diuretics on the glomerular apparatus of the kidney.

The complex mechanism of medication on the heart, the kidneys and the brain is depicted below “See Figure 2.3: Mechanism of action of medication on the kidneys, the heart and the brain (Wilkinson, Waring & Cockcroft, 2003)”
In the next section the trials that have brought changes to clinical practice and underpinned the evidence for the use of various antihypertensive agents are critically reviewed.

2.5 Critical review of hypertension trials

There is a consensus that large randomised trials measuring fatal and non-fatal events represent the strongest type of evidence available. However, these RCTs have limitations.
where uncomplicated or younger age groups are not included, as the trials need high risk or older populations to power the study. The therapeutic programmes of trials often diverge from usual therapeutic practice because drugs randomly allocated at the beginning of a trial continued even in the absence of BP lowering effects while, in practice, such medication may not be prescribed, hence in trials, not in practice benefits occurring in subjects responsive to the allocated treatment are diluted by the lack of benefit in non-responsive subjects (ESC and ESH guideline, 2007).

In the ALLHAT study, all cause mortality did not differ between groups. There was no significant difference between the three groups in lowering the primary end points. SBP was 2 mmHg higher in the Lisinopril than the Chlorthalidone group (P = <0.01) and 0.8 mmHg higher in the Amlodipine vs Chlorthalidone (P = <0.01). The benefit on primary endpoints were, Amlodipine vs Chlorthalidone P = 0.81. (The ALLHAT officers and co-ordinators for the ALLHAT collaborative research group 2002). The diabetic group showed a minimal reduction in BP; previously in many large clinical studies, it has been shown particularly in older patients, that a diuretic was the best option for lowering BP as well as preventing stroke and heart attack and importantly, in all ethnic groups. In cost-effectiveness they are certainly superior agents, and have been recommended as first line antihypertensive agents in all international hypertensive guidelines (Beevers, Lee, & Lip, 2003).

The antihypertensive treatment that did not include a thiazide diuretic was associated with an 85% increased risk of ischaemic stroke when compared with the use of an anti-hypertensive drug regimen, which did include a thiazide (Klungel et al, B2001). In the PROGRESS trial a significant reduction in second stroke was seen with a Perindopril-Indapamide (ACE inhibitor-thiazide diuretic) combination, whereas the stroke reduction with Perindopril monotherapy was not statistically significant (PROGRESS collaborative group, 2001). So the diuretic effect is not novel to the ALLHAT study only. ALLHAT included 35% of black
Americans, a subgroup in which a greater response was both expected and observed with Chlorthalidone compared with Lisinopril. African Americans are known to have a higher prevalence of hypertension, diabetes, CVD, stroke and renal disease than white Americans. In this study overall poorer BP control among black Americans on Lisinopril was evident. The RRR (Lisinopril vs Chlorthalidone) were 1.40 (95% CI: 1.17-1.68) and 1.00 (95% CI: 0.85-1.17) for stroke and 1.19 (95% CI: 1.09-1.30) and 1.06 (95% CI: 1.00-1.13) for combined CVD in black and non-black participants respectively (ALLHAT collaborates 2002). Indeed for many years, there have been concerns that ACE inhibitors may be less efficacious in black patients with hypertensive heart failure, or non-diabetic kidney disease. In the recently published African-American study of kidney disease and hypertension (AASK) study an ACE inhibitor (Ramipril) was superior to both a CCB (Amlodipine) and a beta-blocker (BB) (Metoprolol) in preventing the progression of renal disease in non-diabetic black hypertensives with mild to moderate renal disease (Wright et al, 2002).

Given the fact that black hypertensive people on Lisinopril clearly had higher absolute BPs (4 mmHg SBP) than white participants on Chlorthalidone in ALLHAT, the question of whether black hypertensive people were less ACE responsive is not an important issue; the issue is whether the difference in SBP could explain the higher relative risk of stroke combined CVD and heart failure in black hypertensives on Lisinopril. In contrast, there is no clear pathophysiological link between the prevention of atherothrombosis and the diuresis induced by a diuretic, besides lowering of BP (Beevers, Lee & Lip, 2003). It is interesting to note that diuretics are known to trigger the RAS, worsen glucose tolerance and lipid profile. It counteracts the expected benefits of an ACE inhibitor (Lisinopril) over a diuretic. Could the 2-mmHg difference in BP favour a diuretic? One may have to ask if some of the study patients were resistant to the ACE inhibitors or due to the black Americans, or is there a hidden action potential exerted by Chlorthalidone? The ALLHAT authors concluded that
diuretics should be the first line antihypertensive agent, a conclusion that raised much controversy. An irrefutable conclusion would be that the study showed the equivalence of diuretics, CCBs, and ACE inhibitors in their ability to reduce the primary endpoint of fatal heart disease and non-fatal myocardial infarction.

The second Australian National Blood Pressure Study Group (ANBP2) study randomised older hypertensive patients to initial treatment with an ACE inhibitor (n = 3044) or a diuretic (n = 3039) (Wing et al, 2003). In this study, treatment with ACE inhibitors resulted in a lower incidence of cardiovascular events or death that was of borderline significance (RR 0.89; 95% CI: 0.79-1.00; P =0.05). This difference was not significant when considering the 51% of the study population who were female (RR 1.00; 95% CI: 0.83-1.22; P = 0.98). The ANBP2 study has been said to show the opposite of ALLHAT, but in fact the main lesson from both these trials is that there cannot be marked differences between diuretics and ACE inhibitors in reducing adverse clinical events in hypertensive patients (Frohlich, 2003).

In a Meta analysis by Psaty et al, (2003) collected data from 42 clinical trials involving 192,478 patients found that antihypertensive drug treatment compared with placebo was associated with reduction in risk of all major outcomes. This analysis again revealed that diuretics were superior to all other antihypertensive drugs. Diuretics were superior to CCBs in reducing cardiovascular events (RR 0.94; 95% CI: 0.89-1.00) and heart failure (RR 0.74; 95% CI: 0.67-0.81). Diuretics were also superior to ACE inhibitors in reducing cardiovascular events (RR 0.94; 95% CI: 0.89-1.00), heart failure (RR 0.88; 95% CI: 0.80-0.96) and strokes (RR 0.86; 95% CI: 0.77-0.97). Diuretics were superior to BBs in reducing cardiovascular events (RR 0.89; 95% CI: 0.80-0.98) and to alpha-blockers in reducing cardiovascular events (RR 0.84; 95% CI: 0.75-0.93), and heart failure (RR 0.51; 95% CI: 0.43-0.60). This analysis also demonstrated that SBP reduction was larger in the patients treated with diuretics than
those on other classes of drugs. Thus, it is again questionable whether the better clinical outcome is related to the reduction in BP or the chosen antihypertensive agent.

The United Kingdom Prospective Diabetes Study (UKPDS, 1998) examined the effects of rigorous BP control on the occurrence of the complications of type 2 diabetes. Unlike the marked differences occurring between those with tight BP control, there was no significant difference between the Captopril (an ACEI) and Atenolol (a BB) groups in strokes, myocardial infarction, and deaths related to diabetes and/or in all cause mortality. This study thus suggests an equivalent effect of a beta-blocker and an ACE inhibitor in target organ protection of diabetic hypertensive patients. The outcome of this study gives the impression that the intensity of BP control is more important than antihypertensive vascular outcomes. However, in this study around 30% needed three or more drugs for adequate BP control; thus it is not right to attribute the BP control to the first line of medication alone. The Captopril Prevention Project (CAPP) (Hansson et al, 1999) after 6.1 years, myocardial infarction, stroke or cardiovascular death, individually and its composite primary endpoint, were equal on Captopril and diuretic/beta-blocker. Despite a lower incidence of diabetes mellitus, patients on Captopril had more strokes.

In the Nordic Diltiazem Study (NORDIL), Hansson et al, (2000) there was no difference in the primary end point per 1,000 patient years, BP/diuretic 16.2 deaths per 1,000 patient years; RR 1.0: P= 0.97. This study was paralleled with previous major studies except the incidence of stroke was lower on Diltiazem, raising the possibility of CCBs being particularly useful for cerebrovascular protection. However, the use of CCBs as first line agents has been subjected to heavy debate, as Pahor et al, (2000) in their Meta analysis found CCBs to be less effective in cardiovascular events (with the exception of stroke) compared to other first-line antihypertensives.
It should be noted that CCBs are a very heterogeneous group of drugs with properties differing significantly from one drug to another. Even different formulations of the same molecule have significantly different effects on cardiovascular pathophysiology. Besides lowering BP. The data from the various Meta analyses of the use of CCBs in preventing hard end points was largely fragmented because of many sub groupings across the class, e.g., Dihydropyridine vs non-Dihydropyridine CCBs, patients with diabetes vs non-diabetics and end points such as cardiovascular vs renal. Such Meta analyses have limited statistical power to really determine whether the small but often significant differences detected can be generalised to all CCBs (Beevers, Lee & Lip, 2003). Furthermore due to the heterogeneity of CCBs, clinical effectiveness must be assessed separately in well-designed clinical studies to add to what is already known.

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) (Dalhöf et al, 2005) contributes to the guidelines from NICE or the BHS, as BBs are not the first line choice for hypertension. What ASCOT does suggest is that using high doses of BB followed by thiazide diuretics may lower BP less than other potential combinations of drugs. Although one can question the relevance, as existing UK guidelines do not advocate this approach, this finding is important at a population level as a 2-3 mmHg difference in BP translates to thousands of events avoided. However, at an individual level, such differences are unlikely to change outcomes and ironically, poor proficiency in measuring BP or the use of badly maintained equipment, is more likely to be relevant (Hird, 2005). In October 2004, the Data Safety Monitoring Board recommended that the trial be stopped as the Atenolol/thiazide arm had significantly higher mortality than the amlodipine arm, bearing in mind that ASCOT was stopped early when interim analysis showed significant disadvantages for patients on the atenolol-based regimen. All cause mortality was 8.5% with Atenolol/thiazide and 7.7% with Amlodipine/Perindopril
(P = 0.0247). NNT = 115 over 5.5 years and CV mortality of 3.6% with Atenolol/thiazide and 2.7% with Amlodipine/Perindopril (P=0.0010), NNT = 121 over 5.5 years.

When trials are stopped early there is a possibility that follow up will not be long enough for sufficient end points to be reached, leaving the trial underpowered for these endpoints. When ASCOT was set up it was estimated that at least 18,000 patients would need to be followed up for an average of five years. This was on an average of 1,150 patients experiencing a primary event of 0.84 and a power of 80%. When the trial was stopped fewer primary endpoints than this had been reached, 903 in total, but the trial had continued for 5.5 years with 19,257 patients (Maskrey & Underhill, 2005). A Meta analysis of the effect of Atenolol on cardiovascular morbidity or mortality in hypertensive patients revealed a significantly higher mortality (1.13[1.02 – 1.25]) with Atenolol treatment than with other active treatment, in the five studies comprising 17,671 patients who were followed up for a mean of 4-6 years (Carlberg, Samuelsson & Lindholm, 2004). Although this was an impressive study, BBs will not be the drug of choice even if there was no difference in target organ protection, in the current evidence-based practice as BBs are found to have adverse effects in the absence of known CVD. Though BBs have been downgraded they will still be in use for patients who require this medication for various reasons as an alternative medication or as a part of treatment for RH (Hughes 2006).

ASCOT and LIFE are similar in that they both used Atenolol, but the LIFE study gave considerable support to the view that the FDA approved the combination of Losartan with hydrochlorothiazide. No other study showed a special benefit from the ARB in preventing stroke. However, Losartan was significantly better than Atenolol (P= 0.021). So the ASCOT trial supporters started patients with diuretics. The incidence of primary composite end points was similar in both groups; 10.6% in Valsartan-treated patients vs 10.4% in Amlodipine-
treated patients. The importance of prompt BP control in hypertensive patients to reduce mortality and morbidity was reinforced by the ASCOT study. The VALUE and LIFE studies underscore the fundamental importance of BP control in the patient population (Hariharan, 2004).

In the HOPE (2002) study the findings are similar to those reported in the BP Lowering Treatment Trialists Collaboration (2003). The in-study clinic BP difference was reported to be 3/2 mmHg in favour of Ramipril; however, a subsequent small study in the HOPE patients reported a mean 24 hr ABPP difference of 11/4 mmHg in favour of Ramipril, even though the clinic pressure was similar to that reported for the main HOPE study population (Svensson et al, 2001).

The PROGRESS (1997) was started by an independent collaborative research group in an effort to resolve clinical uncertainty about the efficacy and safety of routine BP lowering therapy for patients with a history of stroke or transient ischaemic attack (Progress management committee, 1997). The major failure in this study is that the patients were to include a group randomised to Indapamide alone, and so the benefits in reduction of stroke cannot be attributed to Indapamide alone because of the number of strokes observed in the Perindopril group. The author agrees that the BP difference between the two arms, (5/3 mmHg for Perindopril alone vs 12/5 mmHg for the combination therapy) are unlikely to explain the large difference in stroke reduction (Psaty et al, 2002). Studies that are included in the literature review, along with groups of studies, which demonstrated the degree of BP reduction and benefits on target organ damage are listed in the appendices (appendix 1).

Summary

The mechanism of action for each antihypertensive agent was explained to underpin the complex nature of each agent in treating hypertension. There are a vast number of studies in
the literature related to treating hypertension. Trials that have brought changes to practice have been reviewed critically and presented succinctly to enable the reader to understand more easily. Implications and controversies in treating hypertension are also explored to demonstrate the practical problems in treating hypertension. In the next chapter the author will explore various barriers to treating hypertension. The focus of the next chapter will be on reasons for poor BP control, the need for long-term treatment and cost-effectiveness in relation to the disease burden and implementing hypertension treatment. Although the study focuses on BP reduction and the length of time taken to achieve the reduction in BP, it is important to understand various barriers to BP control. Such an exploration may help the reader to understand the various factors to be included in treating hypertension and emphasize the need for a comprehensive assessment.
CHAPTER 3
BARRIERS TO HYPERTENSION CONTROL

Introduction

This study was developed to compare the management of hypertension with or without the use of a biochemical test. In order to do this efficiently it was imperative that the reader was provided with a background to the management of hypertension. The following chapter therefore discusses the various factors associated with treating hypertension. These factors were systematically searched on electronic databases, using terms such as obstacles, barriers, failure, adherence, and non-compliance as text and search words and presented comprehensively using available literature. This was undertaken in an attempt to understand the enormity of the global problem of hypertension and explore the complexity in treating hypertension. In this chapter the author aims to explain factors contributing to poor BP control.

It is paradoxical that despite the enormous advances in antihypertensive drug therapy, the number of people with uncontrolled hypertension has continued to rise. Mancia & Grassi (2002) highlight that even in the case of an ideal scenario, whereby patient compliance and physician’s expertise were ensured, attaining SBP control would neither frequently nor easily be obtained. The <140/85 mmHg cut-off point (130/80 mmHg for those with diabetes) have been chosen as the treatment goal for patients with hypertension who are treated pharmacologically. These targets or goals are supposed to be pursued aggressively with three or even four drugs if needed, in order to achieve “optimal” or “normal” BP (Pater, 2005). Most patients with hypertension will require two or more antihypertensive medications to achieve their BP goals (Cushman, Ford & Cutler, 2002). The initiation of drug therapy with more than one agent may increase the likelihood of achieving BP goal in a timely manner.
The literature review led to group the reasons for poor BP control under three aspects, which are: patient factors, provider factors and medical environment. These factors apply primarily to patients who are in contact with the health care system (Borzeki, Oliveria & Berlowitz, 2005). As stated previously, this discussion is necessary to provide the reader with an understanding of the many factors, which contribute to poor BP control in RH. These factors are to be taken into consideration when treating individuals with hypertension. These factors may still play a part in influencing this study’s outcome. It is also vital that these factors be taken into consideration when implementing the hypertension protocol.

3.1 Patient factors associated with inadequate BP control

Patient factors work in part through patients not being concordant with their prescribed medication. In this author’s practice poor concordance is a significant issue in treating patients with hypertension.

3.1a Concordance

It has been suggested that half of treated hypertensive patients discontinue drug administration in the first year and it gets worse in the long term where adherence rates are very low (de Souza et al, 2009). Less than 40% will continue taking their medication after 5 to 10 years (Van Wij et al, 2005). When patients are asked to follow an inconvenient and potentially costly regimen, which will likely have a detrimental effect on health-related quality of life, to treat a mostly asymptomatic condition that commonly doesn’t cause problems for many years, patients often express the desire for considerable benefit before they would accept therapy (McAlister et al, 2000). Hypertension has few symptoms and may seem to be a silent disease to the patient, yet antihypertensive medications have many side effects that are experienced by patients and contribute to non-adherence (Bosworth, Olsen & Oddone, 2005). In the author’s own practice it is very common for patients to stop taking the
prescribed medication due to symptoms such as dizziness, tiredness or feeling unwell. However, when starting treatment, patients are warned they may experience the symptoms stated above, but to persevere with the treatment, or if symptoms become troublesome to see their GP to reassess the situation.

Non-adherence to prescribed hypertension therapies is extremely common. There is a clear association between the two (ALLHAT Officers & coordinators, 2002). In general, sociodemographic factors such as age, marital status, socioeconomic status and personality characteristics have weak and inconsistent effects on adherence. To study the non-adherence, different methods of measuring adherence were used which led to open interpretation. The measures used were generally based on surveys, pill counts, or pill bottles with a microprocessor, which are imperfect, as they do not capture whether the medication was actually ingested. Direct measures of adherence, such as drug levels in the blood or urine, have not been applied to hypertension care (Borzecki, Oliveria & Berlowitz 2005). Such measurements are common in assessing Digoxin levels in atrial fibrillation and lithium levels in mental illness.

It should be emphasised that simplification of the treatment regimen is only one strategy for improving adherence (Gradman et al, 2010). The relationship between the number of medications and adherence is not clear. In patients with established disease, compliance improved as the number of medications increased. The situation is further complicated by the fact that patients who perceive that they are on too many medications are also less compliant (Ren, Kazis & Lee 2002). Recent research has indicated that persistence, defined as the duration of time a patient remains on a prescribed antihypertensive medication, may also play a crucial role in patients being more compliant with their treatment. For many patients cost is a critical issue, branded combinations that are not available generically are often more
expensive and can, in some cases, result in significant copays that adversely affect adherence (Gradman et al., 2010).

Long-term adherence to treatment is necessary to control BP and combination regimens can facilitate this objective (Gradman et al., 2010). Single pill combinations may promote convenience, as it will be easier for patients to comply with a regimen that included fewer pills (Egan, 2009). Faselis, Doumas & Papademetriou (2011) suggest that using close contact of health care professionals with patients seems effective in promoting concordance but lacks wide application. Nurses may come into their own in this area, to enhance concordance, and to take a comprehensive history to address the problem of poor concordance.

3.1b Depression

There is evidence that depression is a significant, independent influence on cardiac mortality (Child et al., 2010). Depression has an impact on quality of life and is associated with poor self-management and health outcomes, as well as increased incidence of cardiac events (Frasure-Smith & Lesperance, 2003). It may increase non-compliance of medication because positive expectations and beliefs in the benefits of treatment are essential to patient adherence, and lack of self worth and reduced cognitive function may be associated with poor adherence (Bosworth, et al., 2005).

3.1c Race

Hypertension occurs at a younger age and with higher prevalence and severity in black people than in white people. It is not clear whether this association is direct or due to other factors like cost of medication, accessing health services or due to body mass ((Bosworth, Olsen, & Oddone, 2005). An exploration of the extent to which the number of medications on compliance is attributable to age was analysed, stratifying age <65 and ≥65 years of age. and
suggested ($p < 0.01$) that only older patients who took more medications were more likely to be compliant (Ren, Kazis & Lee, 2002). As stated previously BP elevation is multifactorial, making it very difficult, if not impossible, to minimise pressure by interfering with only a single mechanism. In addition, drug therapy directed at any one component routinely evokes compensatory responses that reduce the magnitude of response, even if it was accurately directed at the predominant pathophysiologic mechanism. As a sequence, limited BP reduction is seen with all antihypertensive medication (Gradman et al, 2010). In the Strategies in Treatment of Hypertension study, treatment initiated with a low dose combination was compared with a monotherapy arm. At the end of nine months a significantly higher percentage of patients randomised to the low dose combination achieved target BP compared with those receiving sequential monotherapy (62% vs 49%, $p = 0.02$) (Mourad, Waeb & Zinnad, 2004).

3.2 Provider Factors

A number of provider factors have an impact on BP control. This discussion will provide the reader with the importance of equipment used and care of these instruments.

3.2a Measuring BP

It is true that BP remains dynamic, varying from stroke to stroke. The accuracy of BP recording using the BP apparatus therefore relies heavily on taking multiple readings, having a relaxed patient who has been sitting for at least several minutes before entering the clinic, and most importantly having a competent operator (Watson & Lip, 2006).

It is undisputed that the mercury sphygmomanometer (BP apparatus) has the highest accuracy, with a high degree of technical agreement between devices of different producers (Pickering, 2003). The most specific advantage of mercury based manometer devices is the
simple technique and a simple baseline correction (Tholl, Forstner & Anlauf, 2004). The common issues with the mercury manometer have been poor maintenance and calibration. A check of the devices in a major teaching hospital showed that only 5% of the investigated instruments had been properly serviced (Markandu et al, 2000). An inspection in general practice found that only ~30% of the devices had been properly maintained (Knight et al, 2001).

Restrictions of the use of mercury in medical devices have already been imposed; this was felt to be necessary to avoid occupational health hazards and environmental contamination. In a busy clinic situation it is difficult to have a delicate apparatus to measure BP, also having enough time to help patients relax, and measuring several times may prove to be impossible. However, it is widespread practice to use an automated BP apparatus or aneroid manometers.

Aneroid manometers

These are the most commonly used devices for BP measurement in clinical practice. Instead of transferring pressure to a mercury column, they are designed to transfer the detected pressure via a mechanical system and an elastic expansion chamber to a gauge needle (Beevers, Lip & O'Brien, 2001). Reading errors occur more frequently in the range of big BP values where aneroid manometers tend to underestimate the BP of the patient. (In practices the percentage of regularly serviced and recalibrated instruments is sometimes below 5%, Knight et al, 2001). If however aneroid manometers receive regular technical maintenance, their measurement accuracy is identical to the standard mercury manometer devices (Tholl, Forstner, & Anlauf, 2004).
Automated devices

By providing timed measurements many of the sources of error associated with the conventional auscultatory technique are removed, and thereby improve the overall accuracy of measurement, provided, of course, that they themselves are accurate (Watson & Lip, 2006). These devices contain no mercury; therefore there are no safety concerns. They are simple to use and remove the user bias, which exists with mercury manometers. (Williams et al, 2004). The quality of BP monitoring does not only depend on possible limitations arising from technical aspects, but more commonly also depend on the correct handling by the user (Tholl, Forstner & Anlauf, 2004). Guidelines on the correct method of BP measurement, as published by various professional societies, are however, insufficiently followed. This is particularly true for a resting period prior to BP measurement (Tholl, Forstner & Anlauf, 2004). It is vital to use the appropriate BP cuff size also. A cuff that is too small or too narrow can cause the BP to be overestimated by up to 30 mmHg; similarly the use of too large a cuff can lead to underestimations (MacGregor & Kaplan, 2001).

All participants attending hypertension clinics in both hospitals had their BP recorded using BHS accredited BP apparatus, and variable cuffs were available for use. On arrival at the clinic, participants have their BP measured by the clinic nurses, but their BP measurements were repeated after the consultation when they had had the opportunity to sit. Several readings were taken, and on first visit the BP is checked in both arms to avoid any significant difference due to vascular disease. Those individuals, whose BP measurement remained elevated every time it was measured, were given a 24-hour ambulatory BP measurement to avoid white coat reaction (MacGregor & Kaplan, 2006). In this study, 24-hour measurement was used to diagnose and to assess the BP control on treatment.
Accuracy of BP measurement

BP measurement is one of the few scientific measurements undertaken in the course of the consultation, and the consequences of decisions arising from the measurement of BP may be crucial to patient management, both in the short term and, more importantly, the level of BP recorded may influence the quality of existence for the remainder of a patient's life (Beevers, Lip & O'Brien, 2001). Use of good BP measurement technique is essential to the accurate diagnosis of RH, including having the patient sit quietly in a chair with his or her back supported for five minutes before taking the measurement. Also, it is vital to use the correct cuff size with the bladder encircling at least 80% of the arm and supporting the arm at heart level during the measurement (Pickering et al, 2005). Even small errors underestimating BP can cost lives by failing to prevent cardiovascular disease through effective and safe therapy (WHO, 2002). Despite the clear guidelines on BP measurement technique, there seems to be large inter-observer variations, both among nursing staff and physicians as well as between the two groups. A questionnaire meant to focus this issue, encompassing 28 senior nurses and 55 health professionals from 28 different clinics in the UK, highlighted considerable such variation leading consequently to inappropriate action (McVicker, 2001). There is extensive literature on the source of error encountered with BP measurement. These can be divided into those that are associated with the observer, with his/her bias or inaccuracy, the physiology of the patient coupled with the variability of BP, the manometer itself, which may be inaccurate or damaged and the cuff may be the wrong size (Gelfer, 2003). The requirements for accurate BP measurement have been standardised (Pickering et al 2005) and incorporated in the guidelines for the management of arterial hypertension (Mancia et al, 2007, Chobanian, et al, 2003).
Faulty equipment

In the area of BP measurement adding to the human error is the universally poor state of the measurement devices, their inaccuracy and unreliability. A British study carried out in 18 practices and 67 GP offices showed digit bias in systolic and diastolic readings to the nearest 10 mmHg (Ali & Rouse, 2002). Errors in BP measurement are common in clinical practice but using validated, calibrated equipment can improve accuracy of BP measurement and dramatically reduce human and equipment error. A BP should be measured carefully in both arms and the arm with the higher pressures generally should be used to make future measurement (Calhoun et al, 2008). In this cohort the consultant cardiologist who is a hypertension specialist, senior registrars and advanced nurse practitioners measured these patients BPs. The BP measurement was carried out according to the BHS guidelines. Patients are asked to remove tight clothing covering the arm if it appears to be tight, and the arm is supported during the measurement as recommended by Pickering et al, (2005). The BP apparatus is calibrated and used according to the manufacturer’s recommendations. The hospital maintenance department regularly maintains the equipment and tags it with the date of inspection. It is standard practice in these clinics that neither the patient nor the practitioner, are allowed to talk during the measurement. The measurement was always carried out in the middle of the consultation, when the patient had had time to sit and relax. Three readings were taken, and the lowest was recorded. When there was a spurious reading, more than three readings were taken. These readings were immediately recorded in the patient’s notes (Pickering et al, 2005). Traditionally, health care professionals are trained in BP measurements as part of their training in physical assessment. In these clinics the consultants, are European Hypertension Society members, and the senior health care professionals who were involved in these specialist clinics were adequately trained to measure BP. The consultants on these areas were considered as the “gold standard” and to do a clinic with them, professionals were expected to measure BP according to the BHS guidelines. All
of the above professionals were trained to the highest standard and used their skills according to their professional code of conduct.

3.3 Medical Environment

This encompasses access to care, patient provider interaction, and practice setting. These factors have a profound impact on BP control.

3.3a Access to healthcare

Patients may have trouble getting health care because of cost, transport problems, inadequate system or practice-related problems such as difficulty getting appointments, tests etc. Little has been written about how system or practice-related access factors influence BP control. In a survey of ambulatory hypertensive patients, inconvenient office hours and prolonged office waiting times were perceived as barriers to BP control, but the actual association with BP control was not examined (Mouton, Beaudouin & Troutman, 2001). In the author's own experience, patients often report problems with transport. Some patients have to walk a long distance before they can get to public transport, and fear of missing the transport and eventually missing their appointment can result in a high BP reading in the clinic.

3.3b Patient provider interaction

The most common causes are poor patient physician communication concerning BP goals and the importance of achieving them, potential side effects and high cost (Wildman et al, 2005). Successful interactions can only help patient adherence to medical regimens. In addition, how the provider views the relationship will influence how he or she communicates with the patient. Further, patient adherence will impact the provider's perception of the patient (Borzecki, Oliveria, & Berlowitz, 2005). Nurses have played a key role in cardiac rehabilitation and in the heart failure service helping patients to understand the need for their
treatment, life style changes etc, so the same can be implemented in hypertension management to improve BP control.

3.4 Implementing guidelines

Clinical practice guidelines for hypertension care have been widely disseminated, even though these guidelines document their best practice for achieving optimal BP control. Evidence suggests that clinicians often do not agree with the guideline recommendations, and even when they do agree, their practices are not consistent with them (Oliveria, et al, 2002, Mancia, et al, 2007). In general, evidence suggests that, physicians' attitudes and behaviours account for 76% of the underachievement of BP control among the adults who are treated for hypertension in the USA (Philips et al, 2001).

3.5 Hypertension and cost-effectiveness

Although studies of implementation have become increasingly popular, little attention has been paid to the economics of implementation (Mason et al, 2005). In the UK the UKPDS group assessed the economic efficiency of tight BP control with an ACEI or BBs compared to less tight control. 20 hospital based clinics in England, Scotland, and Northern Ireland included 1,148 hypertensive patients from the UKPDS study. These patients were randomised to tight control of BP (n = 758) or less tight control (n = 390). This analysis demonstrated, as expected, that the tight control of BP increased the cost of antihypertensive drugs by an average of £613 (95% confidence interval £520 to £706) compared with less tight control over a median follow up of 8.4 years. The increased cost of antihypertensive treatment in the group under the tight control of BP was offset by lower complications cost. In this study a within analysis shows that compared with less tight control, tight control of BP resulted in significant gain in time free from end points without significant increase in total cost – with a
point estimate of cost-effectiveness ranging from £390 to £1,049 per extra year free from endpoints (UKPDS Group, 1998).

This is the first study to show that tight BP control for patients with DM provides a cost-effective means of reducing the risk of complications and improving health. When the medication choices and cost of antihypertensive regimens in elderly patients in a large state drug assistance program over a one-year period was measured, the cost implications of evidence-based drug substitution were assessed. A large proportion of existing prescribing for hypertension was out of publishing guidelines. Adherence to established guidelines for treating hypertension would have resulted in considerable savings to the healthcare delivery system. There are many possible reasons for this large divergence between routine practice on the one hand and clinical trial data and evidence-based recommendations on the other. Foremost among these is the vigorous marketing of newer more costly agents compared with virtually no marketing for older, off patent vs physician factors causing these differences (Fischer & Avorn, 2004).

3.6 Importance of long term treatment

At present, unless there is a curable cause of hypertension, treatment should be persistent and last for lifetime (Giles, 2007). A population study was set up to describe health care costs for outpatient hypertension treatment, in comparison with diabetes mellitus and chronic bronchitis and to examine the cost-effectiveness of different classes of antihypertensive drugs in southern Brazil. 1,968 participants were interviewed. 462 had a BP ≥ 160/95 mmHg or were taking antihypertensive drugs. These individuals had a mean age of 52.5 ± 10.5 years, had 6.7 ± 4.6 years of school education and were predominantly female (73%). Treatment of hypertension consumed 22.9% of per-capita income, corresponding to $392.76 spent per year exclusively on BP lowering drugs (da Costa et al, 2002).
Due to the cost of medication it is our practice to advise patients to get a prepaid prescription. It works out to be cheaper. It also encourages individuals to get repeat prescriptions. In some situations patients may not tolerate the medication or develop side effects and then have to change their prescription. In this situation patients have complained that it is a costly business and to keep changing medication does not help them to continue with their treatment. There are occasions when patients have failed to get a repeat prescription. There are no studies to show how many have stopped taking medication due to their financial situation. It is also equally difficult to explore these issues in a clinic situation because of its delicate nature.

3.7 Implementing hypertension treatment

A study to assess the potential cost-effectiveness of implementing new guidelines for the treatment of hypertension in general practice by Richardson et al, (2004), included a large general practice in North Yorkshire UK with 16 GPs and seven practice nurses. The practice had a population of approximately 25,000 and broadly represented the majority of socioeconomic variables. The study population was made up of 2,023 new adult patients (45.9% male, 54.1% female) with a mean age of 34 years, presenting for new patient health checks at the study practice in the 18 months prior to the introduction of new guidelines for hypertension. Using the estimates of cost and effect per year under the old and new guidelines for the 2,023 patients, a mean cost and a mean effectiveness for the old and new guidelines were calculated. Using the old guidelines 90.4% of patients would have received no treatment, 5.5% would have been observed and 4.1% would have received medication for hypertension. Under the new guidelines, no immediate action would have been taken for 77.3% of patients, but they would be reassessed in five years, 3.8% would be reassessed in one year. 13.4% would have been observed, and 5.5% would have been prescribed hypertensive medication. In a situation like this the probability of new guidelines being cost-effective depends on the value placed on the avoidance of CVD events.
Effective treatment of RH still remains an unmet goal of antihypertensive drug treatment. It is a major opportunity for prevention of CAD. Despite the widespread dissemination of consensus, the approaches that are used assume that all patients with RH are the same. It is important to tailor the treatment by selecting the appropriate therapy for a patient depending on the cause of hypertension (Spencer 2010). The aetiology of RH is almost always multifactorial (Pisoni, Ahmed & Calhoun 2009) and the prevalence from population studies and clinical trials suggest that it is a common clinical problem. Therefore holistic assessment and care are vital in the management of patients with RH. As this is projected to increase due to the aging population, increasing trends in obesity, chronic illness such as DM, kidney diseases and sleep apnoea (Acelajado & Calhoun 2009).

3.8 Hypertension Clinic

In this thesis, patients who attended this specialist clinic were specifically referred by their GP. This is because the JBS2 guidelines and BHS guidelines recommends that patients with RH be referred to a specialist in hypertension management. Some patients were seen due to their inadequate control, others because their GP felt that a specialist must see and advise as to what was best for their client. In the author’s own clinical practice it was common to encounter the above-mentioned issues in relation to poor BP control. Successful treatment requires identification and reversal of life style factors contributing to treatment resistance. The recommendations for the treatment of RH remain empiric. Expanding our knowledge and understanding of causes and thereby aiming to address these more effectively will be important (Calhoun et al, 2008). Thus in the authors practice the ARR is used to select an appropriate medication to tailor the treatment according to the individual patients’ blood test result. However education and reinforcement of life style issues that affect RH such as the need for adhering to low salt, low fat diet, reducing alcohol intake and weight reduction are critical in treating RH (Sarafidis & Bakris 2008). The barriers in poor BP control can be
overcome by having dedicated hypertension clinics, and easy access for frequent review may help to address this problem.

Summary

In this discussion the exogenous factors that contribute to poor BP control are explored. In this thesis the percentage of contribution from these factors is difficult to identify. We have to bear in mind these factors are applicable to any study related to BP control, and this study, being a small study, focused only on BP reduction and length of time to achieve the target BP with or without the biochemical profile. However, in this thesis the focus on the length of time taken to achieve target BP was also looked into. This discussion also highlights that RH is commonly found in everyday clinical practice, it is multifactorial and the reversible causes can be addressed through patient education. A comprehensive assessment is important to prioritise, plan and implement effective patient education. In the next chapter the author will be discussing the study methods, inclusion, exclusion criteria, and various statistical tests considered for this thesis analysis.
CHAPTER 4
METHOD

Introduction:
In this chapter the research method used in this thesis is explained along with the aims, summary of the problem and a rationale for undertaking this research. This chapter also describes the sampling technique used; the rationale for this and ethical considerations are provided. The reader is provided with details of the research design in depth, which is supported with relevant literature. The data analysis and statistical technique used within the study are discussed, with an explanation for choosing these techniques.

4.1 Statement of the problem
As stated previously, achieving BP control in RH is difficult. In this study comparison of RH treatment between two hospitals was undertaken. On one site, medication was initiated as recommended by the JBS2 guidelines and on the second site the choice of medication was guided by the ARR blood result.

4.2 Rationale for the research and the use of the ARR
The British Hypertension Society (BHS) guidelines emphasise that BP lowering is the key driver of the cardiovascular benefits from treating hypertension (Williams, et al, 2004). The overriding conclusion of the guideline is that the priority is controlling BP, rather than the class of drugs used to achieve this aim. The BHS thus felt it was important to provide advice on logical drug sequencing and combinations. Beyond studies of two-drug combinations, there is little data assessing the efficiency of specific combinations of three or more drugs. Accordingly, recommendations of specific multidrug combinations is largely empiric and/or anecdotal. The widespread difficulty in controlling BP has lead to a proliferation of treatment
algorithms for prescription of antihypertensive agents as monotherapy and in combination. These algorithms rely primarily on the likely presence or absence of inappropriate volume expansion and suppressed renin levels. It is recommended that renin levels be measured directly or presumed based on ethnicity and age.

The algorithm is based on an assumption such as low renin, whereas the ARR will make treatment more specific to the individual patient. In this specialist clinic, patients were seen with a history of RH; hence it is essential that the ARR is checked to identify the patients who would benefit from the correct drug of choice. Knowing the ARR will help to guide treatment and is therefore more likely to be effective in these groups. RH is common among adults with hypertension affecting up to 30% of patients. The treatment in this case is important because suboptimal BP control is the leading preventable cause of death worldwide (Williams et al, 2011). The ARR ratio can be utilised to exclude secondary causes and the interpretation could help to identify an appropriate combination of medication (Das & De 2010). If the renin is low and aldosterone is high this indicates PA; the best treatment in this situation is an aldosterone antagonist. When the renin is high, the best medication is an ARBii. If renin and aldosterone are both low this demonstrates excessive activity of renal sodium, hence Amiloride, a potassium sparing diuretic would be the drug of choice (Spence, 2010).

It is known that in patients with hypertension the degree of plasma aldosterone suppression in response to salt loading is impaired, compared with the normotensive population. As an indicator of inappropriate aldosterone activity, the ARR may allow the effect of aldosterone on BP to be evaluated. Perhaps this could guide drug therapy in patients with RH. Random ARR is a simple and worthwhile test to help to detect hypertensive patients with PA. Ideally this test should be offered to all patients with hypertension as this test has a high diagnostic yield, or at least should be done in patients with RH or those needing more than two
antihypertensive medications for BP control. This strategy will likely result in a reduction in long-term morbidity and mortality in many patients with otherwise undiagnosed PA and poor BP control (Lim, Jung & MacDonald, 2002). Therefore, identifying and initiating appropriate treatment tailored to the individual patient would be of great benefit.

These algorithms have not been validated in large, diverse cohorts such that the recommendations are largely empiric (Brown et al, 2003). At present ARR is not measured in clinical practice to identify the drug of choice. In the era of evidence-based practice, there is no proven evidence for choosing a particular drug on the basis of a clinically significant assessment. There is no evidence to prove or disprove the effectiveness of aldosterone renin use in practice. There are pragmatic considerations around using this as another option in treating hypertension. In recent years there has been a move to measure the ARR. However, aldosterone can be high or the renin low in elderly people or people of African origin. A high ARR is also seen in chronic renal disease, where high potassium stimulates aldosterone release, and in the case of rare genetic mutations leading to increased aldosterone levels (Pimenta & Calhoun, 2006).

4.3 Hypothesis

Patients whose treatment is guided by ARR will achieve target BP more rapidly than those whose treatment is guided by algorithm.
4.4 Research design

This study has adopted a non-randomised quantitative cohort study. The intention of this cohort study is to compare the efficacy of two decision-making tools that inform the treatment option in the management of RH in two neighbouring hospital clinics.

Randomised controlled trials

Although the randomised controlled trial (RCT) is considered the gold standard in research design, in the real world experience, the RCT may not always be feasible or appropriate. The present design has been adopted for a number of reasons. The two methods being investigated are currently in use in the two study sites, and have been for some time. The aim of this study was to identify which method of treating RH is more effective. Therefore a cohort study was deemed to be the most pragmatic alternative that would still yield clinically credible results.

Experiments for the scientist are the ideal way of collecting knowledge. They allow for the identification of separate variables and keep all extraneous variables controlled. The skill of an experiment is in the ability to control these variables, including assignment to the experimental and control groups. Ideally, the experimental and control groups need to be the same before the experiment starts (Balnaves & Caputi, 2001). Experimental research designs are used for the testing of causal process. A true experimental design requires an artificial environment so as to control for all spurious intervening and antecedent variables (Hicks, 2004). Experiments are attempts to measure observations directly and to ensure that confounding and extraneous variables are removed. However, direct observations of, and interventions into, large populations are difficult, if not impossible, in social science research (Balnaves & Caputi, 2001). In medical research randomisation is often used to test drug effect and interventions. This is to reduce the risk of bias. Most trials are blind, which means the respondents are not aware whether the treatment they are receiving is placebo or true
treatment. Whereas in the double blind trials neither the respondent nor the health professional knows which intervention the respondent is receiving. However, many studies do not lend themselves to a randomised approach.

In this study it was not feasible to randomise patients before starting the study. This type of experimental design is difficult in the real world situation, particularly in health care as it is often difficult, if not unethical, to reduce the level of treatment for a control group so the control group may receive normal care. (Rogers, Lawes & MacMahon, 2000). It is often regarded as unethical to have a placebo group that receives a dummy treatment or in effect no treatment, particularly when it is believed that an alternative treatment to the experimental treatment is likely to have some beneficial effect (Bowling, 2002).

One could argue this could have been undertaken as a retrospective study. Again it takes time to select the patients, and obtain their consent. In practice this means having a dedicated individual to go through the system to identify all hypertensive patients, in which case the time stipulation would not have permitted this study to be completed within the time of the course.

Survey

Surveys are conducted for the general purpose of obtaining information about attitudes, practices and other characters of people (Knapp, 1998). A survey is a method of collecting data from people about who they are, what they are doing or how they think or feel (Balnaves & Caputi, 2001). A survey is useful for collecting large sample sizes over a long period of time. Surveys are carried out for a specific purpose. The serving of that purpose makes an implicit assumption that the material produced by a survey will be an accurate reflection of the reality it describes. In other words, it assumes its validity (Davies, 2007). Considering the limitations,
the survey method could not be utilised for this research, because in a survey the questions the researcher want answered often dictates the range of answers that may be given (Sapsford, 1999). As BP is a physiological measurement, it has to be measured for each individual. The researcher must acknowledge the limitations of this method and determine whether study interests are best served this way.

**Cohort Study**

This type of study uses the same group of respondents who are followed over a period of time. It is used in longitudinal studies. Researchers who want to know whether a particular piece of educational advice is durable will have to collect data at intervals over a period of time; such a design is called longitudinal and is appropriate for a phenomenon that changes over time (Parahoo, 2007). A cohort study follows a group of subjects over a period of time. The design has the advantages that information on the risk factors is blind to the outcome and risk and relative risk can be calculated directly. A cohort study does not require strict random assignment of subjects, which is in many cases, unethical and they are naturally forming.

It is an appealing and useful technique because it is highly flexible (Grimes & Schulz, 2002). It provides insight into the effects of maturation and social cultural and political change, hence follows the normal course of life. This design can be used with either original data or secondary data. In some instances this can be less expensive than experiments and surveys (Bland & Peacock, 2000). The results that are obtained from long-term cohort studies are of substantially superior quality to retrospective/cross-sectional studies. This is because in a prospective cohort study the researcher does not control the interventions but the effect of different interventions are observed as they occur (Bryant, Willits & Hanson, 2002). Perhaps the most important advantage associated with prospective studies is that they allow a determinant of the temporal sequence of events (Kelsey et al. 1996). In the present study the
prospective cohort method was employed to study the two methods of treating hypertension from two hospitals. These two groups were compared.

In this study clinicians were not asked to compromise their clinical judgement and patients received the treatment that they would usually receive. Therefore it was a feasible design for the chosen question. Longitudinal studies track the same people, and therefore the differences observed in those people are less likely to be the result of cultural differences. Because of this benefit, longitudinal studies make observing changes more accurate and they are applied in medical science. The results that are obtained from long-term cohort studies are of substantially superior quality to retrospective/cross-sectional studies and cohort studies are considered the gold standard in observational Epidemiology (Grimes & Schultz 2002). In this study the chosen method was deemed to be the best way to ascertain both incidence and natural history.

4. 5 Inclusion criteria

Patients with a history of RH who were referred by their general practitioner to be reviewed by a consultant cardiologist at Site 1 or Site 2 were included in this study.

- Diabetic patients with a BP >130/85 mmHg
- Non-diabetic patients with a systolic BP ≥159-160 mmHg and a diastolic BP ≥90 mmHg.
- Patients <85 years.
- Patients >18 years.

4. 6 Exclusion criteria

- BP >220/120 mmHg
- <18 years of age
• > 85 years of age
• Secondary hypertension
• Those who cannot give consent
• Those taking Lithium Carbonate
• Those who are planning to become pregnant

Justification for inclusion and exclusion criteria

A number of criteria were chosen to reduce the influence of extraneous variables. These patients were seen in the specialist out patients' service. It is important to reduce extraneous variables that are listed under inclusion and exclusion criteria. This is to help the reader to understand the need for considering these factors. The JBS 2 guidelines suggest that patients with a history of DM should have a target BP of 130/80 mmHg and for non-DM patients a target BP of <140/85 mmHg. The rationale behind including patients under the age group of 85 was that there are not many studies to substantiate the hypertension medication regimen. In this population the sympathetic drive is not as effective in elderly people. The use of ARR will not have a significant effect in the option of an antihypertensive medication. Although the cardiovascular risk stratification is necessary in patients over 85, the physician has to make use of both clinical judgement and the risk stratification charts in making the decision about drug therapy. Considering the ARR will not be the indicator for starting them on treatment.

In the outpatients service only adults aged >18 are seen, and the <18s come under paediatric classification. Patients who were seen in both hospitals were attending the adult outpatients' service. Patients under the age of 18 are considered to be under age for this clinic, therefore they were not included in this study. A BP reading of >220/120 mmHg is regarded as malignant hypertension and these patients require admission or immediate attention by way of treatment while identifying the underlying cause.
It is unethical to include patients in a vulnerable situation and their rights must be respected.

To avoid drug interaction and the potential alteration in kidney function, those taking lithium carbonate are not included in this study. For those planning to become pregnant regular antihypertensives cannot be used at this important time of their lives due to the possible teratogenic effect on the foetus.

4.7 The research process

SITE - 1 (SHH)

When a patient is referred to the hypertension clinic by their GP, the consultant cardiologist requests a blood test for ARR. This is requested prior to the patient’s review in the clinic as part of the pre-clinic preparation. A standard letter explains the reason for this blood test and a completed blood test request will be sent to the patient asking them to attend the Site 1 (SHH) pathology lab for this test. This allows the blood result to be available to inform the treatment decision. They will also receive a letter from the hospital about the date and time of their appointment.

SITE -2 (MRI)

Whereas at Site 2 the current practice when a patient is referred to the consultant cardiologist with a history of RH by their GP, ARR is not requested as a pre-clinic blood test. They receive a standard appointment letter from the hospital inviting them for their clinic appointment with the date and time. In this clinic the patient’s treatment is chosen from the A or B/C or D algorithm without the aid of ARR (JBS 2, 2005). When initiating the treatment the most recent electrolyte value will be reviewed, to understand the kidney function, prior to initiating treatment. The figure number 4.1 depicts the flow of patients in these specialist clinics in both the hospitals. This chart also illustrates the information collected during each
clinic visit. This flow chart is designed to help the reader to understand the standard practice in these clinics.

Figure 4.1 - Research Flow Chart

Patients with a diagnosis of RH

↓

Referred by their GP to a consultant cardiologist

↓

pre clinic blood test was ordered for patients at Site 1.

↓

Specialist consultants and their team review the patient in hypertension clinics in either centre

↓

Information such as age, gender, medical history, BP etc were collected

↓

Second outpatient attendance (BP readings were collected)

↓

Third outpatient attendance (BP readings were collected)

The same information was collected on the subsequent reviews.

Data were collected after patient review in the clinics from both centres.
In order to establish parity between the groups at baseline the following data were obtained. Date of birth, age, gender, BP on referral, antihypertensive medication, risk factors, allergies, recommendations. These data were retrieved from patient's case notes or clinic letters after their first and subsequent reviews in the clinic.

4.8 Sampling

In any research study, if the research outcome is to be generalised, a representative sample becomes key to achieving representativeness of the population. The logic of quantitative sampling is that the researcher analyses data collected from the sample, but wishes to make statements about the whole target population from which the target was drawn (Punch, 2001).

In a quantitative research study, the right sample should represent the research population as defined by the researcher. They must be accessible, quantifiable and related to the purpose of the researcher (Balnaves & Caputi, 2001).

There are various methods that can be employed to ensure accurate and appropriate sampling, which represents the research population. In probability samples, every element in the population gets an equal chance of being drawn into the sample, whereas non-probability sampling includes all techniques in which chance does not play a part in the formation of the sample frame. Random sampling is considered as a commonly used desirable technique (Bowling, 2002). Therefore, each sample unit can only appear once in the sample. This method results in more precise population estimates. Thus, at its most basic, names can be pulled out of a hat (Bowling, 2002). Other probability sample designs include stratified random sampling, a commonly-used method of guarding against, obtaining by chance, an unrepresentative sample which under- or over-represents certain groups of the population: where the population of interest is divided into pre-defined strata and subjects are allocated to each stratum prior to randomly selecting subjects from each stratum (Bowling, 2002). If the
sampling fractions vary from each stratum the sampling procedure is known as disproportionate stratified sampling. A disproportionate stratified sample would be taken if some population strata were more heterogeneous than others, making them more difficult to represent in the sample. In this situation a larger sampling fraction is taken from the heterogeneous strata in order to provide results for special sub groups of population (Bowling, 2002).

Multi-sample cluster sampling is another method used in large-scale national studies (Balnaves & Caputi, 2001). As not all populations defined by a researcher are easily assessable, or easily quantifiable, the researcher cannot guarantee every member of the population has an equal chance of being selected (Balnaves & Caputi, 2001). The non-probability technique can provide some systematic framework to sampling in which chance does not play a part in the formation of the sample. There are a number of types of non-probability test used in quantitative research and probably the most commonly used in nursing research is convenience sampling (Knapp, 1998). In this approach the researcher utilises the available respondents.

A similar principle is utilised in volunteer sampling, except that the participants respond to a request in the media, but one drawback in this is that the participants are by nature motivated to participate actively. This may not be representative of the population. Purposive sampling is a technique where the researcher identifies and targets individuals who are believed to be typical of the population being studied (Davies, 2007). In research terms, there is no way of knowing to what extent the sample so chosen is indeed representative of the whole, or in fact has typical qualities. Scientifically it offers no improvement on convenience sampling, and because it fails to make explicit the qualities being employed during sample collection, it is
inferior to quota sampling (Davies, 2007). The criticism of this sampling method is that it may not consist of the representative population.

This study used convenience sampling, sometimes called accidental sampling. The researcher simply takes what he or she can get where it can be obtained easily. However it is acknowledged that the convenience sample does not give any confidence in drawing conclusions about the total populations from which the sample was drawn (Davies, 2007). Therefore, the study’s sample characteristics were compared with that of other larger studies and the results are discussed later under discussion.

The sample size of this study included 100 patients from each hospital site, to give a 90% power to detect differences of 20% or more between the sites in those achieving BP control (15% of patients from one site and 35% of patients from the other site), and 80% power to detect differences of 17% or more (e.g. 15% of patients from one site and 32% of patients from other site). These calculations assumed a simple chi-square test was used with conventional 5% significance level (Statistical Software n Query Advisor Version 7.0).

4.9 Validity

There are three major kinds of validity: construct, internal and external (Balnaves & Caputi, 2001). Construct validity is corroboration that the instrument is measuring the concept it purports to measure (Bowling, 2002). Internal validity is the extent to which the research design allows the researcher to draw conclusions about the relationship between variables (Balnaves & Caputi, 2001). External validity is the extent to which the sample is genuinely representative of the population from which it has been drawn (Balnaves & Caputi, 2001). From these definitions it is clear that construct validity is concerned with measurement, whereas the latter two aspects are the components of a research design.
4.9a Internal validity

Quantitative research concerns the soundness of an investigation. In particular, studies of cause and effect need to be internally validated to explain if the effects observed can be correctly attributed to the treatment administered or the independent variable. This implies that confounding variables and extraneous variables have been controlled for any possible error or bias, due to those variables having been removed or reduced (Bowling, 2005).

There are many threats to internal validity; hence it is important that this is considered at the early stage of the study design. Threats to internal validity include history, time dependent internal changes, practice effects, instrument error, instrument selection error, attrition and regression to the mean (Bowling & Ebrahim 2005).

The threats that can affect this study

There were a number of threats identified. The change in life style, where the events that intervene between a baseline measurement before the treatment and the effect it has on the treatment outcome, e.g. hypertensive patients starting to take a low salt diet in addition to treatment. Practice error where participants may worry about their BP measurement, therefore can have an elevated reading. Using various types of BP apparatus to measure, or the accuracy or precision of a measuring instrument, could introduce instrument error. To reduce this potential source of error, the same BP apparatus is used in the hypertension clinics. The observer should be in a comfortable and relaxed position, because if hurried the pressure will be released too rapidly, resulting in underestimation of systolic and overestimation of diastolic pressures. If any interruption occurs, the exact measurement may be forgotten and an approximation made, so the BP should always be written down (Beevers, Lip & O’Brien, 2001). In the hypertension clinics, BHS-accredited BP apparatus was in use in both centres. The BP apparatus used in these clinics had a biomedical department tag certifying the date it
was checked and the date it is next due for a check. This helped in controlling the potential errors discussed earlier in this chapter. To avoid errors in recording BP, as soon as the BP was measured it was recorded. This is the standard practice at both sites.

Selection or assignment errors

The groups being compared may be different due to the assignment procedure. The researcher is well aware that the non-equivalence of groups will make it impossible to conclude that any difference in outcomes was due to the different antihypertensive agents. Hence, for this study purpose the outcome is measured as percentage of patient’s BP reduction, and length of time, rather than making a direct comparison between the groups. In this study the stated objectives will be looked at. The ethnic variability will not be explored, as this study is not aiming to do a comparison of groups, because ethnic representation may not be equal. The other reason is that there are numerous studies, which have looked into the need for considering ethnicity when treating hypertension.

In the present study, strict inclusion criteria have been developed to limit the effect of confounding factors. Hence, base line characteristics of all patients including risk factors, and other influencing factors like age and gender, were recorded. These data allow the researcher to identify any clinically significant difference at baseline indicating the need for interpreting the data in that particular group.

4.9b External validity

Black (1999) argues that when the independent variable is an observed trait, such as gender or ethnicity, it is important to obtain representative samples of each if results will generalise to them. Furthermore, he also insists that the sample population must only be influenced by time and in experimentation, but subjected to treatment in the normal context if the outcomes are to
be generalised. To increase the external validity it is important to study the population as they are in practice. In this study it was exactly employed. They were studied as they came to be reviewed in the OP service to increase this study’s external validity.

4.10 Ethical consideration

Ethical approval was obtained from the local research committee, the Pan-Manchester R&D department at Manchester Royal Infirmary, in addition to Salford University Research Governance and Ethics sub-committee. The author attended the LREC meeting. The author was asked to amend the patient information sheet. The amendment was to include the title of the study and the name of the researcher was to be added. To personalise the study information leaflet by referring to the patient as ‘you’ rather than the patient (where appropriate) and was advised to include the “patient advice liaison service” (PALS) number in the event the patient wished to complain about this study to an independent body. The second amendment was about the consent opt out slip. Here the suggestion was to add the patient’s number or date of birth rather than name to avoid confusion. The committee wanted to be clear that only patient data was being used and no additional blood tests were involved. The appropriate amendments were made and a favourable ethical opinion for the study was obtained (Ref 06/Q1401h4). Please see a copy of the information sheet, invitation letter and the consent form in the appendices. To obtain the Pan Manchester Research and Development Committees’ approval a copy of the LREC approval was required and submitted. Subsequent approval was obtained from the Pan Manchester Research and development Committee (Ref: 10317-LTR 2 Prab). As a research student from the University of Salford and for my research supervisor to supervise me; Salford research committee approval was obtained (code-RGEC06124).
4.11 Consent

In this observational study informed consent was obtained through the opt-out method, to use the secondary data. A pragmatic method of opting out from the study was adopted. Patients received the study information, with an opt-out form along with their clinic appointment. Only one patient opted out of the study. A copy of the letter of invitation (appendix 2), patient information sheet (appendix 3) and consent form (patient refusal form, appendix 4) are listed in appendices.

4.12 Data analysis

This study consisted of two sets of data, both nominal, ordered categorical and continuous data were obtained from the two study groups of subjects; hence parametric and non-parametric statistical tests were used. A database was created and data were entered using the software package SPSS (Version 15, 2007, SPSS Inc, Chicago IL). Descriptive summary statistics were derived and the following statistical tests were used with the conventional 5% significance level adopted. The primary outcome was BP control. Achievement of BP control at a particular time point was defined for non-diabetics as whether or not BP was <140/85 mmHg, and for diabetics whether or not BP was <130/80 mmHg (See Chapter 5, section 5.3). Secondary outcomes were the actual BP reduction by the second clinic visit, i.e. the absolute BP reduction, (defined as the difference between the BP reading at the first visit and the BP reading at the second visit) and the percentage BP reduction, i.e. the relative BP reduction, (defined as 100 x the difference between the BP reading at the first visit and the BP reading at the second visit, divided by the BP reading at the first visit).

Chi square test

The chi square test (conventionally used to assess the relationship between two categorical variables) was used here primarily to assess the relationship between two groups. (i.e. hospital
Site 1 vs Site 2) (Balnaves & Caputi, 2001) and achievement of BP reduction (yes vs no). That is, to look at the percentage of BP reduction between the two hospitals.

**Two-sample t-test**

The t-test (conventionally used to assess the difference in means between two groups) was used to compare the age distribution of patients from the two hospitals. Comparisons between hospital sites were made using t-test for data that were considered to have an adequate approximation to normal distribution (Pallant, 2001).

**Multiple logistic regression analysis**

A multiple logistic regression analysis was employed as the most appropriate test for this study to assess the relationship between a binary outcome measurement (BP control) and a number of independent (predictor) variables (including hospital site and patient characteristics). This analysis was used to examine the relation between the care setting (i.e. hospital) and the achievement of BP control after adjusting for other factors. The other factors related to potential confounding factors such as number of clinic visits, smoking etc. which, if different between hospital sites and be related to BP control, may impact on the relationship between site and BP control to give misleading results if no adjustments made. This also gave an insight into the variables that were independently related to the endpoint of this study, namely BP control. The analysis assessed the difference between hospitals after adjusting for the length of time in the study and other potential confounding factors with the achievement of BP control. The adjustment for length of time is implemented, as length of time is a covariate in the regression model.

In treating hypertension the JBS 2 guidelines recommended treatment with different antihypertensive agents for patients less than and greater than 55 years. The reason
underpinning this is that patients <55 years tend to have higher renin concentrations than patients aged >55 years (JBS, 2005). In this study the BP control was analysed for the age group ≤55 years and >55 years of age as recommended by the guidelines.

4.13 Confounding Variables

The inclusion and exclusion criteria have been used to control a number of confounding variables. To gain additional control of confounding variables, i.e. (variables which may differ between hospital sites and be related to BP control), multivariate analysis was carried out to explain the difference between the two groups after controlling the confounding variables.

Summary:

In this study, two methods of treating hypertension with or without the use of a biochemical test were compared between two hospitals. As proposed at the outset of the study, it was possible to do multiple regressions with the data collected. In the next chapter the reader will be presented with this study’s results, which will be explained with the use of statistical analysis. The outcome of the study will be discussed and compared with the findings of other contemporary studies.
CHAPTER 5

RESULTS

Introduction

In this chapter the results will be presented to prove or disprove the hypothesis, which was proposed at the outset of this study. This study set out to identify if the use of the ARR blood test helps to achieve target BP earlier than use of the conventional A, B, C or D algorithm. The baseline characteristics of the sample group were analysed and both hospital groups compared and data are presented. The data analyses are presented as, the medication that these patients were on, those with DM, length of time in the study. BP control at different fixed periods. As stated previously these patients were reviewed at different times. The treatment recommendations are different for the age group <55 and >55. hence BP control in this age group was explored. Multiple regression was employed to identify if any factor had a significant influence on BP control. There was a high degree of variability between patients in terms of the number of BP reviews over the study period and of the length of time between reviews. Thus, achievement of BP control (yes vs no) within specific fixed time periods was considered to be the most appropriate simple outcome measure to compare between hospitals.

5.1 Baseline characteristics of study sample

To understand the basic characteristics of the study participants, demographic details such as age, gender and risk factors, where available, were collected. These characteristics for the whole cohort are depicted in Table 5.1. As mentioned previously, the baseline characters were recorded to assess the parity between groups.
Table 5.1 – Patient characteristics for whole cohort (combining two sites)

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Number/220 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>104 (47.3%)</td>
</tr>
<tr>
<td>Male</td>
<td>116 (52.7%)</td>
</tr>
<tr>
<td>Age: mean (sd); range</td>
<td>54.4 (15.5); 20.5-85</td>
</tr>
<tr>
<td>Ethnic status</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>169 (80.5%)</td>
</tr>
<tr>
<td>Non-white</td>
<td>41 (19.5%)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>156 (78.0%)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>13 (6.5%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>31 (15.5%)</td>
</tr>
<tr>
<td>Diabetic</td>
<td>23 (11.2%)</td>
</tr>
<tr>
<td>High cholesterol#</td>
<td>92 (64.3%)</td>
</tr>
<tr>
<td>Family history of CHD $</td>
<td>76 (71.0%)</td>
</tr>
</tbody>
</table>

# Data available for only n=143 patients in all

$ Data available for only n=107 patients in all

As this study was conducted between two groups of hypertensive patients attending hypertension clinics, it was vital to assess the parity between the groups. A comparison of general characteristics between the two groups was undertaken to establish whether there were any statistically significant differences between the two groups at baseline. The comparison of general characteristics of patients referred to the hypertension clinics is depicted in Table 5.2.
Table - 5.2 Comparison of baseline characteristics between the two centres

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Site 1 (n=109)</th>
<th>Site 2 (n=111)</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>58 (53%)</td>
<td>58 (52%)</td>
<td><em>P</em> = 0.99<em>1</em></td>
</tr>
<tr>
<td>Age; mean (sd)</td>
<td>53.6 (14.4)</td>
<td>55.1 (16.4)</td>
<td><em>P</em> = 0.46<em>2</em></td>
</tr>
<tr>
<td>Ethnic status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>99 (94.3%)</td>
<td>70 (66.7%)</td>
<td><em>P</em> &lt; 0.001<em>1</em></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>77 (76.2%)</td>
<td>79 (79.8%)</td>
<td><em>P</em> = 0.03<em>1</em></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>11 (10.9%)</td>
<td>2 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>13 (12.9%)</td>
<td>18 (18.2%)</td>
<td></td>
</tr>
<tr>
<td>Diabetic</td>
<td>7 (6.8%)</td>
<td>16 (15.5%)</td>
<td><em>P</em> = 0.077<em>1</em></td>
</tr>
<tr>
<td>High cholesterol §</td>
<td>46 (54.1%)</td>
<td>46 (79.3%)</td>
<td><em>P</em> = 0.004<em>1</em></td>
</tr>
<tr>
<td>Family history of CHD §</td>
<td>41 (63.1%)</td>
<td>35 (83.3%)</td>
<td><em>P</em> = 0.024<em>1</em></td>
</tr>
</tbody>
</table>

1 chi-square test, 2 t-test  # Data available for only n=85 patients at SHH and n=58 at MRI
$ Data available for only n=65 patients at SHH and n=42 at MRI

5.2 Prior antihypertensive medication

As these patients with a history of RH were seen in the clinic, their initial, i.e. current medications with which they were referred to be seen in the clinic were explored. Table 5.3 highlights the number of different classes of drugs that the whole cohort was receiving and a comparison of prior antihypertensive medication between the two centres. A comparison between the two sites has demonstrated that first drug of choice was an ACEI. The use of an alpha-blocker was higher at Site 2, which was statistically significant.
Table 5.3 – Prior Antihypertensive medication for the whole cohort at baseline

Comparison of prior antihypertensive medication between centres

<table>
<thead>
<tr>
<th>Names of prior antihypertensive medication</th>
<th>Whole cohort</th>
<th>Site 1</th>
<th>Site 2</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin Converting Enzyme Inhibitors (ACEI)</td>
<td>94 (47.5%)</td>
<td>45 (48.9%)</td>
<td>49 (46.2%)</td>
<td>P=0.81&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Angiotensin Receptor Blockers (ARB)</td>
<td>63 (32.3%)</td>
<td>27 (30.0%)</td>
<td>36 (34.3%)</td>
<td>P=0.63&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Beta Blockers (BB)</td>
<td>60 (30.5%)</td>
<td>23 (25.3%)</td>
<td>37 (34.9%)</td>
<td>P=0.19&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Calcium Channel Blockers (CCB)</td>
<td>88 (44.9%)</td>
<td>36 (39.6%)</td>
<td>52 (49.5%)</td>
<td>P=0.21&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diuretics</td>
<td>86 (43.9%)</td>
<td>34 (37.4%)</td>
<td>52 (49.5%)</td>
<td>P=0.12&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Statin therapy</td>
<td>56 (28.7%)</td>
<td>26 (28.6%)</td>
<td>30 (28.8%)</td>
<td>P=1.0&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Aldosterone Blockers</td>
<td>9 (4.6%)</td>
<td>2 (2.2%)</td>
<td>7 (6.8%)</td>
<td>P=0.24&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Alpha Blockers</td>
<td>47 (23.9%)</td>
<td>15 (16.5%)</td>
<td>32 (30.2%)</td>
<td>P=0.037&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup> Chi-square test

The medication used in both sites is depicted in figure 5.1 to give the reader a visual comparison.
Figure 5.1 – Prior antihypertensive drug use:

The figure 5.1 shows the percentage of patients on each individual drug by site.
5.3 Study Period

BP control definition

The BP values for each subject were assessed to see if BP control had been achieved. The criterion used for BP control varied with diabetes status. The target BP for non diabetics is regarded as <140/85 mmHg, and for diabetic patients it was considered to be <130/80 mmHg as recommended by the European Hypertension Society, The American Society of Hypertension and the BHS guidelines (2005). Hence the achievement of BP control at a particular time point was defined for non-diabetics as whether or not BP <140/85 mmHg, and for diabetics whether or not BP <130/80 mmHg.

Table 5.4 – DM status by hospital site

<table>
<thead>
<tr>
<th>DM Status</th>
<th>Site 1</th>
<th>Site 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not DM</td>
<td>87</td>
<td>78</td>
</tr>
<tr>
<td>DM</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

5.4 BP control

5.4a BP control achieved by the end of follow-up

BP control was compared between the two groups to establish if the ARR had an impact on BP control. Only 29 (30.5%) participants from SHH and 32 (32.3%) from MRI achieved BP control during the study time. This difference was not found to be statistically significant. See table 5.5 below.

103
Table 5.5 – A comparison of BP control over the whole study period

<table>
<thead>
<tr>
<th>BP Control</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Site 1</td>
</tr>
<tr>
<td>No control</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>%</td>
</tr>
<tr>
<td>Control</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>%</td>
</tr>
<tr>
<td>Total</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>%</td>
</tr>
</tbody>
</table>

Chi-square test, $X^2(1) = 0.0; p=0.91$

The length of time taken to achieve BP control was explored. The number of reviews, and the duration of time between reviews, differed greatly between subjects. Therefore the total number who had one or more BP assessments was 213. Of these 213 participants, 19 had their BP assessed once only. See Table 5.6 below.
Table 5.6 – Number of reviews per subject during the course of the study

<table>
<thead>
<tr>
<th>Number of Reviews</th>
<th>Sites</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Site 1</td>
<td>Site 2</td>
</tr>
<tr>
<td>0</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>5.5%</td>
<td>.9%</td>
</tr>
<tr>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>N</td>
<td>7.3%</td>
<td>9.9%</td>
</tr>
<tr>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>26</td>
</tr>
<tr>
<td>N</td>
<td>29.4%</td>
<td>23.4%</td>
</tr>
<tr>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>49</td>
<td>39</td>
</tr>
<tr>
<td>N</td>
<td>45.0%</td>
<td>35.1%</td>
</tr>
<tr>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>N</td>
<td>10.1%</td>
<td>10.8%</td>
</tr>
<tr>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>N</td>
<td>2.8%</td>
<td>12.6%</td>
</tr>
<tr>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>N</td>
<td>.0%</td>
<td>7.2%</td>
</tr>
<tr>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>109</td>
<td>111</td>
</tr>
<tr>
<td>N</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.5 Length of time in the study

This is defined as the time between the first hospital visit, at which BP was measured, to the last recorded hospital visit. The total number of participants who had one or more BP assessments was 213. This comprised 103 from Site 1 and 110 from Site 2. There were 19
patients who had their BP assessed once only. Of these 19, eight (7.3%) were from Site 1 and 11 (10%) were from Site 2.

For the 194 subjects with two or more readings (95 from Site 1 and 99 from Site 2) the length of time in the study was calculated as the difference in the date between the first and last recorded BP measurements. The maximum length of time in the study was 19 months for Site 1 and 18 months for Site 2. This is highlighted in Table 5.7. The analysis demonstrates that the Site 2 patients spent statistically significantly longer under review compared to Site 1 patients (Mann-Whitney U-test; p=0.001).

Table 5.7 – Length of time (months) in study

<table>
<thead>
<tr>
<th>Hospital</th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site 1</td>
<td>95</td>
<td>0</td>
<td>18</td>
<td>4.0</td>
</tr>
<tr>
<td>Site 2</td>
<td>99</td>
<td>0</td>
<td>20</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Bearing in mind that this study focused on BP reduction and the participants were reviewed at different times, as an alternate way of looking at the data, fixed time periods of three, six and nine months were selected for each period, the percentages of patients who achieved BP control within that time period were derived. All patients who had achieved control within the specified period were counted as controlled. All other patients were counted as uncontrolled. Thus the BP control rates presented below can be considered as cumulative BP control rates.

5.5a Three-month period BP control

At the three-month stage 10 (10.5%) patients from Site 1 compared with 16 (16.2%) patients from Site 2 achieved BP control. This difference was not statistically significantly (10% vs 16%; chi-square test p=0.35). See Table 5.8 below.
Table 5.8 – A comparison of three-month period BP control

<table>
<thead>
<tr>
<th>Month 3 BP control</th>
<th>Sites</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No control</td>
<td>Site 1</td>
<td>85</td>
<td>89.50%</td>
<td>83</td>
<td>83.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>Site 1</td>
<td>10</td>
<td>10.5%</td>
<td>16</td>
<td>16.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>Site 1</td>
<td>95</td>
<td>100.00%</td>
<td>99</td>
<td>100.00%</td>
<td></td>
</tr>
</tbody>
</table>

Chi-square test, $x^2(1)=0.9; p=0.35.$

5.5b Six-month period BP control

At the six-month point, 19 patients (20.0%) from Site 1 and 22 (22.2%) patients from Site 2 had achieved BP control. When the cumulative number of patients from both groups was compared again, a higher number of patients achieved BP control from Site 2. However, this was not statistically significant. See Table 5.9 below.

Table 5.9 A comparison of six-month period BP control

<table>
<thead>
<tr>
<th>Month 6 BP control</th>
<th>Sites</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No control</td>
<td>Site 1</td>
<td>76</td>
<td>80.0%</td>
<td>77</td>
<td>77.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>Site 1</td>
<td>19</td>
<td>22.0%</td>
<td>22</td>
<td>22.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>Site 1</td>
<td>95</td>
<td>100.00%</td>
<td>99</td>
<td>100.00%</td>
<td></td>
</tr>
</tbody>
</table>

Chi-square test, $x^2(1) = 0.04; p=0.84$
5.5c Nine-month period BP control

At the nine-month stage a total of 51 (26.3%) patients achieved BP control, of which 22 (23.2%) patients were from Site 1 and 29 (29.3%) from Site 2. The control rate was similar between Site 1 and Site 2 (23% vs 29%; chi-square test p=0.42). See Table 5.10

Table 5.10 – A comparison of nine-month period BP control

<table>
<thead>
<tr>
<th>Month 9 BP control</th>
<th>Sites</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Site 1</td>
<td>Site 2</td>
<td></td>
</tr>
<tr>
<td>No control</td>
<td>73</td>
<td>70</td>
<td>76.8%</td>
</tr>
<tr>
<td>%</td>
<td>76.8%</td>
<td>70.7%</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>22</td>
<td>29</td>
<td>23.2%</td>
</tr>
<tr>
<td>%</td>
<td>23.2%</td>
<td>29.3%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>95</td>
<td>99</td>
<td>100.0%</td>
</tr>
<tr>
<td>%</td>
<td>100.0%</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Chi-square test, $x^2(1) = 0.6; p=0.42$

As the BP control was not statistically significant at fixed different times, it was necessary to assess an actual percentage of BP reduction. This was employed to assess if the percentage of BP reduction was significantly different between the groups and one of the aims of the study was to assess the percentage of BP reduction between the centres; in order to do this, the first and second clinic visit was utilised.

5.6 Actual and percentage BP reduction

The actual BP reduction and the percentage reduction achieved between the first and second clinic visit was calculated. This analysis was restricted to the 194 patients (95 from Site 1 and 99 from Site 2) who had at least two clinic visits. The mean reduction of BP for Site 1 was 1.7 mmHg for systolic BP and 1.8 mmHg for diastolic BP compared with 6.5 mmHg and 2.3 mmHg for the Site 2 patients respectively. These were not found to be statistically significant (two-sample t-test; systolic p=0.18, diastolic p=0.79). See Table 5.11
Table 5.11 – A comparison of actual BP change between the 1\textsuperscript{st} and 2\textsuperscript{nd} clinic visit

<table>
<thead>
<tr>
<th>Site</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>SITE 1</td>
<td>95</td>
<td>-1.7</td>
<td>23.8</td>
<td>-68</td>
<td>43</td>
</tr>
<tr>
<td>SITE 2</td>
<td>99</td>
<td>-6.5</td>
<td>25.5</td>
<td>-100</td>
<td>68</td>
</tr>
</tbody>
</table>

T-test; \( t(192)=1.3; p=0.18 \)

<table>
<thead>
<tr>
<th>Site</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>SITE 1</td>
<td>95</td>
<td>-1.8</td>
<td>12.3</td>
<td>-39</td>
<td>30</td>
</tr>
<tr>
<td>SITE 2</td>
<td>99</td>
<td>-2.3</td>
<td>14.0</td>
<td>-34</td>
<td>43</td>
</tr>
</tbody>
</table>

T-test; \( t(192) = 0.3; p = 0.79 \)

Note: a negative value for the mean, minimum or maximum indicates a reduction; a positive value indicates an increase over the period.

When the mean percentage reduction was assessed, the value for SHH was -0.3\% for systolic BP and 1.0\% for diastolic BP compared with 2.6\% and 1.0\% for the MRI patients respectively. These differences were not statistically significant (two-sample t-test; systolic \( p=0.20 \), diastolic \( p=0.98 \)). See Table 5.12

Table 5.12 – A comparison of percentage BP reduction between the 1\textsuperscript{st} and 2\textsuperscript{nd} visit

<table>
<thead>
<tr>
<th>Site</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>SITE 1</td>
<td>95</td>
<td>0.3</td>
<td>15.1</td>
<td>-32</td>
<td>31</td>
</tr>
<tr>
<td>SITE 2</td>
<td>99</td>
<td>-2.6</td>
<td>15.9</td>
<td>-41</td>
<td>53</td>
</tr>
</tbody>
</table>

T-test; \( t(192)=1.3; p=0.20 \)

<table>
<thead>
<tr>
<th>Site</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>SITE 1</td>
<td>95</td>
<td>-1.0</td>
<td>14.2</td>
<td>-31</td>
<td>47</td>
</tr>
<tr>
<td>SITE 2</td>
<td>99</td>
<td>-1.0</td>
<td>16.3</td>
<td>-32</td>
<td>74</td>
</tr>
</tbody>
</table>

T-test; \( t(192) = 0.02; p = 0.98 \)

Note: a negative value for the mean, minimum or maximum indicates a reduction; a positive value indicates an increase over the period.

The effect of patient characteristics such as ethnic origin, diabetes, smoking status and gender on BP control were analysed to identify if there was any evidence of a statistically significant relationship between these factors and BP control. This was undertaken to assess if there was a factor that had an impact on BP control.
5.7 Impact of patient characteristics on BP control

The relationship between BP control and specific patient characteristics was assessed in the 194 patients with at least two sets of BP readings.

**Diabetic status**

As highlighted earlier, there were 23 (10.7%) participants known to have diabetes in this study group. Of these, only three participants (1.4%) achieved BP control. A lower percentage of patients with diabetes achieved BP control compared to those without diabetes, but this difference was not statistically significant (14% vs 34%; chi-square test p=0.12). See Table 5.13 below.

<table>
<thead>
<tr>
<th>BP control</th>
<th>Diabetic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>No control</td>
<td>N 115</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>% 66.5%</td>
<td>85.7%</td>
</tr>
<tr>
<td>Control</td>
<td>N 58</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>% 33.5%</td>
<td>14.3%</td>
</tr>
<tr>
<td>Total</td>
<td>N 173</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>% 100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Chi-square test, $x^2(1)=2.4;p=0.12$

**Smoking status**

Data on 182 patients were available to assess the relationship between smoking status and BP control. A lower percentage of current smokers achieved BP control compared to ex- and non-smokers (22% vs 46% vs 32%) but this difference was not statistically significant; chi-square test $p=0.30)$. See Table 5.14 below.
Table 5.14 – Relationship between smoking status and BP control

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Non Smoker</th>
<th>Ex Smoker</th>
<th>Current Smoker</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No control N</td>
<td>96</td>
<td>7</td>
<td>21</td>
<td>124</td>
</tr>
<tr>
<td>%</td>
<td>67.6%</td>
<td>53.8%</td>
<td>77.8%</td>
<td>68.1%</td>
</tr>
<tr>
<td>Control N</td>
<td>46</td>
<td>6</td>
<td>6</td>
<td>58</td>
</tr>
<tr>
<td>%</td>
<td>32.4%</td>
<td>46.2%</td>
<td>22.2%</td>
<td>31.9%</td>
</tr>
<tr>
<td>Total N</td>
<td>142</td>
<td>13</td>
<td>27</td>
<td>182</td>
</tr>
<tr>
<td>%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Chi-square test, $x^2(2)=2.4; p=0.30$

This may be due to a small number of patients with a history of smoking.

Ethnic origin

Data on 185 patients were available to assess the relationship between ethnic origin and BP control. The percentage achieving BP control was similar for patients of white ethnic origin compared to non-white ethnic origin. This was not statistically significant (31% vs 34%: $p=0.74$). See Table 5.15 below.

Table 5.15 – Relationship between ethnic origin and BP control

<table>
<thead>
<tr>
<th>BP Control</th>
<th>Ethnic Origin</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White</td>
<td>Other</td>
</tr>
<tr>
<td>No control N</td>
<td>103</td>
<td>23</td>
</tr>
<tr>
<td>%</td>
<td>68.7%</td>
<td>65.7%</td>
</tr>
<tr>
<td>Control N</td>
<td>47</td>
<td>12</td>
</tr>
<tr>
<td>%</td>
<td>31.3%</td>
<td>34.3%</td>
</tr>
<tr>
<td>Total N</td>
<td>150</td>
<td>35</td>
</tr>
<tr>
<td>%</td>
<td>100.00%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Chi-square test, $x^2(1)=0.1; p=0.74$
Gender

There were 105 (100%) males and 89 (100%) females in this cohort. Of these, 26 (24.8%) males and 35 (39.3%) females achieved BP control during the study period. A statistically significant lower percentage of males achieved BP control compared to females (25% vs 39%; chi-square test p=0.043). See Table 5.16 below.

Table 5.16 - Relationship between gender and BP control

<table>
<thead>
<tr>
<th>BP Control</th>
<th>Gender</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>No control</td>
<td>N</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>75.2%</td>
</tr>
<tr>
<td>Control</td>
<td>N</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>24.8%</td>
</tr>
<tr>
<td>Total</td>
<td>N</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Chi-square test, $x^2(1)=4.1; p=0.043$.

After looking at the BP control and baseline characters, it was necessary to identify if there was a single factor, which had an influence on BP control. In order to see if this was so, a regression model was employed. A conventional approach was used to build a regression model to identify if there was any difference in BP control between the two patient groups after adjusting for any influencing (confounding) factors. The influencing factors were selected for inclusion on the basis of a significant difference in the distribution of these factors between sites and/or a significant relationship with BP control.

5.8 Comparison of BP control between sites adjusting for confounding factors

A logistic regression analysis was used to examine if there was any relationship between hospital (SHH vs MRI) and achieving BP control, whilst adjusting for the length of time in the study, the number of reviews, smoking status, diabetes status, ethnic origin, gender and age. The results showed no statistically significant difference in BP control between the
hospitals (odds ratio for control in MRI patients compared to SHH = 1.27; 95% CI 0.56 to 2.91; p=0.57). See Table 5.17 below.

Table 5.17 – Multiple logistic regression analysis results

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in study (months)</td>
<td>1.09</td>
<td>0.99, 1.19</td>
<td>p=0.077</td>
</tr>
<tr>
<td>No. of reviews</td>
<td>1.33</td>
<td>0.78, 2.28</td>
<td>p=0.30</td>
</tr>
<tr>
<td>Diabetic</td>
<td>0.26</td>
<td>0.05, 1.44</td>
<td>p=0.12</td>
</tr>
<tr>
<td>Non-white ethnic origin</td>
<td>0.71</td>
<td>0.23, 2.22</td>
<td>p=0.56</td>
</tr>
<tr>
<td>Female</td>
<td>1.68</td>
<td>0.79, 3.55</td>
<td>P=0.18</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.99</td>
<td>0.96, 1.01</td>
<td>P=0.26</td>
</tr>
<tr>
<td>Smoking status (overall)</td>
<td>1</td>
<td>-</td>
<td>p=0.14</td>
</tr>
<tr>
<td>Ex vs non</td>
<td>3.23</td>
<td>0.85, 12.25</td>
<td>p=0.084</td>
</tr>
<tr>
<td>Current vs non</td>
<td>0.62</td>
<td>0.20, 1.87</td>
<td>p=0.40</td>
</tr>
<tr>
<td>MRI vs SHH</td>
<td>1.27</td>
<td>0.56, 2.91</td>
<td>p=0.57</td>
</tr>
</tbody>
</table>

As stated previously the BP control below and above the age of 55 was analysed.

The reason for this was the treatment recommendations are different for age group <55 years and >55 years.

5.9 BP control in patients aged less than or equal to 55

Of the 99 patients aged less than or equal to 55 years, 55 (36.4%) were from SHH and 44 (29.5%) were from MRI. There were 20 (36.4%) participants from SHH and 13 (29.5%) from MRI who achieved BP control from this sub group. The crude (unadjusted) BP control rate (that is, the simple percentage relating to whether BP control was achieved, unadjusted for any confounding factors such as number of reviews, smoking status etc.) was similar between SHH and MRI (36% vs 30%; chi-square test p=0.62). See Table 5.18 below.
Table 5.18 – A comparison of BP control over the whole study period for patients aged less than or equal to 55

<table>
<thead>
<tr>
<th>BP Control</th>
<th>Sites</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Site 1</td>
<td>Site 2</td>
</tr>
<tr>
<td>No control</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>35</td>
<td>31</td>
</tr>
<tr>
<td>Control</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>55</td>
<td>44</td>
</tr>
</tbody>
</table>

Chi-square test, $X^2(1)=0.2; p=0.62$

Using logistic regression analysis to examine if there is any relationship between hospitals (Site 1 vs Site 2) and achieving BP control, in age group <55 years, whilst adjusting for the length of time in the study, the number of reviews, smoking status, ethnic origin and gender, the results showed no statistically significant evidence of a difference in BP control between the hospitals (odds ratio for control in Site 2 patients compared to Site 1 = 1.17; 95% CI 0.33 to 4.19; $p=0.81$). See Table 5.19 below. Total number of reviews ($p=0.079$) and gender ($p=0.065$) showed no significance with BP control. The greater the number of reviews, the greater the possibility of control (odds ratio for each additional review=2.20) and females had a greater possibility of control (odds ratio for control in females compared to males=2.49). However, they were not found to be statistically significant.
Table 5.19 – Multiple logistic regression analysis results for age ≤55 years

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in study (months)</td>
<td>1.02</td>
<td>0.90, 1.16</td>
<td>p=0.76</td>
</tr>
<tr>
<td>No. of reviews</td>
<td>2.20</td>
<td>0.91, 5.29</td>
<td>p=0.079</td>
</tr>
<tr>
<td>Non-white ethnic origin</td>
<td>0.36</td>
<td>0.06, 2.02</td>
<td>p=0.25</td>
</tr>
<tr>
<td>Female</td>
<td>2.59</td>
<td>0.94, 7.13</td>
<td>p=0.065</td>
</tr>
<tr>
<td>Smoking status (overall)</td>
<td>1</td>
<td>-</td>
<td>p=0.53</td>
</tr>
<tr>
<td>Ex vs non</td>
<td>3.09</td>
<td>0.29, 33.2</td>
<td>p=0.35</td>
</tr>
<tr>
<td>Current vs non</td>
<td>0.69</td>
<td>0.19, 2.56</td>
<td>p=0.58</td>
</tr>
<tr>
<td>SITE 2 vs SITE 1</td>
<td>1.17</td>
<td>0.33, 4.19</td>
<td>p=0.81</td>
</tr>
</tbody>
</table>

Diabetic status was omitted from the analysis because there were only six patients in this age subgroup with diabetes of whom none achieved BP control, thus causing mathematical uncertainty in the regression model.

5.10 BP control in patients aged greater than 55

Of the 95 patients aged greater than 55 years, 40 were from Site 1 and 55 were from Site 2. Only nine (22.5%) patients from Site 1 and 19 (34.5%) from Site 2 achieved BP control during the study period. The crude (unadjusted) control rate was similar between Site 1 and Site 2 (22% vs 34%; chi-square test p=0.30). See Table 5.20 below.
Table 5.20 – A comparison of BP control over the whole study period for patients aged greater than 55

<table>
<thead>
<tr>
<th>BP control</th>
<th>Sites</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Site 1</td>
<td>Site 2</td>
</tr>
<tr>
<td>No control</td>
<td>N 31</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>% 77.5%</td>
<td>66.5%</td>
</tr>
<tr>
<td>Control</td>
<td>N 9</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>% 22.5%</td>
<td>34.5%</td>
</tr>
<tr>
<td>Total</td>
<td>N 40</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>% 100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Chi-square test, $X^2(1) = 1.1; p=0.30$

Using logistic regression analysis to examine if there is any relationship between hospital (Site 1 vs Site 2) and achieving BP control, whilst adjusting for the length of time in the study, the number of reviews, smoking status, ethnic origin, diabetic status and gender, the results showed some limited evidence of a difference in BP control between the hospitals (odds ratio for control in Site 2 patients compared to Site 1 = 3.10; 95% CI 0.86 to 11.1; $p=0.082$). This is a really large variation, but not statistically significant. See Table 5.21 below. Total time in study ($p=0.024$) showed a statistically significant relationship with BP control. The longer the time in the study increased the possibility of control (odds ratio for each additional month in the study = 1.20).
Table 5.21 – Multiple logistic regression analysis results for age >55 years

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in study (months)</td>
<td>1.20</td>
<td>1.02, 1.40</td>
<td>p=0.024</td>
</tr>
<tr>
<td>No. of reviews</td>
<td>0.82</td>
<td>0.37, 1.80</td>
<td>p=0.62</td>
</tr>
<tr>
<td>Non-white ethnic origin</td>
<td>0.93</td>
<td>0.18, 4.82</td>
<td>p=0.93</td>
</tr>
<tr>
<td>Diabetic</td>
<td>0.28</td>
<td>0.04, 1.99</td>
<td>p=0.20</td>
</tr>
<tr>
<td>Female</td>
<td>0.81</td>
<td>0.25, 2.65</td>
<td>p=0.73</td>
</tr>
<tr>
<td>Smoking status (overall)</td>
<td>1.00</td>
<td>-</td>
<td>p=0.14</td>
</tr>
<tr>
<td>Ex vs non</td>
<td>3.79</td>
<td>0.66, 21.8</td>
<td>p=0.40</td>
</tr>
<tr>
<td>Current vs non</td>
<td>0.23</td>
<td>0.02, 2.47</td>
<td>p=0.22</td>
</tr>
<tr>
<td>SITE 2 vs SITE 1</td>
<td>3.10</td>
<td>0.86, 11.1</td>
<td>p=0.082</td>
</tr>
</tbody>
</table>

Summary

It is evident from this study that controlling hypertension to achieve the target BP is difficult. Using a special biochemical test made no statistically significant difference in achieving target BP against the conventional method of treating BP. Though the perception of using a special test to identify a treatment was high in a district general hospital, the overall results did not differ in the two care settings. The findings of the study support the fact that achieving target BP is neither simple nor easy. The results of this study refute the hypothesis proposed at the beginning of the study. Although these patients were seen in a specialist clinic supervised by a specialist in managing hypertension, the results of this study would suggest that on the basis of this finding alone BP reduction was similar in both groups. However it should be remembered that the analysis was based on a relatively small population of patients with hypertension over a short period of time. This lends support to the A or B or C or D algorithm set out by the JBS2 guidelines, but the BP control in this cohort was not significant either. Perhaps one could argue that the biochemical profile is as effective as the A or B or C or D algorithm to guide the treatment in RH.
In the light of this study it is vital to conduct a larger study including the new evidence of targeting the SBP. The methods used in this study were appropriate to demonstrate whether the target BP was achieved with or without the aid of a biochemical test. In the next chapter the author will discuss the study results with evidence from the literature to aid in understanding this study’s outcome. The next step would be to explore the impact on this study’s outcome on clinical practice, policy, education and research.
CHAPTER 6
DISCUSSION

Introduction

This study set out to establish whether there was any difference in BP reduction with or without a biochemical profile, and to identify if there were differences in BP reduction at different points, i.e. three, six and nine months. The study was conducted in two NHS hospitals in the North of England. The study undertaken was a cohort study, where two treatment methods were compared in the current clinical setting. The sample population included 223 patients with a history of RH, who had been referred by their GP to be seen in specialist hypertension clinics. This current study focused on patients aged less than 85 years, two patients were excluded as they were over 85 and one patient opted not to be included in this study. This resulted in the analysis of 220 patients. Although 220 patients were recruited for the study seven patients failed to attend for their review. Therefore 213 patients were seen in the clinic. Of these, there were 19 patients reviewed by the specialist on only one occasion. The characteristics of the sample such as age, gender, and ethnicity risk factors were compared with those of patients in hypertension studies and were found to reflect these similarities with this study group.

The benefit of this research was that the current clinical practice between two areas has been compared, as the need for proving or refuting the use of a biochemical test was long overdue in the author’s practice setting. This study was conducted to scrutinise the use of a biochemical profile, which has been in use in the author’s clinical setting. It gave the author the opportunity to compare the BP control method used in the author’s practice against an alternative method.
In hypertension management, there are a vast number of control trials that have compared the efficacy of anti hypertension medication. Whilst it was not their primary intention, these studies highlighted the characteristics of their sample. It was thought appropriate to compare the sample within this current study with other studies; therefore it was necessary to extrapolate data from these studies to identify the current study population and where possible identify UK data to make the comparison possible. As mentioned earlier this being a comparative study, it was necessary to look at the study population as a whole to understand their basic characteristics.

In this discussion the author’s study will be referred to as “in this thesis” and “in this study” will refer to the studies from the literature review. This structure was adopted to enable the reader to read with ease and clarity, the discussion part of this thesis.

6.1 Baseline Characteristics for the whole group

To understand the participant’s base line characteristics in this thesis, the whole groups’ characteristics were analysed. There were 220 patients in this cohort, of which there were 104 (47.3%) female and 116 (52.7%) male. The age distribution ranged from 20 to 85 years and the mean age was 54.4 years. Evidence from the literature review suggests that the prevalence of hypertension is between 30%-50% in the over 65s, but in practice a significantly lower proportion of patients are identified, treated and ultimately attain good BP control (Wilkinson, Waring & Cockcroft, 2003).

Although there is a notion that increasing age, >65years old is associated with a higher prevalence of RH (Sarafidis & Bakris, 2008), this was not reflected in this current thesis population. In this thesis the age ranged between 20.5 and 85 years with a mean of 54.4 years with a mean standard deviation of 15.5. There is an understanding that increasing age is
associated with a higher prevalence of arterial stiffening which is not only responsible for a falsely elevated systolic BP reading, but is also a major cause of true elevations (Chobanian, Bakris, Black, 2003). An observational study in the UK demonstrated a greater frequency of hypertension in the younger cohort (<50 yrs). The results from the Health Survey for England 1998, showed that isolated systolic hypertension was found in about one fourth of men and women age ≥30 years, and over the age of 50 the majority of cases of hypertension were isolated systolic BP (Primatosta, Brooks & Poulter, 2001).

In this thesis when ethnic background was explored, information regarding ethnic background was available for 210 patients only. Of these there were 169 (80.5%) white patients, of which 99 (94.3%) patients from site 1 and 70 (66.7%) patients from site 2. This reflects the population these hospitals serve. There were 41 (19.5%) non-white patients. Gupta et al, (2010) highlight that the BHS and NICE do not recommend taking ethnicity into account when treating hypertension. This may be because there are few reliable comparisons between ethnic groups except for patients of white European or black African origin. It is not known whether south-Asians from India or other oriental populations differ in their response to BP control drugs compared to white and black patients. In the ASCOT trial, analysis demonstrated that Amlodipine was effective in lowering BP as a first line of treatment in black, white and those of south-Asian origin (Brewster, van Montfrans & Kleijnene, 2004) whereas the second line of treatment response was different in all these three groups. The impact of ethnic background on the BP control with a diuretic and an ACEI as a second line of treatment, as demonstrated by the ASCOT group, was a new finding (Gupta et al, 2010). Though these findings are impressive the results must be extrapolated with caution, as the black and south-Asian participant numbers were relatively small. But these findings suggest that ethnic difference must be accounted for in combining antihypertensive treatment. The next step was to assess this cohort’s risk factors. When their risk factors were explored, there
were 156 (78%) non-smokers, 13 (6.5%) ex-smokers and 31 (15.5%) current smokers in this cohort (p= 0.031). Only 23 (11.2%) patients were diabetic, 92 (64.3%) had a high cholesterol level and there were 76 (71%) with a family history of known CHD in this whole group. It is known that a high proportion of patients with known or suspected hypertension have additional cardiovascular risk factors (Lima et al, 2009). Hypertension is considered a major risk factor for the development of cardiovascular diseases (Shapo, Pomerleau & McKee, 2003). It has been suggested that hypertension is only one of the many risk factors for cardiovascular disease and patients' prognosis depends more on the sum of their risk factors than on their BP alone (Van Den Hoogen et al, 2000). This is reflected in this thesis study population also. However, all of the risk factors were not identified in 47% from site 2 and 22% from site 1, indicating a lack of holistic assessment. This thesis was a comparative study; therefore a comparison of the two groups' general characteristics was undertaken. As stated previously this was necessary to establish the parity between the groups at base line.

6.2 Comparison of baseline characteristics between the two groups

In total there were 111 (100%) participants from Site 2 and 109 (100%) participants from Site 1. There were 58 (58%) male participants from Site 2 and a similar 58 (52%) from Site 1. The mean age for Site 2 was 55 years and 53 years for Site 1. There were 16 (15.5 %) from Site 2 and 7 (6.8%) from Site 1 known to have DM. There were 46 patients from both sites known to have a cholesterol level >4 mmols/litre. The comparison of these patients' characteristics from both hospitals showed no statistically significant difference in their baseline status, except for ethnic background and overall smoking status, which were found to be statistically significant.

As ethnic background showed a statistical significance, this was explored. There were 70 (66.7%) from Site 2, and 99 (94.3 %) from Site 1 (p=<0.001) who were white. As this current
study’s focus was BP control as stated previously, the non-white ethnic classification was not further explored to get the exact ethnic classification. The ethnic classification data is not collected routinely and as such it was not possible to know the exact classification. Therefore the ethnic background was classified as white and non-white. The difference in the ethnic distribution between the groups reflects the population served by these hospitals. The data regarding elevated BP and a greater prevalence of hypertension among ethnic groups in the UK is not as consistent as data from the US.

The precise reasons for the inconsistency in the data from studies of ethnic groups in the UK are uncertain, but may partly relate to the different populations studied and the fact that the UK ethnic population is predominantly first-generation (Lane & Lip, 2001). There is some evidence that the rates of detection, treatment, and control are higher among black populations in Britain, indicating a greater awareness among the general public and physicians of the importance of detecting and managing hypertension, particularly in black populations (Lane & Lip, 2001). It appears that rates of detection, treatment, and control of high BP among people of South Asian origin may be similar to those of the white population (Primatesa et al, 2000).

In this thesis a statistical significance was found in the white population. This could be due to the small number of non-white participants. Several population-based studies in the UK have investigated ethnic differences in BP, in order to explain the variability in CHD mortality and morbidity. Most studies reported a higher prevalence of hypertension among Afro-Caribbean populations and among South Asians (Primatesa, Bost & Poulter, 2000). In addition, the majority of these studies have also reported significantly high mean BP levels amongst both Afro-Caribbean populations (McKeigue, Shah & Marmot 1991, Primatesa, Bost & Poulter, 2000), and South Asian men compared to their white counterparts. A systematic review of evidence to see if the levels and prevalence of hypertension are higher in south Asian adults living in the UK compared to the white population showed that BP levels and prevalence of
hypertension differ across groups. This could be due to the variations in methods of measuring BP and classification of minority groups (Agyemang & Bhopal 2002). It is difficult to draw data from major trials in relation to race and ethnicity as there is a suggestion that most of the major studies without race or ethnicity data were conducted in the European Union, where trial reports are five times less likely to contain data on race and ethnicity than US trials (Sheikh, Netuveli & Kai, 2004). This could be due to numerous factors complicating the reporting of racial demographic and outcomes data in clinical trials. The race and ethnicity defined by the National Institute of Health may well be suited to research in the USA, but may be difficult to apply to large multinational studies in which participating nations do not routinely collect individual racial data, or may classify race in a different manner than in the US (Park & Taylor, 2007). It is important to include a larger number of minorities and race specific analyses in clinical trials to identify important differences in pathophysiology and treatment response – differences that may lead to a reduction in disparities in health care (Park & Taylor, 2007). The literature review suggested that there is inconsistency in data relating to ethnic groups and BP. In the current thesis the number of non-white patients was too small to make any significant statistical difference to relate to their BP control. The comparison of risk factors between the two groups is discussed in the following section.

6.3 Comparison of the base line characteristics of risk factors between the two groups

6.3a Smoking

Cigarette smoking is a known risk factor for CHD (Halperin, Gaziano & Sesso, 2008). There were 18 (18.2%) patients from Site 2 and 13 (12.9%) patients from Site 1 who were current smokers. There were two ex-smokers (2.0%) from Site 2 and 11 (10.9%) from Site 1 (p=0.03). Given the importance of smoking, BP and their interaction in the determination of cardiovascular risk, surprisingly, smoking status was not documented in 20 patients. Assessing risk factors in treating hypertension is vital. Overwhelming evidence supports that
cigarette smoking causes various adverse CHD events. (Primatesta et al, 2001). The finding of this thesis reflects the need for assessing and addressing the risk factors in patients with RH.

Epidemiological risk factors for atherosclerosis, such as hypertension and smoking, are known to cause endothelial dysfunction, which is an early event in the atherosclerotic process. They also may be considered in the light of their effects on adhesion molecule expression and release. When 51 smokers and 52 non-smoker’s plasma concentrations of soluble intercellular cell adhesion molecule-1 (sICAM-1), soluble endothelial leukocyte adhesion molecule-1 (sELAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) were quantified, there was a significant increase demonstrated in smokers ($P=<0.001$ and $P=<0.05$ respectively). This data reinforces the fact that the two risk factors, smoking and hypertension are additive risk factors in generating endothelial dysfunction and vascular damage, which plays a key role in atherogenesis (Mazzone et al, 2001).

When 13,529 male participants from the Physicians’ Health Study free of baseline hypertension and CHD provided information about smoking status, smoking status was categorised as never, past or current <20 cigarettes a day, or current $\geq$20 cigarettes a day. Over a mean follow up of 14.5 years, 4,904 men developed hypertension. This study revealed that compared with never smokers, past smokers and current smokers had corresponding relative risks of 1.8 and 1.15 of developing hypertension. The risks of smokers did not differ based on number of cigarettes smoked daily. It is evident that cigarette smoking may be a modest but important risk factor for the development of hypertension (Halperin, Gaziano & Sesso, 2008). However the latest evidence from the association between smoking and BP in a population-based sample of Vietnamese men ($n= 910$), suggests that hypertension was associated with smoking in a dose response manner when characterised as number of years of smoking and lifetime cigarette consumption, but was not associated with current status (Thuy,
Because of the role of smoking in enhancing hypertension, smoking cessation advice is imperative. Because smoking and BP have been shown to exert synergistic effects on the risk of CHD, it is critical that persons with raised BP are advised to stop smoking. Furthermore because BP levels in smokers are rarely recorded during or immediately after smoking, when the acute rise in BP occurs, usual BP levels of smokers tend to be systematically underestimated. (Primatesca et al, 2001). In light of the evidence relating to smoking and hypertension, it is important that patients' smoking status is assessed and addressed appropriately.

6.3b Diabetes

In the current study group 23 patients with a history of DM were included, of which 16 (15.5%) and seven (6.8%) of the sample were from Site 2 and Site 1 respectively. Though there were more patients with DM from Site 2 compared to Site 1, the difference was not statistically significant. The lack of significance may be due to the small number of patients with DM. Hypertension is an extremely common co-morbid condition in DM, affecting ~20%-60% of patients. (Arauz-Pacheio, Parrott & Raskin, 2002). DM status in the current study is nearer to the lower end of that scale. DM is associated with hypertensive heart disease, which could lead to a direct effect on the myocardium and LV geometry (Shang & Yip 2011). Compelling evidence from well-designed, randomised clinical trials demonstrated that control of blood glucose, BP and cholesterol levels dramatically delay or prevent complications (Diabetes control and complications trials/Epidemiology of Diabetes/interventions and complications Research group, 2008).
In observational studies, people with both DM and hypertension, have approximately twice the risk of CHD as non-diabetic patients and are also at increased risk for DM specific complications including retinopathy and nephropathy. In the UKPDS epidemiological study each 10 mmHg decrease in mean SBP was associated with reduction in risk of 12% of any complication related to DM, 15% for deaths related to DM, 11% for MI and 13% for microvascular complications (Arauz-Pacheio, Parrott & Raskin, 2002).

In a larger prospective cohort study that included 12,550 adults, the development of DM type 2 was almost 2.5 times more likely in persons with hypertension than in their normotensive counterparts (Gress et al, 2000). Both hypertension and DM affect the same major organs. The common denominator of hypertensive/diabetic target organ disease is the vascular tree; hence combination therapy is usually required to achieve BP control (Grossman & Messerli, 2008). In the light of the evidence, patients with hypertension and DM require both conditions to be treated to achieve recommended target BP, therefore risk factor assessment and documentation has to play an important part in these patients' treatment plans.

6.3c Cholesterol Status:

High cholesterol and hypertension are major risk factors for atherosclerosis and their combination is associated with a yet greater increase in the incidence of cardiac events. Data regarding cholesterol status was not available for 53 and 24 participants from Site 2 and Site 1 respectively. Therefore, cholesterol data was available for 58 (100%) and 85 (100%) patients from Site 2 and Site 1 respectively. Of this there were 46 (79%) from Site 2 and 46 (54%) from Site 1 (p=0.004) who were found to have cholesterol levels >4 mmols/L. The cholesterol level was not documented in 53 out of 111 patients and 24 patients out of 109 of the sample from Site 2 and Site 1 respectively.
In these specialist clinics it appears that these patients were not risk assessed properly and therefore the approach to their care was not holistic. To underpin the comprehensive holistic approach the JBS2 guidelines (2005) recommends total cardiovascular risk assessment including all risk factors. As this study was focusing on BP control, the reason for not documenting cholesterol levels was not explored further. Perhaps there could be another study to assess the risk assessment in these types of specialist clinics.

In this current thesis a higher percentage of patients from Site 2 were found to have elevated cholesterol. Though this group had a higher number of patients with elevated cholesterol, the rate of BP control was not different from that of the Site 1 patients. The prevalence, treatment and control of combined hypertension and hypercholesterolaemia in US adult’s aged ≥20 years (n= 2,864) was examined. This study revealed that the prevalence of hypertension and hypercholesterolaemia was 18%. This accounted for 20% in women vs 16% in men. Of those with combined hypertension and hypercholesterolaemia, 29% were being treated. Overall control of hypertension and hypercholesterolaemia was only 9%. This highlighted the need for an increased effort to improve treatment of combined hypertension and hypercholesterolaemia, which was suboptimal at the time of this study (Wong et al, 2006). Evidence shows that it is possible to modify risk factors such as hypercholesterolaemia. A decrease in fat intake results in a decrease in LDL and HDL cholesterol, but the overall effect on lipoproteins depends on which nutrients replace the saturated fat (JBS2, 2005). The findings of this thesis highlights the need for holistic risk assessment to help patients to modify their risk factors. Every time a patient is reviewed, risk assessment and evaluation of the management of risk factors is important, the reason being, that the treatment can be changed or adjusted according to the outcome of the evaluation.
6.3d Family history of CHD

This is arbitrarily defined in relation to CHD as the development of coronary disease in a male first degree relative <55 years and a female first-degree relative <65 years. The first-degree relatives of such people are at increased risk of developing CHD and in some cases these families will have a genetic dyslipidaemia (JBS2, 2005). In the current thesis, of the whole group, data regarding CHD was available for 107 participants, of which 71% (n=76) had a family history of CHD. This consisted of 35 (83%) patients from Site 2 vs 41 (63%) from Site 1. It is one of the un-modifiable risk factors in hypertension management. Having a family history of CHD in hypertension increases the risk of sustaining CHD (Padwal, Straus & McAlister, 2001).

6.4 Need for risk factors assessment

This current thesis demonstrated that risk assessment was not recorded in many cases thereby suggesting that patients were not properly risk assessed. The mortality and morbidity of hypertension is likely to contribute to the growing prevalence of clusters of risk factors associated with hypertension including hyperlipidaemia, glucose intolerance, DM, cigarette smoking, LVH and impaired renal function. Identifying risk factors not only provides information about their health status, but also provides an important marker for risk stratification (Izzo, Ruilope & Weir, 2010). The evidence suggests that the lifetime risk of atherosclerotic CHD for persons at age 50 years, on average, is estimated to be 52% for men and 39% for women, with a wide variation depending on risk factor burden (Adler et al, 2000). Assessing a patient’s cardiovascular risk may be used for the targeting of preventive treatments of individual patients who are asymptomatic, but at sufficiently high risk for the development of CHD (Chobanian et al, 2003). Evidence strongly supports the predominant role of primary prevention, which can substantially minimize the number of persons at high risk in need of medical treatment for hypertension. This could be achieved by the adoption of
healthy life styles to improve the quality of life (Bovet et al, 2006). In assessing the potential impact of a risk factor, such as BP or cholesterol, on the chances of an asymptomatic person developing CHD, it is important to estimate their total CHD risk. Those who are at highest total CHD risk are then identified and the management of their BP or lipids can be addressed in this overall context (JBS2, 2005).

There is evidence to suggest that ~50% of patients with essential hypertension can be considered to have insulin-resistance, and these metabolic changes increase their CHD risk (Lima et al, 2009). Furberg (2009) reports a good analogy of the current state of treating hypertension. A century ago it was thought that fever was a single phenomenon. Bleeding the patient treated it. Later on it was understood there were various causes for fever, which required various interventions. Today we treat hypertension in a similar way. Current recommendations for the diagnosis and treatment of hypertension give consideration to the global CHD risk of patients, rather than an isolated focus of BP control alone. This approach emphasises the fact that each additional risk factor that is present in the setting of hypertension has a synergistic and compounding adverse effect on cardiovascular outcome (Sharman & Prins, 2009). Please “see figure No – 6.1: CVD risk calculation chart for non-diabetic women and men and Figure No 6.2: CVD risk calculation chart for Men (JBS2 2005)” below.
Figure No 6.1 –CVD risk calculation chart for Women

NON-DIABETIC WOMEN

Non-smoker   Smoker

Age under 50 years

SBP = systolic blood pressure
TC = total cholesterol
HDL = high-density lipoprotein

SBP ≥ 140
TC ≥ 200
HDL < 35

SBP ≥ 160
TC ≥ 200
HDL < 35

CVD risk < 10% over next 10 years
CVD risk 10–20% over next 10 years
CVD risk > 20% over next 10 years

Age 50–59 years

SBP ≥ 140
TC ≥ 200
HDL < 35

SBP ≥ 160
TC ≥ 200
HDL < 35

CVD risk < 10% over next 10 years
CVD risk 10–20% over next 10 years
CVD risk > 20% over next 10 years

Age 60 years and over

SBP ≥ 140
TC ≥ 200
HDL < 35

SBP ≥ 160
TC ≥ 200
HDL < 35

CVD risk < 10% over next 10 years
CVD risk 10–20% over next 10 years
CVD risk > 20% over next 10 years

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As routine standard care, risk assessment should play an important role in patients with a history of hypertension. In the current study’s population it has been identified that risk factors were not assessed properly. Therefore risk factors must be assessed and documented as a routine in patient’s notes.
In the current thesis group data were collected about their medication prior to their assessment in these specialist clinics. These patients were found to be on various antihypertensive medications, which will be discussed in the following section.

6.5 Prior medication use in the sample population

Patients who were seen in the clinic were receiving a number of medications. In both the hospitals, patients were on ACEIs, ARBs, BBs, CCBs, alpha-blockers and diuretics. The use of CCBs, BBs, a statin and diuretics were similar in both hospitals. Aldosterone blocker use was slightly higher in Site 2 compared to Site 1 (7% vs 2%). The alpha-blocker use was higher in Site 2 (30.2%) than Site 1 (16.5%) which was statistically significant p=0.037. The exact reason for this is unknown. A fourth drug of choice, the aldosterone blocker (spironolactone) or an alpha-blocker (Doxazosin) could be prescribed. This depends on the type of patients and their medication history. Rodilla, Costa & Perez–Lahiguera (2009) evaluated the use of spironolactone and Doxazosin in 181 patients with a history of RH. In this retrospective study patients were prescribed spironolactone (n =88) and Doxazosin (=93) in addition to their antihypertensive therapy. In the spironolactone group mean BP reduction was 28/12mmHg (SBP 95%CI, 24 –32 mmHg; p = <0.001, DBP 9 –14mmHg; p <0.001). In the Doxazosin group the reduction was 16/7mmHg (95%CI, 13 – 20mmHg; p=<0.001 for SBP and (95%CI, 5-9mmHg; p = <0.001 for DBP). At the end of these patients follow up, 30% had achieved BP control. The addition of either one of these medications should aid in BP control. When prescribing an alpha - blocker to a female patient, one should warn the patient about stress incontinence as a side effect. Male patients should be warned that aldosterone blockers could cause nipple tenderness and gynaecomastia. Anecdotally, the use of an alpha-blocker as an add-on appeared to be favoured at Site 2. This type of prescribing is common practice.
Evidence suggests hypertensive patients require two or more drugs to achieve the target BP (Cushman et al, 2002). In the current thesis the findings were similar to those of previous studies. The rationale for intervention in RH is to ensure that all possible mechanisms for BP elevation are blocked. Patients' characteristics, such as age, probable pathogenic mechanisms involved and concomitant disease will determine the best combination of agents needed to achieve BP goal.

Clinical trial outcome data proves that lowering BP with several classes of drugs, including ACEI, ARBs, CCBs, diuretics and BBs, will reduce the complications of hypertension, (Xin et al, 2001). The NICE hypertension guidelines (NICE, 2006) also highlight that many patients will require more than one antihypertensive drug to achieve adequate BP control. The use of more than one medication is common in RH, which is reflected in this current study. It is increasingly recognised that monotherapy is usually insufficient. The recent NICE (2006) guidelines and the BHS guidelines differ in their outline of treatment. NICE recommends that a thiazide diuretic should be used as initial therapy for most patients, whereas the BHS recommends that treatment be based on a patient's age using the AB/CD algorithm (Williams et al, 2004). The initiation of drug therapy with two drugs, either separate or in combination, may increase the likelihood of achieving the BP goal in a more timely fashion (Chobanian, Bakris & Black, 2003). In general, most patients should be on a blocker of the RAS along with a CCB and an appropriately dosed diuretic (Sarafidis & Bakris, 2008). In the current thesis, participants were on a blocker of the RAS as suggested in the literature.

The current thesis' focus was to compare the two methods of controlling BP between two hospitals. As stated previously Site 1 used a special blood test (ARR) to treat hypertension, and Site 2 followed the algorithm. In the following section, the discussion will be focused on BP control. Initially the BP control between the two groups for the whole length of time was
explored, subsequently BP control at various fixed times, impact of patient's characteristics on BP control, and percentage of BP reduction and in the age group below and above 55 years, were assessed.

6.6 Discussion on BP control

In this thesis the BP control was initially compared between the two groups over a 20-month period. The comparison between the two groups for the study period showed no statistically significant difference in BP control (Site 2 = 32% vs Site 1 = 30%, p = 0.91). Therefore it can be said that the use of the ARR blood test was not found to be superior in achieving target BP compared to a nationally recognised algorithm. Only one third of patients in this thesis with clinically significant hypertension have achieved adequate control; this could in part be related to lack of risk assessment and management. This is supported by other studies.

As comparison of BP control between the two groups over the whole study period demonstrated no statistical significance, bearing in mind that these patients were reviewed at different times, fixed time periods were selected to see if they achieved their target BP within these fixed time frames. The length of time taken to achieve BP control was then assessed based on these set points in time. At the end of the three-month period, comparison between the two groups showed 16 (16.2%) and 10 (10.5%) (p = 0.35) from Site 2 and Site 1 respectively achieved BP control. The comparison between the groups at six months showed 22 (22.2%) and 19 (20%) (p = 0.84) from Site 2 and Site 1 respectively achieved BP control. This does suggest there was a gradual increase in the number of participants achieving BP control between the two centres. Whereas at nine months, 29 (29.3%) and 22 (23.2%) (p = 0.42) from Site 2 and Site 1 respectively achieved BP control. Once again there appeared to be improvement in the number of participants achieving BP control. Though there was a trend, the BP control was not statistically significant at fixed different times. This
demonstrated that BP control was not different at different time points. The next step was to assess if patient characteristics had an impact on BP control.

When the BP control and the impact of patient’s characteristics (DM, smoking and ethnic origin) were analysed, it was not found to be statistically significant. The impact of DM and BP control showed that only three (1.4%) patients out of 23 (10.7%) in the whole diabetic sub-group achieved BP control, which was not statistically significant (p=0.12). When smoking status (p=0.30), and ethnic origin (p=0.74) were explored, they also showed no statistical significance, whereas gender difference and BP control showed a small statistical significance. This current study’s outcome is similar to that of the International Survey Evaluating Microalbuminuria Routinely by Cardiologists in patients with Hypertension. It has been suggested that sex hormones contribute to gender difference in BP control (Ong, Tso & Lam, 2008).

As patients’ characteristics and impact on BP was not statistically significant, the next step was to identify and control for, any factors that had an impact on BP control and might confound any relationship between sites and BP. For this a logistic regression was employed to assess if there was any relationship between the two hospitals adjusting for smoking, DM, age, gender, ethnic background and the length of time they were in the study. Regression analysis was carried out to adjust for any imbalance in patient characteristics between two hospitals when comparing BP reduction, and thus enable a fairer comparison of the study patients from different hospitals. Again the result showed no significant difference in BP control (odds ratio for control in Site 2 vs Site 1 = 1.27; 95% CI 0.56 to 2.91; p = 0.57).

As no single factor or site had an influence on BP control, naturally the next step was to see if there was a difference in actual and percentage of BP reduction. The actual and percentage BP
reductions were assessed to give additional information about BP reduction and the comparison between the hospitals. These give quantitative measures of the BP reduction to compliment the dichotomous categorical outcome of achieved /not achieved BP goal. The comparison between the two groups showed no statistically significant difference in BP control indicating that the use of the blood test had no influence on the percentage or actual BP control. Therefore the next step will be to assess patients’ characteristics that had an independent significant relationship with actual and percentage of BP reduction between first and second visit after adjusting for time between visits, a multiple regression was used. The gender and age showed a significant independent relationship with the actual SBP. Males had a much lower percentage reduction in SBP compared to females (mean reduction = 0.3% in males vs 5.7% in females). The reduction in SBP increased with age by an average of 0.2% for every extra year of age.

The nationally agreed algorithm recommends a different drug choice for age <55 years and > 55 years, therefore the difference in BP control for the current study’s cohort below 55 years and above 55 years was explored. 44 (100%) and 55 (100%) from Site 2 and Site 1 were aged less than, or equal to, 55 respectively. Of these 32 (70.5%) and 35 (63.6%) achieved BP control. Whereas in the age group >55, there were 55 (100%) and 40 (100%) from Site 2 and Site 1 respectively. 36 (66.5%) from Site 2 and 31 (77.5%) from Site 1 achieved BP control. This demonstrated that the BP control was similar between Site 2 and Site 1 patients for less than 55 years age (P= 0.62) and >55 years (0.30). This again proved that controlling RH in practice is not easy.

In this thesis the actual mean BP reduction was 1.7/1.8 mmHg vs 6.5/2.3 mmHg SI and S2 respectively. As stated earlier this reduction was not statistically significant. In a major trial such as ASCOT-BPLA, the mean BP reduction in the CCB/ACEI group was 2.9/1.8 mmHg.
albeit a small reduction proved to be clinically significant and suggested treatment success. The ALLHAT trial, the largest ever RCT of antihypertensive treatment trial suggests that small reductions in BP such as 2-4mmHg in a large clinical trial can impact on significant risk reduction. Even a small reduction in BP is clinically important. In this thesis, the exact impact of the mean BP reduction was not explored, as the main focus was to compare the two methods that informed treating RH and the reduction in BP. Perhaps this could be explored at a later date as a sub study.

In summary, when comparing the literature with the results of this current thesis, a number of similarities were found. However, there were some notable exceptions. Patients within this thesis demonstrated that there was no difference in gender distribution, only a small population were diabetic and were less likely to be smokers. Most of them were on more than one antihypertensive medication, which is the case in RH. This emphasises that more than one antihypertensive medication is required in treating RH. Even then BP control was not significant in this cohort. Recommendations on the modification and intensification of antihypertensive regimens for a given patient taking three or more drugs, is based on pharmacological principles in the context of the underlying pathophysiology that portends hypertension, clinical experience, and available treatment guidelines. The present rationale for intervention in RH is to ensure that all possible mechanisms for BP elevation are blocked (Sarafidis & Bakris, 2008). As BP control is not easy or simple, treatment aimed at modulating the RAS constitutes the corner stone in CHD prevention strategies. It has been suggested that the failure of healthcare providers to initiate therapy when indicated, or intensify therapy where required was found to be related to clinical inertia (Weber, Gradman & Basile, 2010). Although these are the main ingredients in controlling BP, patients' perception and psychosocial aspects must also be explored. Patients have to be risk assessed properly, and this must be documented in order to evaluate the effectiveness of their
treatment. Comprehensive risk assessment must be emphasised. Assessment alone is not adequate; it must be documented on patients' notes to evaluate the effectiveness of their treatment. The focus in treating hypertension will not come from BP control alone. Addressing other CHD risk factors is important. In order to do that, clinics must be organised in such a way as to address these factors. This is an area where nurses have proved that they are efficient in addressing these factors as part of a patient's treatment.

During this current study period there were a few changes in practice introduced, which were as follows.

6.7 New Drivers in Health care

Since the start of the study a few changes in the management of hypertension have taken place. It is worth considering the implications they may have had on hypertension management in the current NHS practice and on the current thesis.

6.7a The change to the A or B/C or D algorithm

The A or B/C or D algorithm changed to A/C or D. The implementation of this change was in process. A beta-blocker is no longer considered to be the first line drug of choice in treating hypertension. For the current algorithm A/ or C/ or D. Please "see Figure : 5 Hypertension management algorithm (The change to the previous A or B/C or D algorithm) 2006"
Choosing drugs for patients newly diagnosed with hypertension

Abbreviations:
- A: ACE inhibitor
- B: angiotensin II receptor antagonist
- C: Calcium channel blocker
- D: diuretic or thiazide-type diuretic

Black patients are those of African or Caribbean descent, and not mixed race, Asian or Chinese patients.

Figure 6.3 Current Algorithm
6.7b Changes to patient review management

Chronic disease management

The UK’s healthcare system has undergone a number of wide-ranging reforms in the last decade and more are planned for the years ahead. In 2007 a system of coordinated healthcare interventions and communications for populations with long-term conditions, a definition of chronic disease management was introduced (Royal College of Physicians 2004). Chronic disease management comprises any medical or pharmaceutical intervention designed to improve both outcomes for the patient and cost-effectiveness. In the current climate patients can choose their consultant, although the organisation can place these patients under any consultant.

Choose and book

This was a government initiative, where patients were given the choice to choose the hospital and doctors from the information given by their GP about the available service and clinicians. It was not possible to assess the impact of this initiative on the current study to identify how many patients chose hospitals other than these two sites.

18-week pathway

The aim of this pathway was to see patients in the hospital within 18 weeks from the time of their referral by their GP. It was a government initiative to avoid delay. This is to increase the efficiency in providing the service. Implementation of this framework had an impact on the current study. Follow up dates were not given to the patients after their review in the clinic if the appointment was more than three months. This led to postal appointments being given and some had to rebook their appointment. This in turn led to delays in follow up care. As the current study focused only on BP control, with or without the biochemical profile, it is difficult to explain the extent of its impact on patients BP control. In the following section the
current study’s impact will be discussed. It is vital to explore the implications of the current study’s outcome on practice, education, patient care and research.

6.8 Impact on practice

This current study’s outcome showed no difference in BP control between the two sites. In the current study patients were seen in a specialist hypertension clinic. Their BP control was not significant and patients were not risk assessed properly. The outcome of this current study again demonstrates that achieving target BP in RH in clinical practice is not easy or simple. The clinical outcomes studies indicate that patients with RH do benefit from referral to a hypertension specialist (JBS2, 2005).

As suggested earlier, nurses would be best suited to encompass these factors in treating hypertension. Nurses are known to lead clinics on the bases of a protocol. So there is potential for nurses to provide comprehensive care. These patients would be risk assessed properly and their risk factors would be addressed appropriately. It has been suggested that the initiation of antihypertensive medication is not a satisfactory treatment strategy when it is not combined with close follow-up. Nurses have proved to be good in managing chronic diseases, so nurses would be well placed to manage these patients.

Chobanian et al, (2003) have highlighted that once antihypertensive drug therapy is initiated, most patients should return for follow-up and adjustment of medications at approximately monthly intervals until BP goal is reached. It was identified in the current thesis that patients from MRI were followed up more frequently compared to SHH. Even then at MRI patients’ BP control was similar to SHH patients. Williams (2003) points out that, “What is clear is that improvement of the very poor figures for BP control in the UK will not come from a new
drug but rather from a sharper focus on implementation and process”. To improve BP control a nurse-led clinic may be the future.

6.8a Nurse-led hypertension clinic

This current thesis has proved that the ARR blood test is effective as the BP control in both specialist sites was similar; therefore it negates the need for such a clinic and nurses could conduct these clinics. In this thesis patients were not properly risk assessed and therefore they were not treated holistically. Evidence suggests nurses are known for strict adherence to protocols, better prescribing and regular follow up with better outcomes (Oakshott et al, 2003). Nurse-led clinics have reduced physicians’ workload and are probably cost-effective while maintaining quality of care (Andersen et al, 2010). Mason et al, (2005) suggest that nurse-led clinics are cost-effective. Because of the difference in salary, the total cost may be lower in a nurse-led hypertensive clinic. The results from the nurse-led clinics have highlighted a few advantages. The most important are efficacy in BP outcome, safety and reduction in physician’s workload (Mason et al, 2005). Andersen, Simper, Ibsen et al, (2010) have demonstrated that 95% of severe hypertensive patients with co-morbidities seen in a nurse-led clinic, reached target BP. This was a four-year follow up study, where all follow up visits were by nurses. In this study, nurses initiated and up-titrated hypertension treatment according to the algorithm or the physician’s instructions. Out of 186 patients with a history of hypertension and co-morbidity, 130 patients were treated in a nurse-led clinic and were discharged back to their GP’s care. This study has proved that nurses are known for providing comprehensive and safe service. In line with government policy, there is an increasing role for nurses and nurse practitioners. As a result of the current thesis nurse-led care may benefit from more reliable BP assessment, being more user friendly, accessible and less hurried, improving understanding, encouraging healthy living and forming an alliance with the patient (Beevers, 2000).
The current thesis demonstrated that the BP control in this cohort was suboptimal. Therefore success in future attainment of BP goals appears as a major challenge. Nurses are known to manage chronic disease well and one could argue that nurses would be best suited to meet this challenging role. Now nurses are in new roles and have brought changes to historically doctor-led care. Nurses have proved to be efficient in implementing and adhering to guidelines, hence there is no doubt that patients with a history of RH will benefit from a nurse-led clinic. This study supports the view that resistant hypertensive patients need frequent follow up on a timely basis, which can be offered by nurses who can conduct such clinics in secondary care, as this will give time for more complex cardiac cases to be reviewed by the medical team. A nurse-led clinic will help in promoting lifestyle modification and risk reduction in line with impressing on clients the importance of adherence to treatment. In the following section the author will discuss the impact of the current study’s outcomes on education.

6.9 Impact on Education

The outcomes of this current study showed that these patients were not properly risk assessed, and BP control was not significantly different between the two centres. Therefore it is vital that the importance of risk assessment must be included in their pre-registration curriculum for doctors and nurses. It must be reiterated that documenting these factors in patients’ notes is important as they serve as a tool to assess patients’ lifestyle behaviour changes. Risk factors assessment should be the fundamental block in building the treatment and management plan for these patients. The focus in hypertension management should emphasize the need for proper risk assessment, and these patients’ disease management plan must be based on all of these risk factors rather than BP control alone.
The current thesis' outcome reinforces the fact that in both specialist-led hypertension clinics, it was difficult to achieve target BP in RH. It is clear that achieving target BP is difficult, but increasing the treatment and improving the monitoring of hypertensive patients would substantially reduce the morbidity and mortality associated with hypertension, and could also generate overall cost savings for the NHS. The cardiac network has started to offer specialist training and in a few years' time, nurses with specialist interest will have been trained to implement the standard care. In the next section the current study's impact on patient care will be explored.

6.10 Impact on patient care

The current thesis demonstrated that the BP control in both specialist centres was similar and lacked proper risk assessment. It can be argued that the biochemical test was not superior to that of the algorithm but neither was it inferior and as such it argues that nurses would be able to manage patients adequately. As a result of this thesis it can be suggested that a biochemical profile can be used as a guide to initiate treatment in patients with RH. As a result of this thesis, those working in cardiology that review patients with hypertension need clear guidance on initiating treatment on the basis of the ARR. A simple guideline like the one below “see Table 6.1: Individualised therapy for hypertension (Spence 2006)” should be adhered to in order to treat patients on the basis of their biochemical profile. To improve patients' care as suggested earlier, more frequent review and monitoring along with lifestyle modification would be more beneficial. Appropriate risk assessment and treating their risk factors should improve patient care.
Table no 6.1 – Individualised therapy for hypertension

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Primary hyperaldosteronism</th>
<th>Liddle’s syndrome and variants</th>
<th>Renovascular hypertension</th>
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<tbody>
<tr>
<td>Renin</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
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<tr>
<td>Aldosterone</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Primary treatment</td>
<td>Spironolactone or Eplerenone</td>
<td>Amiloride*</td>
<td>ARB’s</td>
</tr>
</tbody>
</table>

*Amiloride for men, when Eplerenone is not available.

The next step will be to discuss the current study’s impact on research.

6.11 **Impact on research**

This current thesis demonstrated that the risk assessment was inadequate in this study group. Therefore, conducting a study to focus on risk assessment and BP control in these specialist clinics could be recommended. There is a need to undertake further studies with larger sample sizes to demonstrate significance in different time frames. In the same way cost benefit analysis needs to be undertaken to establish the true cost/benefit related to using the biochemical profile. This thesis focused on BP reduction. It would therefore be of interest to study the outcomes of compatible patients, along with the number of antihypertensive drugs used and the number of hospital reviews needed.

6.12 **There are possible limitations of this thesis to be considered**

There were some possible limitations to this thesis, which need to be considered. The sample was not a random selection as such, which might have influenced the outcome. There was no uniform pattern for following up these patients in both sites. Although this is a small study, to
the best of the author's knowledge this remains the only study by a nurse to compare the hypertension management between two established centres. The results of this small study have shown that even patients seen in specialist hypertension clinics did not achieve BP control, and their risk assessment was inadequate.

6.13 Research Challenges and Needs

Assessment of patients with RH in an experimental situation is fraught with danger due to the high cardiovascular risk associated with the withdrawal of medication to explore proposed etiologies. Concomitant disease processes such as diabetes, sleep apnoea, CKD etc. and their treatments are difficult to control for, and make interpretation of study results very difficult. In order to obtain sufficient numbers of participants a consortium of hypertension centres will likely be required (Sarafidis & Bakris, 2008). Multiple studies have indicated that treatment resistance is often related to refractory volume expansion, but there is little objective information on adjusting diuretic therapy, including alternative use and dosing of different types of diuretics. (Sarafidis & Bakris, 2008).

Summary

The outcome of this thesis demonstrated that the biochemical profile and the A, B, C and D algorithm have the same effect on resistant BP control. One could argue that even though the biochemical test was not superior, it nonetheless can be used as a guide to manage patients with RH. As the biochemical profile did not show any significant difference it does not mean that it is an ineffective tool in treating hypertension. Both hypertension clinics are specialist clinics and are managed by experts following evidence-based practice. Even so, the BP reduction between the two hypertension clinics was not statistically significant. The biochemical profile was not inferior to the algorithm used in these specialist clinics. So nurses could manage these patients based on a protocol incorporating these guidelines, as well as the
biochemical profile. Therefore one could argue the need for nurse-led hypertension management clinics to provide holistic care on the basis of an appropriate risk assessment. Such a change would provide holistic cost-effective care to patients with RH. There is evidence to support this view. However, further study with similar groups between these centres, and following them up for three to four years may shed more light on the use of the biochemical profile. Until then the biochemical profile can continue to be used to guide treatment in RH management.

The data analysis demonstrated that the risk assessment was suboptimal in this cohort. Only 32 (32.3%) from Site 2 and 29 (30.5%) from Site 1 achieved BP control in a specialist hypertension clinic. The outcome of this thesis underpins the importance of comprehensive assessment of these patients’ risk factors to aid in attaining target BP. Therefore the specialist nurses in cardiology would be able to meet the growing need of managing RH and could provide as such a structured service. On the basis of the outcome of this thesis, and in the current economic climate it can be argued that nurses will be best suited to lead this service. As stated previously, change in patient care practice, health professionals' education and incorporating more research would be beneficial to the management of patients with RH.

Knowledge in medicine accumulates slowly from the questions that are asked and answered (Psaty et al, 2003). The key debate over the next few years will not be whether one class of BP lowering drug is better than another, but rather what is the most effective therapeutic strategy to reduce the overall cardiovascular risk burden of individual patients (Chobanian et al, 2003). Effective treatment of BP has been shown to cause reductions in morbidity and mortality from CHD and stroke. The modern management of hypertension is even more complex, with the emergence of newer therapies, ageing populations and new clinical trial evidence, as well as the need for multiple agents to achieve target BP, which are much lower
than used to be in the past (Williams et al, 2004). The consequences of poor BP control are
huge. (Lane & Lip, 2001). The prognosis of RH is unknown. The CVD risk is undoubtedly
increased in this group. Identification of broader mechanisms of treatment resistance is
lacking, particularly attempts to elucidate a potential genetic cause of RH. Pharmacological
treatment recommendations for this group are largely empiric due to lack of systemic
assessments of 3 or 4 drug combinations. ARR is a useful screening tool in this population.
Successful identification of reversible life style modification will help to expand our
knowledge. Understanding the causes of RH and thereby allowing for more effective
treatment and prevention will be essential to improve long term benefits (Calhoun, Jones &
Textor 2008). This thesis was conducted with the aim of establishing whether or not the use
of the ARR was more effective than the algorithm in reducing resistant BP. The outcome
demonstrated that the BP control between the two groups was not significantly different.

Strengths and limitations
This is the first study conducted by a nurse to compare the current methods of treating RH.
Patients came from their traditional setting to be reviewed in a specialist hypertension clinic
for their routine care so the results are as would be found in current practice. An adequate
number of patients were recruited as proposed at the outset of this study. This research
imposed no impact on the clinician’s decisions therefore no interventions were used. A
further strength of the data set was that multiple logistic regression was conducted to adjust
for various confounders. This was a quantitative study which meant that there was no
potential contamination of data e.g. information sharing between patient groups and staff.
One of the limitations of this thesis was that the data regarding smoking and cholesterol status
were incomplete. It would have been preferable to investigate the reasons for the failure in
recording this data. This research provides the base for conducting a larger study such as a
case control or an RCT to investigate the use of ARR in patients with RH. A target-oriented approach was used to follow the recommended medication.

If this study was to be repeated the following will be considered. The same methodology would be used over a longer period of time with a fixed follow-up review in the clinic. The same methodology of comparing a selected group of patients such as patients with a history of hypertension and DM. The same study with a third arm of comparison with a cardiology consultant clinic may be an interesting area to explore. A RCT having a similar follow up time would be an interesting study to understand the BP reduction at fixed time intervals. This was a small study and as such generalisations of the thesis result have to be done with caution. It has to be acknowledged that these patients were referred by their GP, and therefore may not reflect the general population. It is not a RCT.

CONCLUSION

In this thesis, two methods of treating RH in two hospital settings demonstrated that the BP reduction was not statistically different between the two hospitals. Only a small number of patients achieved target BP; this reflects the fact that achieving target BP in this group is difficult. It appears that, a comprehensive risk assessment, and multidrug therapy with lifestyle modification is essential in these patients.

Recommendation

On the basis of this thesis outcome there are other areas that can be explored further.

- The holistic management of RH should include comprehensive risk assessment.
- The same comparative study can be conducted as a RCT.
- Nurse led clinics on the basis of a protocol for patients with RH.
- To study the risk assessment methods in these special hypertension clinics.
The same comparative study can be conducted with an added arm of assessing the BP reduction and impact on risk reduction.
### Table 2.6 – Hypertension trials

<table>
<thead>
<tr>
<th>Authors</th>
<th>Aim of Study</th>
<th>Study design</th>
<th>Population sample design</th>
<th>Final outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial Coordinators (2000, 2002) The ALLHAT study.</td>
<td>To compare the long-term effects of treatment with a low dose diuretic, Amlodipine, Lisinopril or Doxazosin.</td>
<td>Randomised double blind, controlled parallel group</td>
<td>There were 33,357 total patients, with 15,255 on Chlorthalidone, 9,048 on Amlodipine and 9,054 on Lisinopril. Population age ≥55 years, with hypertension and at least one risk factor for CHD. Primary combined outcome of fatal CHD or non-fatal MI occurred in 2,958 patients. No significant difference observed for Amlodipine (RR 0.98, 95% CI, 0.90 – 1.07; P = 0.65) or Lisinopril (RR 0.99, 95% CI, 0.91 – 1.08; P = 0.81) vs Chlorthalidone.</td>
<td></td>
</tr>
<tr>
<td>The Heart Outcomes Prevention Evaluation study investigators (2002) The HOPE study.</td>
<td>To evaluate whether Ramipril and/or Vitamin E reduced the incidence of CV mortality and morbidity in a high-risk population. The primary end points were MI, stroke or cardiovascular death.</td>
<td>Randomised, double blind, placebo – controlled parallel group, 2 x 2 factorial.</td>
<td>There were 9,451 patients (6,996 men, 2,545 women) aged ≥55 years with one of the following: previous MI, angina, multi vessel PTCA or CABG, multi vessel coronary artery disease, DM with an additional risk factor. Mean length of study was 4.5 years. The ramipril group reached one of the primary end points (14%) compared to placebo (17.8%) P = &lt; 0.001.</td>
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<td>Authors</td>
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<tr>
<td>Lithell, Hansson, Skoog et al (2003) The SCOPE study.</td>
<td>To assess whether anti-hypertension treatment with angiotensin II receptor blocker Candesartan in elderly patients with hypertension yields a reduction in cardiovascular events, cognitive decline and dementia</td>
<td>Multi-centre, international, prospective double blind, randomised parallel group study</td>
<td>There were 4,964 patients aged 70 – 89 years, with SBP 16-179 mmHg and/or DBP 9-99 mmHg: mini mental examination text score 24. Mini mental state examination is a brief, standardised measure of mental status. A score of 24 is considered to be normal (maximum score 30). Mean follow up 3.7 years. Candesartan 8 or 16mg or placebo.</td>
<td>BP reduction by 21.7/10.8 mmHg in the Candesartan group. In the Candesartan group 242 patients had a first major CVD event vs 268 in the control group. Risk reduction with Candesartan was 10.9% (P = 0.10, 95% CI = 6 to 25.1). The Candesartan group had a marked 27.8% reduction in non fatal stroke (P = 0.04, 95% CI = 1.0 - 47.2. The proportion of patients who had a significant cognitive decline or who developed dementia was limited between groups.</td>
</tr>
<tr>
<td>Authors</td>
<td>Aim of Study</td>
<td>Study design</td>
<td>Population sample design</td>
<td>Final outcome</td>
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<tr>
<td>The PROGRESS collaborative group (2001) The PROGRESS Study.</td>
<td>To determine the effects of BP reduction on stroke risk in patients with a history of CVD</td>
<td>Randomised, double blind placebo controlled trial.</td>
<td>There were 6,105 Normotensive or hypertensive with proven TIA or stroke in the past 5 years. Mean follow up period was 3.9 years. Perindopril, 4mg/day if necessary plus Indapamide, 2.5mg/day or matching placebo.</td>
<td>The active treatment reduced overall by 9mmHg (SBP) and 4 mmHg (DBP) compared to placebo. 10% of patients on active treatment suffered a stroke compared to 14% on placebo (RR 28%; P = &lt;0.0001). The risk of total major vascular events in the active treatment group was 15% compared to 20% in the placebo group.</td>
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<td>Authors</td>
<td>Aim of Study</td>
<td>Study design</td>
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<tr>
<td>Dahlof, Devereux,</td>
<td>To compare the long term effects of Atenolol and Losartan on cardiovascular</td>
<td>Randomised, double blind, double dummy,</td>
<td>There were 9,193 patients aged 55-80 years (4,605 Losartan,</td>
<td>BP fell by 30.2/16.6 mmHg with Losartan and 29.1/16.8 mmHg with Atenolol.</td>
</tr>
<tr>
<td>Kjeldsen et al (2002)</td>
<td>mortality and morbidity in hypertensive patients with left ventricular</td>
<td>multi centre, parallel group study.</td>
<td>4,588 Atenolol) with hypertension and LVH documented by ECG.</td>
<td>The primary composite end points (cardiovascular death, MI and stroke) occurred in 508 Losartan patients and 588 Atenolol patients (P = 0.021). There was a greater reduction of LVH with Losartan than with Atenolol. The new onset of diabetes mellitus was 25% lower with Losartan than with Atenolol.</td>
</tr>
<tr>
<td>The LIFE study.</td>
<td>hypertrophy (LVH)</td>
<td></td>
<td>Follow up period was ≥ 4 years (mean 4.8 ± 0.9 years)</td>
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<td>Losartan 50mg/day, plus Atenolol placebo, or Atenolol 50mg/day plus Losartan placebo with stepwise addition of hydrochlorothiazide, 12.5mg/day, at 2 months, followed by double of Losartan or Atenolol dose at 4 months to target BP 140/90mmHg.</td>
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### Appendix 1

#### Table 2.10 – Hypertension trials

<table>
<thead>
<tr>
<th>Authors</th>
<th>Aim of Study</th>
<th>Study design</th>
<th>Population sample design</th>
<th>Final outcome</th>
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<tbody>
<tr>
<td>Dahlof, Server, Poulter et al (2005) The ASCOT trial.</td>
<td>To compare the effect on non fatal MI and fatal CHD of combinations of Atenolol with a thiazide versus Amlodipine with Perindopril</td>
<td>It was a multicentre, prospective, randomised controlled parallel group 2 x 2 factorial.</td>
<td>There were 19,257 patients with hypertension who were aged 40-79 years and had at least three other cardiovascular risk factors. Patients were assigned either Amlodipine 5-10mg adding Perindopril as required (n = 9639) or Atenolol 50 – 100mg adding Bendroflumethiazide 1.25 – 2.5mg and potassium as required (n = 9618) Median follow up of 5.5 years.</td>
<td>The primary end point of non fatal MI plus fatal CHD was non significantly lowered by 10% in those allocated the Amlodipine based regimen compared with those allocated the Atenolol based regimen. The finding of this study showed that in hypertensive patients at moderate risk of developing CVD events an antihypertensive drug regimen starting with Amlodipine adding Perindopril as required is better than starting with Atenolol and Thiazide in terms of reducing the incidents of all types of CVD events and cause mortality.</td>
</tr>
</tbody>
</table>
## Appendix 1

### Table 2.11 – Hypertension trials

<table>
<thead>
<tr>
<th>Authors</th>
<th>Aim of Study</th>
<th>Study design</th>
<th>Population sample</th>
<th>Final outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>European trial on reduction of cardiac events with Perindopril in stable coronary artery disease. Fox, Henderson, Bertrand, et al (1998) The EUROPA trial.</td>
<td>To assess whether Perindopril reduces cardiovascular risk in patients with stable coronary artery disease but no clinical heart failure.</td>
<td>Randomised double blind, placebo controlled multi centre trial.</td>
<td>This study involved 12,218 patients aged 2-89 years (mean age 60 years) from 24 European countries with documented coronary artery disease. Patients were randomised to an ACEI (Perindopril 8mg) or placebo, in addition to optimised conventional therapy and followed for an average of 4 years</td>
<td>The composite primary end point of cardiovascular death, non-fatal MI or cardiac arrest with successful resuscitation was reached by 8.0% of patients receiving Perindopril and 9.9% of patients receiving placebo (relative risk reduction 20%; P = 0.0003). The mechanism of the beneficial effects of Perindopril in the EUROPA study does not seem to be due to BP reduction alone which was (5 mmHg SBP and 2 mmHg DBP). The treatment with Perindopril modifies biological markers involved in the inflammation and thrombosis of coronary arteries and improves endothelial dysfunction through mechanisms dependent mainly on levels of bradykinin.</td>
</tr>
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</table>
### Table 2.12 – Hypertension trials

<table>
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<tr>
<th>Authors</th>
<th>Aim of Study</th>
<th>Study design</th>
<th>Population sample Author design</th>
<th>Final outcome</th>
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</thead>
<tbody>
<tr>
<td>Julius, Kjeldsen, Weber et al (2004) The Value study.</td>
<td>To investigate whether, for the same level of BP control, Valsartan is more effective than Amlodipine in reducing cardiac mortality and morbidity.</td>
<td>It was a prospective, international double blind, randomized active controlled, parallel group trial.</td>
<td>There were 15,245 patients aged 50 years with BP ≥ 10/115 mmHg if receiving antihypertensive treatment or SBP/DBP 16-210/115 mmHg or ≥ s10/95 – 115 mmHg if newly diagnosed and with a high risk of cardiovascular event. Mean follow up 4.2 years, range 4-6 years. Valsartan 80 mg/day or Amlodipine 5 mg/day: both titrated upward as needed to reach target BP of &lt;140/90 mmHg. Hydrochlorothiazide, 2.5 mg/day and 25 mg/day followed by addition of other antihypertensives (excluding ACEI, CCB's, ARBs or diuretics other than Hydrochlorothiazide) but these were allowed only if clinically indicated for reasons other than hypertension.</td>
<td>Both treatments caused a reduction in BP but the effects of the Amlodipine based regimen were more pronounced, especially early in the trial (BP 4/2.1 mmHg lower in the Amlodipine than in the Valsartan group after 1 month and 1.5/1.3 mmHg lower after 1 year [P = 0.001] between groups). The main outcome of cardiac events did not differ between the Amlodipine and Valsartan based treatment groups. The results draw attention to the clinical relevance of small differences in BP within the high to normal range. They also emphasise the importance of rapid BP control i.e. weeks rather than months.</td>
</tr>
<tr>
<td>Authors</td>
<td>Aim of Study</td>
<td>Study design</td>
<td>Population sample design</td>
<td>Final outcome</td>
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<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Wing, Reid, Bellin et al (2002) The ANBP2 study.</td>
<td>To determine whether in hypertensive patients aged 65-84 there is any difference in total cardio vascular events (fatal and non fatal) between antihypertensive treatment with an ACEI –based regimen and treatment with a diuretic based regimen over a 5-year treatment period.</td>
<td>It was a randomised open trial with blinding of endpoint assessment.</td>
<td>Over a 3 year period 54,288 patients were screened and 6,083 were randomised (approximately 50% men and 50% women), 3,044 to ACEI and 3,039 to diuretic treatment. Median observation was 4.1 years.</td>
<td>No difference was seen between the two treatment groups with regard to BP drop except for a slight difference in BP (2/1 mmHg) in favour of the diuretic group seen at the 1 to 2 year interval. Total CVD events were reduced by 12% (p = 0.07) in the ACEI group compared with the diuretic group.</td>
</tr>
<tr>
<td>Wright, Bakris, Greene et al (2002) The AASK study.</td>
<td>To compare the effects of 2 different levels of BP control and 3 different antihypertensive medication classes on the decline of glomerular rate in patients with hypertension.</td>
<td>Randomised, double blind, 3X2 factorial, multicentre study.</td>
<td>There were 1,094 African Americans aged 18-70 years with renal disease caused by hypertension and no other cause of renal insufficiency. Patients were randomised to a goal mean arterial pressure of 102-107 mmHg or to the lower goal of mean arterial pressure &lt;92 mmHg. Patients were also randomised to 1 of 3 antihypertensive medications (metoprolol 50-200mg, ramipril 2.5 to 10 mg, amlodipine 5-10mg).</td>
<td>The lower BP goal did not show any apparent additional benefit in retarding progression of hypertensive nephrosclerosis. ACEIs were more effective in slowing decline of GFR compared to BBs or CCBs.</td>
</tr>
</tbody>
</table>
### Authors | Aim of study | Study design | Population sample design | Final outcome
--- | --- | --- | --- | ---
Hansson, Lindholm, Niskanen et al (1999). The CAPPP study. | To investigate whether antihypertensive treatment with Captopril reduces cardiovascular mortality and morbidity more than a therapeutic regimen that does not include an ACEI. Secondly to compare total mortality and morbidity the development of deterioration of IHD, LV failure atrial fibrillation, DM, and possible differences in renal function in the two groups. | Randomised, open, parallel, blinded endpoint. | There were 10,985 patients (5,492 captopril, 5,493 conventional treatment), age 2-66 years with DBP>100 mmHg. | The incidence of fatal and non-fatal MI, stroke, and other CVD deaths were similar in captopril and other conventional groups. CV mortality was lower with captopril than with conventional therapy. Stroke rate was higher with the captopril group. |
Hansson, Hedner, Lund-Johnson (2000). The NORDIL trial. | To compare diltiazem with diuretics, BBs or both on cardiovascular mortality and morbidity in middle-aged hypertensive patients | Prospective, randomised, open trial with blinded end point evaluation. | 10,881 patients aged 56-74 years with DBP 100 mmHg or more. Diltiazem (n = 5410) given as 180-360 mg daily vs diuretics, BBs or both (n = 5471). | A primary end point occurred in 403 patients in the diltiazem group and in 400 in the BB/diuretic group (p = 0.97). Fatal and non-fatal MI occurred in 183 and 157 patients respectively, whilst fatal and nonfatal stroke occurred in 159 and 196 patients respectively (0.04). |
### Table 2.15 – Hypertension trials

<table>
<thead>
<tr>
<th>Authors</th>
<th>Aim of study</th>
<th>Study design</th>
<th>Population sample design</th>
<th>Final outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>The UKPDS Study (1998) The UK Prospective Diabetes Study Groups.</td>
<td>To determine whether blood glucose control and tight control of BP will prevent complications and reduce morbidity and mortality in patients with type 2 diabetes and to determine which if any therapies have a particular advantage in improving prognosis.</td>
<td>A randomised open factorial study.</td>
<td>This study included 4,209 patients (2,505 non overweight, 1,704 overweight) aged 25-65 yrs, with newly diagnosed type 2 DM (1,138 conventional treatment, 2,729 intensive treatment with sulphonylurea or insulin, 342 overweight Metformin. 1148 UKPDS patients (55% men) mean age 56.4 ± 8.1 yrs with hypertension (tight BP control, 400 captopril and 358 atenolol; 390 less tight control.</td>
<td>The tight control of BP significantly reduced the risk of DM related death by 32% (p=0.019), of any DM related end point by 24% (p=0.0046), and of stroke by 44% (p=0.013). The risk of MI was reduced in the tight BP control group by 21% and the combined risk of all macrovascular diseases (including MI, sudden death, stroke and PVD) was significantly reduced by 34% (p=0.019) The risk of heart failure was reduced by 56%(p=0.0043) by tight BP control. By 7.5 years the tight BP control group showed 48% reduction in risk of a Q wave ECG abnormality (p=0.007). Captopril and atenolol were equally effective in reducing the risk of either single or aggregate microvascular endpoints.</td>
</tr>
</tbody>
</table>
### Appendix 1

#### Table 2.16 – Degree of BP lowering

<table>
<thead>
<tr>
<th>Groups and studies</th>
<th>Comparative Studies</th>
<th>Primary End Points</th>
<th>Degree of lowering BP</th>
<th>Benefit on Target Organ Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy of Perindopril in reduction of cardiovascular events among patients with stable coronary artery disease, randomised, double blind, placebo controlled, multicentre trial (the EUROPA study).</td>
<td>Perindopril vs placebo</td>
<td>Cardiovascular death, myocardial infarction, or cardiac arrest</td>
<td>P-value not given but the Decrease in BP of Perindopril is biologically significant.</td>
<td>Perindopril significantly better than placebo</td>
</tr>
<tr>
<td>Randomised trial of a Perindopril-based blood-pressure lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack.</td>
<td>Perindopril vs Perindopril + Indapamide vs Placebo</td>
<td>Total stroke (fatal or non fatal)</td>
<td>P value not given but the reduction in blood pressure both by combination or Perindopril alone was biologically significant compared to placebo</td>
<td>Perindopril significantly better than Placebo.</td>
</tr>
</tbody>
</table>

Reference: Bahiru & Kloner, 2008
### Table 2.17 – Placebo vs Drug, Degree of lowering BP

<table>
<thead>
<tr>
<th>Groups and studies</th>
<th>Comparative Studies</th>
<th>Primary End Points</th>
<th>Degree of lowering BP</th>
<th>Benefit on Target Organ Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects of Candesartan inpatients with chronic heart failure and preserved left ventricular ejection fraction: the CHARM preserved Trial (2003).</td>
<td>Candesartan vs/ placebo</td>
<td>Cardiovascular death or admission to hospital for CHF.</td>
<td>Candesartan significantly better than placebo&lt;br&gt;Baseline BP for Candesartan = 136.0/77.8 mmHg&lt;br&gt;Placebo = 136.3/77.8 mmHg&lt;br&gt;By 6th month&lt;br&gt;Systolic BP reduced by 6.9 mmHg and diastolic BP reduced by 2.9 mmHg more in Candesartan group&lt;br&gt;P &lt;0.0001</td>
<td>Candesartan was borderline better at lowering cardiovascular death than placebo&lt;br&gt;P = 0.051&lt;br&gt;Candesartan was significantly better at lowering admission for CHF&lt;br&gt;P = 0.017</td>
</tr>
</tbody>
</table>

Reference: Bahiru & Kloner, 2008
### Appendix 1

#### Table 2.18 - Degree of BP lowering

<table>
<thead>
<tr>
<th>Groups and Studies</th>
<th>Comparative Drugs</th>
<th>Primary End Points</th>
<th>Degree of lowering BP</th>
<th>Benefit on Primary End Points.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renoprotective effect of the angiotensin-receptor antagonist Irbesartan in patients with nephropathy due to type 2 diabetes.</td>
<td>Irbesartan vs Amlodipine vs placebo</td>
<td>Doubling the baseline serum creatinine concentration, the development of end stage renal disease, or death from any cause.</td>
<td>Both Irbesartan and Amlodipine significantly better at lowering diastolic or mean BP than placebo. The mean arterial pressure was 3.3 mmHg lower in the Irbesartan and Amlodipine groups than placebo. But there was no significant difference in BP between the two drugs.</td>
<td>Irbesartan significantly better than Amlodipine P= 0.006</td>
</tr>
</tbody>
</table>

Continued overleaf
### Appendix 1

Table 2.18 - Degree of BP lowering continued

<table>
<thead>
<tr>
<th>Groups and Studies</th>
<th>Comparative drugs</th>
<th>Primary End Points</th>
<th>Degree of Lowering BP</th>
<th>Benefit on Primary End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular morbidity and mortality in the Losartan intervention of end point reduction in hypertension study (LIFE). A randomised trial against Atenolol.</td>
<td>Losartan vs Atenolol</td>
<td>Cardiovascular death, myocardial infarction, stroke</td>
<td>No significant or minimal difference between the two drugs in lowering BP.</td>
<td>Losartan significantly better than Atenolol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>End of study systolic and diastolic BP:</td>
<td>P= 0.021</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Systolic-30.2mmHg drop in Losartan</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Systolic-29.1mmHg drop in Atenolol</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diastolic-16.6 mmHg drop in Losartan</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diastolic-16.8 mmHg drop in Atenolol</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean arterial pressure at last visit 102 mmHg in both groups</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P= 0.017 for systolic BP</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P= 0.37 for diastolic BP</td>
<td></td>
</tr>
</tbody>
</table>

Reference: Bahiru & Kloner, 2008
<table>
<thead>
<tr>
<th>Groups and Studies</th>
<th>Comparative Drugs</th>
<th>Primary End Points</th>
<th>Degree of lowering BP</th>
<th>Benefit on Primary End Points.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on Valsartan or Amlodipine: the VALUE randomised trial.</td>
<td>Amlodipine vs Valsartan</td>
<td>A composite of sudden cardiac death, fatal myocardial infarction, death during or after percutaneous coronary intervention or coronary artery bypass graft, death due to heart failure and death associated with recent myocardial infarction on autopsy, heart failure requiring hospital management, non fatal myocardial infarction</td>
<td>Amlodipine significantly better than Valsartan, P&lt;0.001 At one month period BP was lowered by 4.0/2.1 mmHg in Amlodipine group than Valsartan group. After six months, the difference was 2.1/1.6 mmHg</td>
<td>No significant difference between the two drugs in lowering the primary end points. P = 0.49.</td>
</tr>
</tbody>
</table>

Continued overleaf
Appendix 1

Table 2.19 –Degree of BP lowering continued

<table>
<thead>
<tr>
<th>Groups and Studies</th>
<th>Comparative Drugs</th>
<th>Primary End Points</th>
<th>Degree of lowering BP</th>
<th>Benefit on Primary End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major outcomes in high-risk hypertensive patients randomised to angiotensin converting enzyme inhibitor or calcium channel blocker vs diuretic. The anti-hypertensive and lipid lowering treatment to prevent heart attack trial (ALLHAT).</td>
<td>Chlorthalidone vs Amlodipine vs Lisinopril</td>
<td>Fatal CHD or non-fatal MI</td>
<td>Systolic blood pressure was 2 mmHg higher in Lisinopril group than Chlorthalidone group (P&lt;0.001). Systolic blood pressure was 0.8 mmHg higher in Amlodipine vs Chlorthalidone (P&lt;0.001).</td>
<td>No significant difference between the three groups in lowering the primary end points.</td>
</tr>
</tbody>
</table>

Reference: Bahiru & Kloner, 2008
### Appendix 1

#### Table 2.20 - Degree of BP lowering

<table>
<thead>
<tr>
<th>Groups and Studies</th>
<th>Comparative Drugs</th>
<th>Primary End Points</th>
<th>Degree of lowering BP</th>
<th>Benefit on Primary End Points.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of cardiovascular event with an antihypertensive regimen of Amlodipine</td>
<td>Amlodipine vs Atenolol</td>
<td>Nonfatal myocardial infarction including silent myocardial infarction, and fatal CHD.</td>
<td>Amlodipine significantly better than Atenolol</td>
<td>No significant difference between the two drugs in lowering the primary end points.</td>
</tr>
<tr>
<td>adding Perindopril as required vs Atenolol adding Bendroflumethiazide as required, the Anglo-Scandinavian</td>
<td>optimal arm (ASCOT-BPLA): a multicentre randomised controlled trial</td>
<td></td>
<td>P &lt; 0.0001</td>
<td>P = 0.105</td>
</tr>
<tr>
<td>cardiac outcomes trial - Blood pressure lowering arm (ASCOT-BPLA): a multicentre randomised controlled trial</td>
<td></td>
<td></td>
<td>Primary end point lowered by 10% in Amlodipine group than Atenolol. Not a significant difference.</td>
<td></td>
</tr>
</tbody>
</table>

Letter of Invitation

Dear Mr/Mrs/Ms

We are conducting a study at Stepping Hill Hospital and Manchester Royal Infirmary to look at the treatment of hypertension. You are due to attend a clinic at one of these hospitals. I am enclosing information about this study. We are interested in collecting only data from your clinic visit. There will be no change to the treatment you receive, and we will not be doing anything different to you as result of this study. We are also enclosing a form for you to use if you do not wish your data to be included in the study. Please bring this with you to your appointment if you don wish to be included. If you do not return this form we will assume that you are happy for us to include your data in the study. Do not worry if you forget your form, as extra forms will be available when you attend the clinic, should you need one. You can opt out of the study at a later date if you wish to.
If you want any further information please contact: Mrs Praba Rabasse at Stepping Hill Hospital, Stockport Foundation Trust, on 0161 419 4772/3225.

Many thanks.

Yours faithfully

Praba Rabasse BSc, MSc, RN
Consultant Nurse - Cardiology
PATIENT INFORMATION SHEET

Study Title – Does Biochemical (aldosterone & renin) profiling reduce the time taken to achieve target blood pressure in hypertensive patients.

Thank you for taking the time to read this information. My name is Praba Rabasse and I am a Professional Doctorate student at Salford University. As part of my course I am conducting a study at Stepping Hill Hospital and Manchester Royal Infirmary to look at the treatment of hypertension. Before you decide to take part in this project it is important for you to understand what it will involve. Please take time to read the following information and discuss it with others if you wish. Please ask the researcher/consultant when you come to the clinic, if there is anything that is unclear or if you would like more information.

What is the purpose of this study?

The purpose of the study is to find out the blood pressure treatment and the patient’s response to the treatment on the basis of a special blood test. To do this, only routinely collected data will be used and this will be compared between Stepping Hill Hospital and Manchester Royal Infirmary. As a result of this study you will not be subjected to any additional blood tests.

Why have I been chosen?

You have been referred to the hospital with a history of hypertension – hence you have been chosen to take part in this study.

Do I have to take part?

You are not required to take part and do not have to give reasons for declining to do so. Similarly, having agreed to take part in the study you may change your mind and withdraw from the study at any time without giving a reason. This will not affect your treatment or care.

What will happen to me if I take part?

Your care will not be altered; we are intending to collect information (data) from your clinic visit and your medical notes regarding your blood pressure, your symptoms and the results of your blood tests, your current treatment and the outcome of your clinic reviews. There will be no change to the treatment you receive and we will not be doing anything different to you as a result of this study.
What do I have to know?

It will not be necessary for you to undergo any additional medical tests or treatments extra to the normal care you would receive for your condition. Similarly, no treatment will be withheld as a result of you taking part in this study. Your care will continue as normal under your hospital consultant. After you have been seen in the clinic and started on treatment, if you decide to stop taking the medication, can you please let the researcher know.

What are the risks or disadvantages of taking part?

You will not be exposed to any risks or hazards by taking part in this study.

What are the possible benefits of taking part?

There are no immediate benefits to you if you decide to take part in this study. However, we hope that the information we gather about you, and patients like you, will help us to improve the future care of patients with a history of hypertension.

Will my taking part in this study be kept confidential?

The information collected about you will remain strictly confidential under United Kingdom law. Any information about you that is held on a computer database will be stored according to the Data Protection Act. It will not be possible for anyone not connected with this study to access any personal or medical information we may hold about you.

What will happen to the results of the study?

It is anticipated that the results of the study will be published in relevant medical/nursing journals. It will not be possible to identify you from the published results of this study.

What should I do if I do not want to take part?

We have enclosed a form for you to use if you do not wish your data to be included in the study. Please bring this with you to your appointment if you do not wish to be included. If you do not return this form we will assume that you are happy for us to include you and your data in the study. Do not worry if you forget your form, as additional forms will be available when you attend the clinic should you need one.

If I want to complain about this study how should I do it?

If you have any complaint about this study you can contact the Patient Advice and Liaison Services (PALS) at MRI on telephone number 0161 276 4261 or at Stepping Hill on telephone number 0161 419 5678. You can talk to PALS who provide confidential advice and support to patients, families and their carers, and can provide information on the NHS and health related matters.

If you need further information please contact the researcher – Praba Rabasse on 0161 419 4772 / 3225.
Hypertension Research

Does biochemical (Aldosterone & renin) profiling reduce the time taken to achieve target blood pressure in hypertensive patients.

I do not wish to take part in the hypertension study therefore do not include my information. Thanks.

Patient Name: ................................................................. Date of Birth: .........................

Hospital Number: ......................................................

Signature: ................................................................. Date: .............................................

Name of the researcher is - Praba Rabasse – Tel – 0161 419 4772 / 3225


British Heart Foundation (2011) Hypertension, Fact File, London, BHF.


Hypertension. 9:(7), pp. 497-499.


Joint British Societies’ guidelines on prevention of cardiovascular disease in clinical practice 2.(2005) Figure 6.1: CVD risk calculation chart for women [Illustration]. Heart.(suppl), p.53.


Maskrey N, Underhill J L (2005) ASCOT soundbites ...or 40 years evidence on the treatment of hypertension? BMJ. http://www.bmj.com/content/331/7521/859.extract/reply#bmj_el_119519 accessed on 14th May 2011 at 12.47 hrs.


O'Brien, E. (2011) Irish medical practice must dispel its ambivalent attitude to the management of hypertension by overcoming therapeutic inertia so as to obtain control of blood pressure. *Irish Medical Times,* 5th May 2011, p.2.


Schiffrin, E.L. (2005) Blood pressure lowering in PROGRESS (Perindopril protection against recurrent stroke study) and white matter hypertensities; should this progress matter to patients? *Circulation*, 112, pp. 1525-1526.


SPSS. (Version 15) 2007, SPSS Inc. Chicago IL. USA


