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Adherence to antihypertensive medication in the United Arab Emirates

Patient and doctor perspectives

University of Dublin

Trinity College

Department of Clinical Pharmacology & Therapeutics

This thesis is submitted as fulfilment of the requirements for the degree of Doctor of Philosophy

Declaration

I declare that this thesis has not been previously submitted as an exercise for a degree at this or any other university

I declare that this thesis is entirely my own work but acknowledge the assistance and collaboration of several colleagues during the clinical data collection (see acknowledgments)

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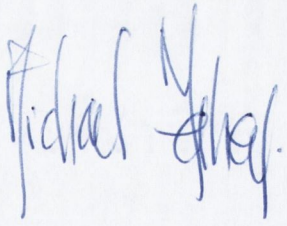

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Abbreviations

$US	USA dollar
ABPM	Ambulatory Blood Pressure Monitoring
ACC	Associated Clinical Condition
ACE	Angiotensin Converting Enzyme
ACEI	Angiotensin Converting Enzyme Inhibitor
AIIA	Angiotensin II (subtype 1) receptor antagonist
ALLHAT	Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial
AT_1	Angiotensin II (type one sub-receptor)
bd	twice daily
BMI	Body Mass Index
BP	Blood pressure
CAPPP	Captopril Prevention Project
CCB	Calcium Channel Blocker
CHD	Coronary heart disease
CI	Confidence Interval
CRF	Chronic Renal Failure
d.DBP	Change in the diastolic blood pressure since the start of treatment
d.SBP	Change in the systolic blood pressure since the start of treatment
DBP	Diastolic Blood Pressure
Dh	UAE Dirham (approximately 4 to the Euro)
ECG	Electrocardiogram
EMRO	Eastern Mediterranean Regional Office for WHO
FACET	Fosinopril versus Amlodipine Cardiovascular Events Study
FDA	Food and Drug Administration
GBP	Great Britain Pounds (approximately 0.63 to the Euro)
GP	General Practitioners
HAART	Highly Active Anti-Retroviral Therapy
HDFP	Hypertension and Detection and Follow-up Program
HDL	High Density Lipoprotein
HF	Heart failure
HIV	Human Immunodeficiency Virus
HOT	Hypertension Optimal Study

HTN	Hypertension
INSIGHT	Intervention as a Goal in Hypertension Treatment
JNCV	Fifth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
JNCVI	Sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
Kg	Kilogram
KMO	Kaiser-Meyer-Olkin
LDL	Low Density Lipoprotein
LES	Life Event Score
LVH	Left ventricular hypertrophy
MEMS	Medication Event Monitoring System
mmHg	Millimetres of mercury
mmol	Millimoles
MOH	Ministry of Health
MONICA	Monitoring Cardiovascular disease
MRFIT	Multiple Risk Factor Intervention Trial
NESH	National Epidemiological Survey of Hypertension
NHANES	National Health and Nutrition Survey
NHLBI	National Heart Lung and Blood Institute
NHS	National Health Service
No.	Number
NORDIL	Nordic Diltiazem study
od	Once daily
OR	Odds ratio
OTC	Over The Counter
PC	Personal Computer
PCA	Principal Component Analysis
PHC	Primary Healthcare Centre
PhD	Doctor of Philosophy
RAS	Renin Angiotensin System
RR	Relative risk
Rx	Prescribed regimen
SBP	Systolic blood pressure

SD	Standard Deviation
SHEP	Systolic Hypertension in the Elderly Program
SPSS	Statistics Package for the Social Sciences
SRA	Self Reported Adherence
SRM	Self Reporting Measure
STOP	Swedish Trail of Old People with Hypertension-2
TDM	Therapeutic Drug-level Monitoring
tds	three times a dya
TOD	Target organ disease
TOMES	Treatment of Mild Hypertension Study
UAE	United Arab Emirates
UCLA	University of California in Los Angeles
UK	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
US	United States
USA	United States of America
vs .	Versus
WHO	World Health Organisation
WHO-ISH	World Health Organisation and International Society for Hypertension Guidelines for the Management of Hypertension
WOSCOPS	West of Scotland Coronary Prevention Study
X^2	Chi Square
Yr	Year

Abstract

Approximately half of the patients taking medication for hypertension have problems following the prescribed regime to the extent that they do not derive optimal clinical benefit. Prior to this study, there was little data on adherence in the Arabian Gulf region and there was no Arabic language instrument for measuring self-reported adherence.

This thesis describes the design and validation of an Arabic / English self-reporting measure for medication adherence. This instrument was used to study the concurrent and predictive validity of the self-reported adherence measure, changes in self-reported adherence and to compare the doctor and patient perspectives on adherence.

A review of the literature relating to adherence includes a critical appraisal of the methods used to measure adherence, a discussion of which of these are most suited to routine clinical practice and emphasises the role of the individual's health beliefs in determining adherence. A large number of factors have been associated with a higher risk of non-adherence and these are discussed in the context of whether they are likely to be modifiable risk factors for non-adherence.

A review of hypertension demonstrates that it is a modifiable risk factor for cardiovascular disease and that there is strong clinical trial and epidemiological evidence for the effectiveness of antihypertensive drugs. Hypertension is therefore not only an ideal model in which to study medication adherence in chronic disease, but an area in which improved adherence will bring enormous clinical and economic benefit.

An English self-reporting measure was translated in to Arabic and adapted for use in the UAE. After validation of the translation and a pilot study, concurrent validity was assessed from a sample of 203 patients. Seven items were selected as a measure of adherence. These seven items provided a one-dimensional instrument with a high degree of internal reliability (Cronbach alpha 0.76). The responses were assigned a score (0-7) and the score was related to high (0), medium (1-4) or low adherence (5-7). Patients who reported high adherence were approximately twice as likely to have reached their target blood pressure than patients who reported medium or low adherence (52% vs. 28%). The adherence score was significantly related to the systolic blood pressure, diastolic blood pressure and the change in systolic blood pressure since the start of treatment.

After 6-9 months, 86 patients were followed up and the self-reported adherence was re-assessed. Over 40% of patients had changed their self-reported adherence and high adherence at the initial study was not related to blood pressure control at follow up. While this showed that the self-reported adherence had a low predictive validity, it continued to show strong concurrent validity. When compared with the initial study, at follow-up the changes in adherence were consistent with changes in the blood pressure control. At follow-up, patients who reported high adherence were twice as likely to have reached their target blood pressure compared with the patients who reported medium or low adherence (67% vs. 32%).

The doctors were asked to give their estimates of the patient's adherence together with their assessments of key aspects of the patient's care. There was very little agreement between the doctors' assessments of adherence and the self-reported adherence reports. The doctor's assessment concurred with the patient's in around 50% (44-56%) of cases. The doctors' perceptions of the quality of patient-doctor communication, patient knowledge and effectiveness of therapy were strongly related to the doctors' assessments of adherence but this was not related to the self-reported adherence. The doctors estimated that those with the more serious cardiovascular prognosis had lower adherence whereas these patients reported higher adherence.

This research has demonstrated important differences in the patient and doctor perspectives on adherence in hypertension, the temporal nature of adherence and suggests that any intervention to improve adherence will have to include the ongoing evaluation of adherence and health beliefs, be multi-faceted, related to the individual and part of a sustained management plan. The scope for greater pharmaceutical care of hypertension patients is described. If further studies confirm the effectiveness of this Arabic / English self-reporting measure, it should be incorporated in to routine clinical practice in the UAE where it would greatly improve the identification of non-adherent patients.

Aims and objectives of the thesis

The aim of this PhD thesis was to devise and evaluate an Arabic / English language instrument for the self-reporting of medication adherence by patients attending UAE Ministry of Health primary healthcare care centres for the management of their hypertension.

The objectives of this thesis were:

- To develop an expert appreciation of medication adherence in hypertension as a result of performing a comprehensive review of the relevant literature
- To devise and validate an Arabic self-reporting measure for patients to relate there perceptions of their medication adherence. The scale should be suitable for use in routine clinical practice
- To derive a scale from the instrument that can be used study the association between self-reported adherence and blood pressure control
- To study the doctor's perceptions of medication adherence and the factors influencing their perceptions
- To compare the doctor's perceptions of medication adherence with the patient's self-reported adherence
- To follow up a group of patients to determine the predictive validity of the self-reported adherence and study changes in self reported adherence over time.

1. Medication adherence

Chapter contents

1.1 Summary

This chapter includes a discussion of the various definitions and classifications of adherence and emphasises the role of health beliefs in determining adherence. It includes a critical appraisal of the various methods used to measure adherence over the last thirty years and a discussion of which of these are most suited to routine clinical practice. Previous research has shown that a large number of factors are associated with a higher risk of non-adherence and these are discussed in the context of whether they are likely to be modifiable risk factors for non-adherence. A better understanding of adherence is a prerequisite for the design of interventions to maximise adherence.

1.2 Describing adherence

1.2.1. What's in a name?

It is widely recognised that on average, 40–50% of patients do not follow their treatment plans as recommended to them. Researchers and commentators have used the terms compliance, adherence and concordance over the last 30 years to describe this subject and adherence is further described according to qualitative criteria such as whether it is intentional, primary or secondary[1].

1.2.2. Adherence versus Compliance

In this thesis, the term adherence is used in preference to compliance when describing how a patient follows the prescribed treatment. The term adherence was adopted to conform to the growing recognition that compliance under-emphasises the extent to which patients make an active decision about how they take their medicines.

A lot of the literature on this subject uses the term compliance. It is unusual to find the term adherence before the late 1980's and then it is usually in the work of behavioural psychologists e.g. Blackwell, 1979[2]. Dictionary definitions barely distinguish between the two terms; however, increasingly, over the years the term compliance has been criticised[3]. Many authors, especially social scientists and health ethicists have encouraged the use of the term adherence. It is believed that compliance suggests that the patient is a passive partner in their disease management and that failure to take the medication is therefore the fault of the patient.

1.2.3. Adherence versus Concordance

There is an increasing change in the distribution of power in the doctor / patient relationship. In most countries, the power of a patient lobby is now well

recognised along with increasing patient expectations and an emphasis on involving the patient in the decisions taken regarding their treatment. The term concordance has recently been proposed as part of a sincere attempt to change the way we think about the doctor, patient relationship. In 1997 the Royal Pharmaceutical Society of Great Britain published a report of their two-year enquiry into what is known about the difficulties patients have in taking medicines as prescribed[1]. Although an interim discussion document adopted the term adherence, the final report introduced the term Concordance.

Concordance is used to describe the process by which an arrangement is forged between the patient and the physician, whereby they are both in agreement about the nature of the illness and its treatment. In this way, patients are more likely to take their medication and get the therapeutic benefit. The report advocated a distinct change in the approach to the problem of adherence and the relationship between prescribing and medicine taking and therefore between the prescriber and patient. Adherence describes what the patient does, but Concordance enhances adherence.

1.3 Defining Adherence and Non-Adherence

Adherence can refer to the extent to which a patient follows any or all aspects of their recommended management including life-style modifications and continuing attendance for the monitoring of their condition, e.g. hypertension and other cardiovascular risk factors.

There is no generally agreed definition. Adherence or compliance has been defined as;

"the extent to which the patient's behaviour... coincides with the clinical prescription" ***Sackett*** [4]

"the point below which the desired preventive or therapeutic result is unlikely to be achieved" ***Gordis*** [5]

"the extent to which the patient fulfils the intention of the prescriber in taking medication". ***McGavock*** [6]

The definitions of Sackett and McGavock both describe the key point that needs to be measured, i.e. the difference between the prescriber's intention and the patient's action. However, both definitions neglect the reality that a good therapeutic outcome does not always require 100% adherence, a point recognised by Gordis.

Sackett' first observed in 1975 that blood pressure does not start to fall significantly until the patient is taking at least 80% of their antihypertensive therapy, and this is still widely accepted. A more difficult question is how far does the blood pressure need to fall. Therefore, one should focus on the level of adherence that is adequate to achieve a desired therapeutic result[7] and very often we do not know what threshold of adherence is "enough". It will be shown in chapter 2, that this threshold to clinical effectiveness is a feature of the drug, the disease and the way the patient is affected by these two factors. The concept of "therapeutic sufficiency" has been introduced to describe the reaching of the therapeutic goal despite "patients imperfect behaviour and clinicians' imperfect prescriptions"[8].

1.4 Qualitative and Quantitative classification of adherence

Research has addressed the *qualitative* nature of non-adherence and the *quantitative* nature of *non-adherence* (the actual methods used are discussed in section 1.6 below). *Qualitative* definitions refer to variables such as intention, memory, health beliefs etc. *Quantitative* definitions refer to the amount of medicine taken over a given period or the accuracy of the dose timing, completion of the prescribed course etc. In both cases, it is essential to understand that in most situations, non-adherence is partial, not total.

If one is attempting to measure adherence quantitatively, one must be clear what one is measuring. If one counts missed doses, how should this be expressed? Is percentage of prescribed doses a useful measure? If so, then how does one compare a missed dose from a once daily regimen with a missed dose from a twice-daily dose?

Consider the patient who, over a 28-day period misses six doses of their once daily regimen. They will have missed more than 20% of their prescribed doses. If a patient misses six doses of their twice-daily regimen, they will have missed just over 10% of their prescribed doses. If a patient is on two medicines, one taken once daily, the other taken twice daily and misses two of the once daily doses and four of the twice daily doses they will have missed 14% of the prescribed doses.

- Which of the above examples is worse for the patient?
- Would the answer be different depending upon the indications for the medicine?

- If the medicines are antihypertensive drugs, all three patients may have lost control of their blood pressure for up to six days.
- Is it more dangerous to miss the morning dose of the antihypertensive or the evening dose?

The answers will depend partly on the duration of action of the medicines. Many modern antihypertensive drugs have half-lives in excess of 24 hours. They have been described as being more "forgiving" as they ameliorate the loss of control due to occasional missed doses.

The above examples of non-adherence, may be contrived but they are an over simplification. More commonly, non-adherence presents as a variant behaviour, taking the form of, omitting doses and the seemingly random stopping and starting of treatment (called drug holidays). Consider the patient who stops taking their antihypertensive for six weeks before restarting regular, daily doses. They will have missed less than 12% of their prescribed doses over a 12-month period. Would this scenario have a greater adverse impact upon the cardiovascular risk of the patient than the above examples?

There are no long-term studies to answer these questions. Most data comes from relatively short-term studies and one must be careful to put these findings in to a clinical context and to recognise that it may not be a wholly reliable representation of long-term adherence behaviour in a patient or population.

1.4.1. Adherence as a process

Perhaps a more constructive approach is to first recognise that medication taking is a process. This is particularly important in the treatment of chronic disease where medicine taking is long-term and may be for life. Waeber and colleagues (1997) describe these as Adoption, Execution and Continuation (or Discontinuation)[9].

Adoption

Adoption describes the first step in the process and is when the patient is given the news that they have a raised blood pressure and drug treatment is proposed. The patient's acceptance of this plan is "adoption". The patient's understanding of hypertension, it's consequences and the role of prescribed medicine is crucial for high levels of adoption, i.e. the patient's decision to follow the treatment plan. The patient's receipt of the dispensed drug and the administration of the first dose mark the move to the "execution" step of the process. However, the patient

may still be weighing the information they have received for some time after receiving the medicine from the pharmacy.

Execution

This is the day to day taking of the prescribed dose at the right time. In hypertension, it is not only the number of tablets taken but also the interval between tablets that is important. Failure of execution will fail to lower blood pressure or will allow blood pressure to rise to untreated levels. It is a part of the patient's life away from the health care workers and the patient has to decide that this activity is going to become part of their lifestyle. If they make this step, they will have gone into the "continuation" step of the medication taking process. Most studies of adherence involve measurement of the "execution" step of the process. In many cases, the patient moves from execution to discontinuation of the treatment.

Continuation* or *Discontinuation

Discontinuation of medication is common to all chronic conditions that require continuous drug treatment. There has been relatively little research work done to understand this step. It is not clear if declining rates of execution is a signal for impending discontinuation or if the reasons for poor execution are the same reasons leading to the discontinuation phase of non-adherence.

These stages are a useful way to structure our thinking about adherence especially when designing studies. However, it is important to remember that there will be different degrees of patient commitment to each stage and that this commitment will vary with time. Therefore, if we are to understand non-adherence and work towards minimising it we will need to evolve both the way we measure and categorise non-adherence in each of these three processes.

1.4.2. Intentional non-adherence

Intentionality has been used to categorise non-adherence. It is a major issue regarding the adoption and execution of treatment. If a patient rejects the doctor's diagnosis and / or treatment, fails to return for follow-up appointments or the patient fails to have their prescription dispensed it is intentional non-adherence. If they fail to have the prescription dispensed because they cannot afford the cost, it is voluntary but not strictly intentional. Intentional non-adherence involves rationality and decision making on the part of the patient.

Intentional discontinuation is not always a bad thing. Intentional non-adherence amongst patients taking long-term medication has been described as "intelligent non-adherence"[10]. Stable, insulin dependent diabetics can adjust their insulin dose according to occasional infections, lapses in diet or exercise. Many patients adjust their medication to ameliorate side effects, often without any detriment to the benefit.

In asthma management guidelines, regular inhaled steroids have become the cornerstone of modern management. There is evidence that patients do not always use inhaled corticosteroids regularly but still derive the additional benefit. This has led some experts to ask if intermittent inhaled steroids are adequate in some patients. Perhaps this is another case of intelligent non-adherence?

There may be reluctance for health professionals to admit that adherence is intentional. Non-adherence by the elderly is often attributed to forgetfulness or dementia; however, in a study of 111 elderly patients taking outpatient prescription drugs, drug-taking behaviour was compared with the behaviour implied by the prescription instructions and the reasons for the differences were sought [11]. It was found that 43% showed such differences in use of one or more prescription drugs. The main type of discrepancy was under-use (90 per cent of non-adherence). A large proportion of non-adherence (73%) was intentional. Intentional non-adherence was more likely to occur in subjects who used two or more pharmacies and two or more physicians. Therefore, the common perception that elderly people are non-adherent because of memory or cognitive problems may be wrong and the non-adherence is part of a conscious decision on behalf of the patient.

1.4.3. Primary non-adherence

Adherence can be described as primary or secondary. Failure to have the prescription dispensed is *primary* non-adherence. Within the process-orientated approach to adherence described by Waeber *et al* (1997)[9], primary adherence refers to the Adoption or Continuation process. Secondary non-adherence describes defaulting behaviour in the execution and factors affecting this are discussed in section 1.4.1 above

Large-scale surveys of primary non-adherence in the UK are lacking and none are specific to hypertension. In an observation study of 4854 patients attending a large National Health Service practice in Scotland, written prescriptions (20,921), were reconciled with those dispensed. It found that 14.5% of patients did not

redeem at least one prescription (5.2% of prescriptions) during the study period[12]. Non-redemption was highest in women aged 16-29 (27.6% of women) and men aged 40-49 (18.3% of men). Of prescriptions issued to women for oral contraceptives, 24.8% were not redeemed during the study period and this accounted for most of the differences between men and women. This study covered a three-month period and in Scotland, a prescription is valid for 6 months from the date of prescribing. Many prescriptions for oral contraceptives are for three to six months and women often have 2-3 months supply in hand. It is possible that some of the oral contraceptive prescriptions were dispensed after the study period; therefore, the study may have overstated the extent of primary non-adherence, especially for oral contraceptives. Patients who had to pay a prescription charge accounted for 33% of unredeemed prescriptions compared with 17% of redeemed prescriptions suggesting that the cost of the prescription was a factor. The non-redemption rate was highest for prescriptions issued at the weekends, although this was a small proportion of all prescribing. Prescriptions issued by trainee general practitioners were also less likely to be redeemed.

A small, short-term study of a single UK NHS practice (13 doctors) involved a survey of prescription non-redemption in 1000 consecutive outpatients (935 patients responded to a questionnaire given to them after their consultation with the doctor. This was followed by an interview of those reporting non-redemption)[13]. Twenty-two patients (2.4%) reported that they had not redeemed their prescription. A total of nine out of these 22 patients reported that their medication was cheaper over the counter and obtained it in this way. Thirteen out of twenty two (1.4% of total) did not obtain their medication. Five patients indicated that cost was a factor in not obtaining their medication. Other factors included the doctor's permission not to cash the prescription, poor understanding of their illness, and the wish to maintain control. It is difficult to compare this small study with the larger survey, especially as the percentage of patients exempt from prescription charges is not given, but it does show that over 40% of apparent non-redemption in the UK could be due to the patient buying the medicine over the counter at a price less than the minimum NHS prescription charge. This would not apply to most drugs for chronic diseases e.g. antihypertensive drugs, as they are not available without a prescription.

In the USA, where prescription co-payments are common, several large surveys have shown the problem to affect 14-63% of prescriptions. The American Association of Retired Persons, 1984 reported that 21% of retired people had decided not to have a prescription filled[14]. A survey conducted in 1985 by the drug company, Upjohn found that 14% of people interviewed had decided not to have a prescription dispensed within the previous twelve months[15]. This survey also showed that patients over the age of 60 years were more than twice a likely to report primary non-adherence than were young adults.

One study in the USA looked at primary non-adherence in patients on long-term therapy[16]. Up to 45% of patients prescribed antihypertensive therapy reported primary non-adherence after 6 months' treatment.

The social situation and cost of treatment is a likely factor in determining whether or not a patient will continue to attend for follow-up or pay to have their prescription re-filled. In a study of an inner city health centre in a deprived area of Atlanta, Georgia, alcoholism and a lack of health care insurance was directly correlated with primary non-adherence in the form of a 40% non-attendance rate[17].

There is no hard data on the level of primary non-adherence in the UAE. The UAE nationals have access to free medical care but personal observation and discussions with colleagues in the Middle East has exposed examples of significant primary non-adherence among UAE nationals. At the government hospitals, following a clinic attendance, the patient will get the prescription dispensed free of charge. If the medicines fail to meet their expectations, they are simply dumped in trashcans on the hospital premises. A similar phenomenon has not been reported in the literature.

In controlled clinical trials, primary non-adherence is unlikely to happen and it is one of the reasons why adherence rates in clinical trials are higher than in real life.

1.5 Health Beliefs relating to medicines and adherence

1.5.1. The patient's perspective on medication

Everyone has preconceived ideas and fears and this extends to the use of medicines and the treatment and causes of disease. These are one's Health Beliefs. The decision by a person to adopt, execute and continue their drug treatment will depend upon how they interpret the information about the disease and treatment[18].

In the traditional model of non-adherence, the situation is perceived as a variance between the doctor's rational treatment and the patient's irrational resistance to that treatment. As a result, research in to adherence has tended to focus on the "defaults" of the patient. However, there is little evidence to support the idea of there being a non-adherent personality. While non-adherence is a variant behaviour, it incorporates a wide range of non-adherent behaviours and a patient may exhibit several of these over time. Research by social scientists has lead to the increasing recognition that patients make active, rational decisions about their medication[19,20]. The decision to adhere or not may, or may not, be well informed, but the logic of the decision will relate to the patients own belief system.

The recognition that non-adherence is the result of a decision on behalf of the patient is an important development. It requires a radical re-think in ones understanding of the problem, in the ways in which one measures the problem, and in the ways in which one attempt to improve adherence. It also requires one to appreciate some of the related psychological theories of why people adopt or reject what appear (to the health professional), to be rational treatment and prevention programs.

Several social cognition models have been developed to relate patient's cognitions, i.e. their beliefs, attitudes and perceptions to their behaviour such as adherence to a treatment program. The term model is used loosely as many are concepts or frameworks that have been derived from broader models. They involve psychological concepts such as social learning theory, attribution theory and information processing.

It has been studied in people who are at risk of developing cardiovascular diseases.

In these people these models have been applied as explanations of:

- Risk behaviour
  e.g. to predict those who will adopt heath-risk behaviours or conversely, those who will adhere to treatment programs (pharmacological and non-pharmacological)
- Preventive/protective behaviour
  e.g. to identify those who will adopt protective or preventive behaviour or change existing health-risk behaviour. This will include adhering to treatment programs.

The models used include

- The health belief model
- The theory of reasoned action
- Health value and self-efficacy
- Health locus of control
- Attribution theory
- Illness representation model
- Self regulatory model of illness

The more recently developed models such as the self-regulatory model of illness have moved away from a rigid view of health behaviour towards a framework that expects beliefs and behaviours to interact in a dynamic way [21]. These are not discussed in detail here, as they are not directly relevant to the research method used in this thesis and there is no published evidence of these models being validated in Arab or Asian populations.

The complexity of the social dimension of adherence is reflected in the diversity of lay views and the array of social cognition models used to describe health related behaviour and reasoning.

1.5.2. Patient views on drugs & medicines in general

It is important that one first understand the range of cognitions that lay people have in relation to medicines and healthcare. The range of cognitions relating to lay people and medicines cover six themes;

- Perceived efficacy
- Natural versus unnatural
- Addiction and dependence
- Anti-drug attitudes (general and disease specific)
- Balancing risks and benefits
- The social context of medicine taking

There have been many surveys of the cognitions of patients with chronic diseases including hypertension. Many of the studies are qualitative and often in small populations. However, in the hands of skilled social scientists these studies can provide a fascinating insight to the range of patient cognitions. All of these have been conducted in Europe or America. Although some studies have

focussed upon Afro-Caribbean people, relatively few of these have been among non-western communities and therefore the applicability to the research population studied in this thesis remains tentative.

1.5.2.1. Perceived efficacy

McGavock[6] quotes an interview based study of 20 patients with rheumatoid arthritis[22], which describes how patients defined efficacy in two ways: the alleviation of specific physical symptoms, and the normalising of their lives (e.g., returning to work). The patients set time limits on how quickly they expected their specific outcomes to be achieved, and on how long they expected the drug to continue working for them. They also had their own methods for assessing efficacy, which included seeing what happened when they stopped taking the drug.

These observations do not bode well where patients may quickly become impatient or disinterested in asymptomatic, chronic conditions such as hypertension. It is easy to see how patients could have difficulty understanding the effectiveness of their treatment when most benefits are in the prevention of sequelae several years hence. Little is known about how patients relate their anti-hypertensive therapy to their physical state. In one study of hypertension in the elderly, headache was associated with the awareness of a diagnosis of hypertension but not with hypertension *per se*. This makes headache a very unreliable indicator by which to moderate treatment as was shown in a study from Finland which found that patients who adjust their treatment according to physical symptoms, such as headache, were less likely to achieve blood pressure control (Odds Ratio 2.1)[23].

A fear of developing a tolerance or immunity to the medicines has been described. Rheumatology patients described how they were not adherent because they worried that their bodies would become accustomed to drugs and would eventually lose their effectiveness[19]. With antibiotics, patients have described a fear of becoming "immune" to antibiotics if they are overused[24]. This misperception could easily arise from a lay misunderstanding of the concept of "antibiotic resistance".

1.5.2.2. Natural versus unnatural

People often consider manufactured medicines as *unnatural*. The logical assumption to make is that the term *natural* is used to compare manufactured medicines with *natural alternatives*. However, it is not always clear if the use of

the term *unnatural* arises from a comparison between the cure (i.e. manufactured medicine) and the *natural* affliction.

A study of parents who had not had their children immunised against whooping cough regarded the whooping cough as a *natural* event, while preventive vaccination was considered to be an *unnatural* intervention [25]. Mothers of non-immunised children believed that *natural* immunity was better than the *artificial* immunity conferred by vaccination [26]. In the context of analgesia for childbirth (a field where the use of terms such as *natural childbirth* is common) women used the term *unnatural* to describe medicines[27]. In another study of women (40-60yrs), they considered the pain and discomfort of the menopause to be *natural* experiences[28]. In the same study, women who were prescribed sedatives expressed concern about taking *"unnatural chemicals"* (benzodiazepines) and went on to give this as a main reason for not taking benzodiazepines.

Morgan, in her study of patient beliefs in hypertension, reported that the *natural* and relatively harmless nature of herbal remedies was seen by patients to be an advantage [6]. The same respondents expressed concern about the powerful nature of modern, scientifically created drugs and their possible long-term harmful effects. Professionals may not see some features of natural preparations that are appreciated by patients as advantages.

1.5.2.3. Addiction & dependence

The need to take a drug long-term can be perceived by many patients as losing control over their life. Patients equate loss of control with dependence and this fear is frequently expressed by patients who refer to a fear of drug addiction to a wide range of drugs, not just psychiatric medication. A quarter of Rheumatology patients were reported to be non-adherent because they were afraid of becoming dependent on drugs[19]. Women considering analgesia at childbirth[27] and patients taking medication to control epilepsy[20] have expressed this view. In epilepsy patients the medication becomes a potent symbol and reminder to the patient of the dependence (on family, friends, doctors etc) created by having epilepsy. Morgan *op cit* found that non-adherence in hypertensive patients was related to fears of becoming addicted to their medicine and this was especially seen in Afro-Caribbean patients[29].

1.5.2.4. Anti-drug attitudes

The above descriptions of anti-drug attitudes are attempts by researchers to categorise some of the more specific reasons given by patients when expressing

their unwillingness to take medicines. There is a danger that one can try to read too much into the descriptions given by patients. Would the average layperson really understand the difference between the term "developing tolerance" and the terms "addiction" or "dependence"? These words, while having a very specific meaning to a health professional, may simply be the patient's best attempt at expressing their distrust of the medicines and the process by which they are prescribed.

It should not be surprising that patients consider medicines dangerous. Since the Thalidomide disaster of the 1960's, public confidence in the drug industry and medical profession has been undermined. The popular media eagerly give prime coverage to subjects like the over-prescribing of benzodiazepines and the right of the patient to be informed means they are more aware of the side-effects and risks of medicines. In McGavock's review, he relates a report that 36 out of 90 Swedish patients on long-term medication for asthma, hypertension or chronic pain spontaneously referred to medicines as "poisons".

A study using semi-structured interviews of 30 adults reported a strong aversion to medicines amongst GP non-attendees in a UK general practice[30]. In a pilot study to determine what the public think of modern medicine, British working class women expressed a strong scepticism about the value of drugs and felt that doctors were too ready to prescribe[31]. One might expect that a patient's views about medicines will be in part related to their views about the doctor who is prescribing the medicine; however, in the above pilot study, this association was not evident. It would be interesting to relate the patient's views with the quality of their relationship with their doctor in a larger study focussing on chronic medication such as for hypertension.

1.5.2.5. Balancing risks and benefits

In most of the studies quoted above, patients also express positive attitudes regarding their medication. While many epilepsy patients said that they "hated" taking medication, almost all of them recognised that medication had helped them to control their seizures[20]. Rheumatology patients were found to conduct their own cost-benefit assessment of their drugs, weighing the risks with the benefits. In most cases, drugs were taken on trial for a period that seemed appropriate to the patient. Patients would then discontinue the drug or reduce the dose according to their experience[19]. Not surprisingly, the experience of, or the fear of side effects has been shown as a major cause of non-adherence in a

variety of conditions: epilepsy[20]; hypertension[29]; rheumatology[19] and immunization[26].

The availability of information about medicines and their side effects is seen as "empowering" patients; however, it can have an adverse effect upon the adoption and continuation of medication, even under controlled circumstances. The research group who conducted the landmark study of lipid lowering drugs as primary prevention in the West of Scotland (WOSCOPS study group) has described such a situation. Their large study was made more difficult by media concern over the safety of lipid lowering drugs in the early 1990's. Because of extensive media coverage, many patients expressed concerns and asked to discontinue treatment[32]. Subsequent analysis of the WOSCOPS data has shown that the incidence of serious adverse reactions due to Pravastatin was no different to placebo.

1.5.3. Patient views on drugs & medicines in hypertension

There has been limited research in to patient perceptions of medicines used to treat hypertension. These studies have not only looked at the perceptions that lead to non-adherence[29,33,34,35] but also at the reasons why patients continue to take medication[36,37]. There are no reports of health beliefs that are specific to hypertension and patients report a similar range of health beliefs in relation to all chronic treatments.

In the most recent of these studies, Benson and Britten used qualitative interviews of 38 treated hypertensive patients to elicit the reservations about using medication and the reasons for taking antihypertensive medication[37]. The range of perceptions was similar to several previous studies looking at chronic conditions and included a distinction between reservations about drugs generally, reservations specific to antihypertensives and reasons to take medication. Individuals balanced their views for and against continued adherence. However, most important was the recognition that the patient's views may be unrelated to the pharmacology of the drug e.g. patient might see the taking of medicines as an indicator of weakness in their character or upbringing. Furthermore, while several patients may have similar perceptions, each patient may weigh that perception differently.

Only by eliciting each individual's health beliefs for and against treatment can a doctor or pharmacist hope to arrive at a treatment plan that is concordant with the patient's beliefs.

1.6 Methods of detecting and measuring adherence to medication

1.6.1. Introduction

The identification and measurement of adherence is an immense subject and so to provide some focus to the thesis, this part of the discussion will focus upon adherence to antihypertensive medication.

An important area requiring a standardised approach is the choice of the *quantitative* criteria used to describe adherence e.g. the percentage of medication taken during a specific time or the percentage of medication doses taken at the correct time and or correct dose. The detection and measurement of adherence has been attempted using a wide range of methods and in many cases it is difficult to make comparison between different studies.

In clinical practice, the need to detect low adherence is driven by the need to distinguish between treatment failure and low adherence. The former can be resolved by modifying the regimen, while low adherence requires the doctor to explore, with the patient, the reasons for the non-adherent behaviour. While the clinical detection of non-adherence is of prime concern, the quantitative measurement of adherence can also fulfil a clinical need. Adherence is rarely absolute, and it is quite possible that both a sub optimal drug regimen and non-adherence are responsible for the failure to reach a therapeutic goal. The necessary level of adherence to antihypertensive drugs to achieve clinical benefit has been described as "at least 80%". While there is evidence to support this generalisation, the actual level will probably vary from patient to patient and from drug to drug[38].

Direct questioning of the patient and self-reporting is the easiest method to use in clinical practice while in recent years, electronic monitoring has been heralded as the "Gold Standard" for adherence monitoring, especially in the research setting. However, these two techniques are only part of a spectrum of methods, most indirect and some direct. In the following sections, these methods are described, compared and contrasted with particular reference to the measurement of adherence to antihypertensive drug treatment.

The methods include:

- Self-reported adherence
- Lack of therapeutic response
- Doctor's perceptions
- Attendance for follow-up appointments
- Tablet counts
- Prescription re-fills
- Monitoring side effects of the drug
- Monitoring the concentration of the drug in urine or blood
- Measuring of the concentration of a marker in urine or blood
- Electronic monitoring

Sophisticated quantitative methods such as electronic monitoring can also help to identify specific patterns of adherence and expose fundamental misunderstandings that the patient may have about the intended drug regimen. As with all clinical research methods, the method selection will depend upon a myriad of factors, not least of all convenience, reliability and cost.

Accurate detection and measurement of adherence is not only an important research goal but is at the heart of clinical decision-making. Most physicians make a subjective judgement of their patient's adherence but many studies have shown this subjective assessment to be frequently inaccurate and inconsistent. It is therefore important for physicians and researchers to have objective and reliable methods of assessing adherence.

1.6.2. **Self-reported adherence**

This method involves direct questioning of patients about how they take their medicines and may involve a structured questionnaire containing direct questions about the way that they take medicines. Many studies have attempted to detect and quantify adherence in several diseases via structured patient interviews (questionnaires). Patient self-reporting is often considered to grossly over estimate adherence[6]. This received wisdom stems from many early studies from the 1960's and 1970's, which compared self-reporting of adherence with tablet counts or with therapeutic monitoring of drug or metabolite concentrations in the urine.

Since the 1980's, self-reporting of adherence has regained favour as a method, mainly due to improvements in the method of eliciting self-reports, a greater appreciation of the patient's perspective on adherence and due to studies that have shown a good correlation with treatment outcome. It is relatively easy to use this method and despite the known tendency for patients to over estimate their adherence, it has been shown to correlate with blood pressure control. In a study of 400 out-patients taking medication for hypertension, a four-item self reported scale measuring medication taking behaviour, was shown to have concurrent and prospective validity with regard to blood pressure over 42 months[39]. This measure is discussed in detail in section 0 below

There have been negative results when trying to use the four-item Morisky measure in Spanish patients treated for hypertension[40], diabetes[41] and dyslipidaemia[42]. In these studies, the four-item self-reporting instrument was compared to five other methods of measuring adherence. However, the validation of the translation is not described and the clinical setting was different and included home visits.

Patient self-reporting of adherence is expected to over estimate the true level of adherence, however, by using carefully crafted questions, it has been shown to be a useful instrument for assessing medication adherence in chronic diseases including hypertension. It does not offer the precision of tablet counts or electronic monitoring but in terms of addressing the important question: "is the lack of therapeutic effect due to low adherence?" self-reporting is a very useful tool. These instruments are simple to use in a clinical setting and, once developed, they are inexpensive to administer. As such, a self-reported measure was chosen as the main adherence-monitoring tool in the research work that is described in chapter 3 below.

1.6.3. Lack of a therapeutic response

In hypertension, the most important clue to non-adherence is a lack of the expected therapeutic response. However, while low-adherence is undoubtedly a major reason for failing to reach the target blood pressure in some patients, across the whole population it may only account for half the problem, suggesting that the drug regimen may be inadequate or inappropriate for that patient. Similarly, many "controlled hypertensives" are found to be non-adherent. The relationship between non-adherence and failure to reach clinical goals in hypertension is discussed in section 2.9.4 below.

1.6.4. Doctor's perceptions

Most doctors will over estimate the medication adherence[4] and this is true even in patients who the doctor has known for long periods of time. Many studies have shown that the doctor's subjective assessment is frequently inaccurate and inconsistent. This has been shown across a variety of conditions and drugs including Digoxin[43], hypertension[4], hyperlipidaemia[44] and asthma[45].

A typical finding is that of Gilbert et al[43]. Ten family physicians were asked to predict adherence to digoxin therapy. This was compared with a pill count at a home visit and measurement of the serum digoxin level at that visit. Out of 74 patients, 70% were found to be taking more than 80% of their pills and 86% had a therapeutic serum digoxin level. The ten physicians were unable to predict compliance better than chance, even for the 58 patients they had known for five or more years.

One study compared the doctor's perceptions of medication adherence with the self-reported adherence of 138 adult patients treated for asthma[45]. The self-reporting measure was a slightly modified, four-item Morisky self-reporting measure (see 1.6.2 above) and doctors were asked to rate the adherence as "High", "Medium" or "Low" but the doctors were not given any guidance as to what each level of adherence equated to. The study is of great relevance to this research as it involved adherence to chronic therapy and the doctor's perception were compared to a variation of the Morisky self-reporting measure, as used in this research. Sixty two per cent of patients reported that they were adherent (38% reported medium to low adherence) compared with the doctors who considered 74% of the patients to have a high adherence to the medication regime. However, there was no association between these two groups at the individual patient level. Of the 81 patients, who reported that they had a high

medication adherence, the doctors assessed only 43% as having high adherence. The study showed that the doctor's assessment of adherence was related to the doctor's perceptions of; the seriousness of the medical situation, the effectiveness of treatment, the quality of communication and the disease knowledge of the patient (each one assessed as "High", "Medium" or "Low"). None of these factors were positively related to the self-reported adherence measure. The doctor's perception of the seriousness of the medical situation was negatively related to the patient's self reported measure. Patients described by doctors as having a serious medical situation were more likely to report high medication adherence, compared with their doctors who were more likely to predict medium to low medication adherence ($p<0.05$).

It would be valuable to have a similar insight to UAE doctor's perceptions of adherence, as this would be a useful starting point in improving doctor patient communication and a first step towards concordance.

1.6.5. Attendance for follow-up appointments

Primary non-adherence can be assessed by attendance for follow up appointments. It is a relatively crude marker but helps to identify those patients in whom adherence is a problem. Various studies in the literature show the dropout rate from keeping appointments varies widely from 50% after 2 years at a private clinic[46] [47], to 15.5% after one year at a hospital hypertension clinic[48]. This method assumes that the clinic under investigation is the sole source of the patient's healthcare. It is easy for this method to overestimate non-adherence in an environment like the UAE where patients have easy access to a choice of government hospitals and health centres, workplace health centres and private healthcare (see section 3.2, Healthcare sector in the UAE). However, if the patient can be persuaded to bring all their medications with them, it is easy data to collect and is a useful cue for the doctor or nurse to ask about the tablet taking behaviour and will help to build up a picture of whether or not the patient is adherent.

1.6.6. Tablet counts

Historically, tablet counts have been the most common method of assessing adherence with anti-hypertensive drugs. It is now generally considered to be an inadequate method of assessing compliance and generally over estimates the consumption of medicines[49]. Controlled studies in a wide range of clinical

situations have consistently shown the tablet counts to be an inadequate measure of adherence.

The number of tablets remaining with the patient can give an indication of tablet under use or overuse. In some studies, the count is done when the patient attends for their follow-up appointment. The tablet container is retrieved and the number of tablets is counted. Alternatively, the count can be performed during a home visit. If the count is to be performed during the follow-up appointment, it is important that the patient receives more tablets than are required to cover the period up to the next appointment, otherwise over-consumption will present as perfect adherence. In many study reports, it is not always clear if excess tablets had been supplied.

Asking the patient to bring their tablet container to the next appointment may prompt patients to discard any unused medication prior to their appointment. It has been shown that weekly tablet counts provide better data on adherence than long-term, average tablet counts[50]. Some researchers consider the technique to be discredited but perhaps overlook the fact that Sackett and colleagues, in their study of adherence in Canadian steelworkers used tablet counts[38]. This research identified that a significant reduction in blood pressure was only seen if more than 80% of doses had been consumed. This figure of 80% is widely accepted despite the criticism levelled at tablet counts.

One study compared tablet counts with the use of a very low dose marker (see section 1.6.11 below) and showed that in a minority of patients (9%) tablet counting is totally misleading[51]. Electronic monitoring has shown that among epilepsy patients taking anti-epileptic drugs, similar tablet counts can be obtained from very different degrees of non-adherence[52]. In a study of adherence to tricyclic antidepressants, in 23% of patients (n=84), the number of tablets removed was very much higher than the number indicated by the number of times the bottle was opened[53]. The tablet count method remains popular in clinical trials partly due to the ease of its use and the need to account for and to trace all clinical trial materials used in the study. It has been used in most major cardiovascular studies during the 1990's including the major lipid lowering studies, WOSCOPS[32] and 4S[54].

1.6.7. Prescription refills

Adherence has been measured by monitoring whether or not prescriptions are taken to the pharmacy for dispensing. Failure to have the prescription dispensed is a component of primary non-adherence may or may not be intentional and can occur despite the patient attending for follow-up appointments.

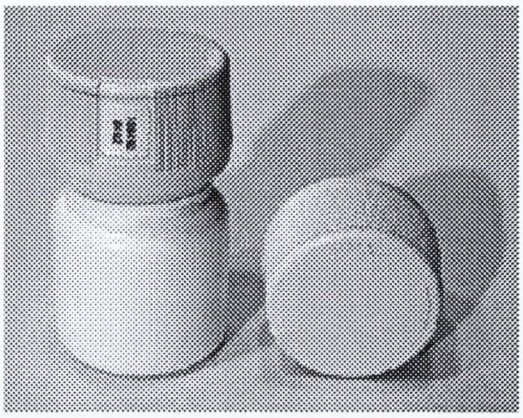
Adherence with hydrochlorthiazide in hypertension was estimated to be 61.2% after studying prescription refills over a 6-month period[55]. The study also found that the refill rate also correlated with reduction in the mean diastolic blood pressure. There have been several reports of this method being a used to identify non-adherence, but most reports find that the pharmacy data is not complete and too difficult to interpret with any certainty[56]. In a review of 41 studies where prescription re-fill data was used as a measure of adherence, the conclusion was that the method could be useful in population-based studies[57]. The validity of this method depends upon the completeness of the pharmacy database and as technology and pharmacy databases become more sophisticated this method will become a useful way of detecting low adherence. Organisations such as the US Veterans Administration have large patient and prescription databases and have reported the method to be useful at identifying adherence differences between different classes of antihypertensives[58]. In the UAE, the "databases" are currently manual, so refill counts would be a very labour intensive task. However, refill rates are probably high as medicines are free for UAE nationals and the pharmacy waiting times are relatively short.

This method shares many of the disadvantages of monitoring clinic attendance. It provides no information about what the patient actually does with the prescription after it is dispensed and therefore must be used along with other adherence monitoring techniques.

1.6.8. Electronic monitoring

The most important development in the measurement of medication adherence is electronic monitoring. Electronic monitoring devices have been developed for a range of dose forms including loose tablets / capsules, unit doses, metered dose inhalers and eye drops. Research into adherence to antihypertensive medication has mainly used a device called the Medication Event Monitoring System (MEMS), which works with loose tablets. The Aardex Corporation of Switzerland (www.aardex.ch) now markets the MEMS device internationally (Figure 1).

Figure 1The MEMS® device by Aardex



It is a standard tablet container with a cap containing a spring-loaded device that, when opened, operates a switch connected to a microprocessor recording the date, day and time of opening. The data is downloaded via an induction device to a PC. The device, developed in the mid 1980's, has been refined into a robust device with a two-year battery life. The device allows one to monitor the frequency and time of opening of the tablet bottle. This allows measurement to move beyond the total number of doses consumed to include delayed or multiple doses. The use of the MEMS device has confirmed the existence of "drug holidays" whereby adherent patients may omit doses for three or more days such as a weekend or longer[59].

While the MEMS device is measuring bottle opening, and not medicine ingestion, the correlation appears to be very good, especially in controlled studies such as clinical trials. The first credible data came not from hypertension studies but from a study of adherence to lipid lowering medicines[7]. This MEMS study found a significant correlation between the percentage of the dose of lovastatin consumed (assessed by bottle opening) and reduction in LDL cholesterol.

The MEMS devices cost between $US 70-100 per device and they can be sent back to the manufacturer for downloading of data or the reader device can be purchased separately. The devices are approved for single patient use only although there is no practical reason for this beyond the risk of cross contamination through drug residues on the cap liner, a low risk with film coated antihypertensive tablets.

The device can record the precise time and date of up to 1800 openings and it is claimed to be accurate to the nearest 30 seconds, but the validity of the data relies upon formal calibration of the device and several assumptions.

Figure 2 Key assumptions with the MEMS device

The MEMS packaged drugs is the only supply that the patient has available to them
The patient takes the full dose each time it is opened
Patients do not decant additional doses from the container
The MEMS cap does not alter adherence behaviour
Patients who consent to use the cap are a representative sample

One must assume that the patient has only one source of the medicine (the one in the MEMS bottle) and that they remove only the dose required at the time of opening the bottle. Clearly, a patient could take only part of the dose if each dose is more than one tablet. Most tablets are now packaged in blisters, especially in hot and humid markets such as in the UAE. While blister strips can be folded to fit into the containers, this gives the patient the opportunity to remove the strip for convenience. The cutting of blisters into individual doses or de-blistering of tablets to go in the MEMS could have a negative effect upon adherence. Many blister packs assist adherence by printing the day of the week on the back of each tablet, and any blister provides a useful check by allowing one to count the number of tablets missing or remaining. These potential benefits would be lost if the blister was cut or discarded. Furthermore, the effect of de-blistering on the shelf life of tablets in a hot and humid environment has not been addressed.

Some commentators have questioned whether or not the use of the MEMS cap is itself an intervention, in that it may encourage patients to be more adherent[60]. However, most MEMS studies are over a period of at least one month or longer and it is hard to imagine a non-adherent patient maintaining the effort to use the MEMS at the right time every day for the duration of the study. However, the MEMS device can be used as an aid to adherence and Aardex do market a version of the MEMS device that is designed to promote adherence through reminding patients with an alarm and showing the number of times it is has been opened that day. Another, unresolved issue relates to assessment of adherence to multiple drug regimes. MEMS hypertension studies have usually involved only one medication, although there have been studies of multi-drug regimes in HIV and AIDS patients. While one could select one of the medications to be a "reference" drug study using MEMS (as in the HIV studies), there is no research

looking at whether this would preferentially enhance the adherence to that medication at the expense of the other medications.

Some of these issues have been highlighted in a study of 64 men taking combination antiretroviral therapy (HAART) in an HIV clinic[61]. Antiretroviral therapy involves multiple medications and adherence is important to ensure effectiveness and to minimise resistance to the drugs, especially the protease inhibitors. The patients received one of their antiviral drugs in the MEMS container. These patients had a variety of reminder techniques including decanting medicines from the dispensed containers. The common use of decanting in to weekly or daily "pill boxes"[E] (42%) reduced the usefulness of the MEMS cap. Seventeen patients (27%) reported that the MEMS cap had altered their adherence. Eight of them (13% total) felt that the MEMS cap had made adherence harder and nine (14% total) felt that it had improved adherence. Two patients mentioned both! However, those consenting to the use of a MEMS cap appeared to be representative of the eligible population. This study may be more applicable to patients taking antihypertensive drugs than it first appears. Many hypertensives are taking more than one antihypertensive drug and up to 30% will be taking medicines for other chronic diseases such as diabetes. Any study that excluded these patients would not be representative of the typical hypertensive population.

As a research tool, the MEMS device has allowed unparalleled insight in to the tablet taking behaviour of patients, and has allowed the spectrum of medication non-adherence to be described more fully than ever. However, there are several practical problems, including cost and it's applicability to multi-drug regimes, which could limit its wider use as a practice based method of monitoring adherence.

1.6.9. Monitoring side effects of the drug

Several antihypertensive drugs have predictable side effects. The absence of these side effects may indicate non-adherence and this has been compared with tablet counts and self-reporting of adherence. Thiazide diuretics promote a dose dependent net loss of potassium, which can be manifest as hypokalaemia during routine blood chemistry analysis. Thiazide diuretics can also cause a dose-dependent rise in serum uric acid. A study of a small sub-group (134) of Sackett's famous cohort of Canadian steelworkers, found that changes in the

serum potassium and uric acid did not correlate well with tablet counts in patients taking chlorthalidone and hydrochlorthiazide[62]. It was found that compared to tablet counts, two thirds (66-67%) of non-adherent patients were identified by the drop in their serum potassium or rise in their serum uric acid, this compared with a 91% detection rate when using self-reporting. The potential usefulness of monitoring serum potassium in modern practice will have been greatly diminished due to the decrease in the use of chlorthalidone, which causes significant potassium loss compared with other thiazides; the common use of effective potassium sparing diuretics and the modern practice of using much lower doses of thiazide diuretics than twenty years ago.

Other side effects may also provide clues to the level of adherence with antihypertensive drugs. Beta-blockers are expected to lower the heart rate; Verapamil is expected to cause constipation, and in the early stages of treatment, many patients taking vasodilating calcium channel blockers such as nifedipine and diltiazem will complain of flushing and tachycardia. However, some of these effects ameliorate with time and as all of these effects are dose dependent side effects, their absence may only be truly indicative of low adherence when the drugs are used at above average doses and therefore be expected to produce clinically detectable side effects in most patients. The absence of side effects is therefore a useful clue to be noted in patients who have not responded to antihypertensive treatment as expected despite maximal doses of the drug.

1.6.10. **Monitoring the concentration of the drug in blood or urine.**

One of the few direct measures of medication adherence is to measure the drug in the blood. For many drugs, urinary drug concentration data could be used in place of serum, especially for qualitative data ("is the drug present?"). Quantitative studies require the collection of cumulative urine data, and hence, multiple samples. Because of the development of accurate and simple tests that use a single serum sample, urine pharmacokinetic analysis is rarely used outside of clinical pharmacokinetic studies.

Therapeutic drug-level monitoring (TDM) has become a valuable tool for optimising therapy with drugs that have a small therapeutic index.

[E] Clearly labelled, compartmentalised trays containing individual doses for a day or week

Figure 3 Examples of where TDM is used in the clinical setting

Antibiotics: aminoglycosides, vancomycin
Asthma / COPD: theophylline,
Cancer therapy: methotrexate
Cardiology: Digoxin, some anti-arrhythmic drugs
Epilepsy: some anti-epileptic drugs.
Psychiatry: Lithium, carbamazepine, valproate
Transplant medicine: ciclosporin

The technique requires there to be a predictable relationship between the dose, blood concentration and clinical effect of the drug. It must also be possible to quickly and accurately measure the concentration of the drug (or a metabolite) in the blood in a clinical setting.

The measurement of the blood drug concentration in one or more accurately timed blood samples can enable one to calculate the optimal dose by using simple first order pharmacokinetic equations. The same method can also be used to compare how the blood concentration compares with what is expected on a certain dose. If one does not have prior data about the pharmacokinetics of the drug in that patient or does not have more than one sample from within a dose interval, then one can use "population" data. Population data describes the pharmacokinetics are derived from controlled pharmacokinetic studies in volunteers or patients and describes the pharmacokinetic behaviour of a drug in an "average" person. However, the application of TDM to outpatient therapy is limited to a relatively small range of drugs such as those in Figure 3, many of which are used parenterally, and does not include anti-hypertensive drugs.

As well as helping to calculate the optimal dose, one can also use pharmacokinetic techniques to study adherence. The pharmacokinetic profiles of, digoxin and lithium are quite easy to predict for a patient given their age, weight and renal function. If one has an accurate timing for the dose taken prior to the sample then it is relatively easy to spot a patient who has missed doses. However, if the drug has a shorter half-life (less than 24 hours), even after missing doses for several days, patients can reach the steady state level quite quickly after re-starting the drug. Therefore, for most medicines the usefulness of this technique is limited to identifying adherence problems during the preceding three to seven days. Most medicines have a half-life that is 24 hours or less and

within five days of stopping the medicine, it would be eliminated from the body. Certain medicines, such as digoxin, have a much longer half-life (30-40 hours), especially in the elderly and in others with diminished renal function. For these groups, changes in the blood level happen quite slowly after changes to the dose. This makes it difficult to be specific about whether or not doses have been missed recently, or if the lower than expected blood level reflects a long-term, partial adherence. The pharmacokinetics of many anti-epileptic drugs are quite variable and for drugs such as phenytoin, population data is not a very reliable basis for predicting what the blood level should be given a particular dose.

TDM assumes a predictable relationship between the dose and blood concentration and conclusions derived from TDM are conditional on this assumption being valid. There are many patient and disease factors that can alter this relationship, therefore a complete patient and drug history and the clinical experience of the TDM researcher are vital. Partial non-adherence is not easily distinguished from high adherence or from low adherence followed by the doubling up on doses during the days prior to the blood sample. This has been described as "white coat adherence" and is thought to be very common in clinical trials[63].

TDM is a useful technique for identifying low-level adherence and discontinuation of certain drugs. This thesis focuses on adherence to antihypertensive medicines and unfortunately, there are no antihypertensive drugs for which TDM is of any practical benefit. Antihypertensive drugs have a poor correlation between dose, blood concentration and effect, and there is very little validated population data regarding their pharmacokinetics at therapeutic doses and the simple drug assays are not routinely available.

It would appear that there is little value in utilizing TDM for common antihypertensive drugs. There have been a few examples of adherence being measured in other disease states by monitoring the drug in blood or urine, even though the drug is not normally associated with therapeutic drug-level monitoring. These include monitoring urinary oxytetracycline in men taking it for non-specific urethritis, the lipid-lowering drug gemfibrozil in the urine and the tricyclic antidepressant dothiepin in the blood. Urinary oxytetracycline was unreliable when compared with patient interviews and monitoring of a low dose marker[64] (low dose markers are discussed in 1.6.11 below). Gemfibrozil urinary monitoring was used in a sub-study of the Helsinki Heart study and was no more useful than

direct questioning or the use of a low dose marker[44]. Monitoring dothiepin blood levels in depressed patients treated as outpatients was generally unacceptable to patients and comparison with electronic monitoring in the same patients showed that the patient's report of the timing of the dose prior to the sample (a crucial piece of data) was almost completely unreliable. Monitoring the blood concentration ratio of dothiepin to it's metabolite, nor-dothiepin could be more useful but only in patients with high blood concentrations of the parent drug[53].

Therefore, quite apart from the absence of a reliable dose-blood concentration relationship or population pharmacokinetic data, there is little evidence to suggest that monitoring the blood or urine would be a useful method of measuring antihypertensive drug adherence.

1.6.11. Measuring the concentration of a marker in urine or blood

An alternative to TDM is to formulate the medicine along with a low level of a marker substance. Such a marker should be clinically inert, have a slow turnover in the body and be easily measured at low concentrations in blood or urine. The most widely reported are phenobarbitone (half life of 50-100 hours) or digoxin (half life of 30-40 hours). As the pharmacokinetic properties of the marker substance are well known and the dose is in a fixed ratio to the dose of the drug under study, then by measuring the concentration of the marker in the blood or urine one can estimate how many doses have been missed. There are several practical and ethical limitations to using this technique.

The use of a suitable marker substance has been used to good effect in several studies. Feely and colleagues in the UK used very low doses of phenobarbitone (2mg compared with an adult therapeutic dose of around 120-180mg per day) as a marker substance to monitor adherence in patients taking methadone for the treatment opiate addiction[65], [66].

In the Helsinki Heart Study, digoxin was used as a very low dose marker to monitor adherence to the lipid lowering drug gemfibrozil. Good adherence, as assessed by the level of digoxin in the blood corresponded with 73% adherence as measured by tablet counts and 89% adherence when measured by self-reporting[44],[67].

Although the marker technique continues to be used in developing countries, most recently as a marker of adherence to the antimalarial artesunate[68], most ethics committees in developed countries would require that the patient must not only be informed of the presence of the marker drug but must also consent to its

use. An editorial in the Lancet concluded that the use of a very low dose marker was an effective method of measuring adherence but that it was best to limit its use to clinical trials[69].

1.7 Usefulness of different methods in routine clinical practice

The selection of a method for detecting and measuring medication adherence will depend upon the setting and reason for studying the adherence. The focus of this thesis is the identification of non-adherence to antihypertensive medication in a routine consultation at a primary health care centre.

There are several characteristics for an ideal instrument to detect non-adherence in such a setting but three key considerations will be; reliability, convenience and cost. Figure 4 below, presents a summary of this author's subjective assessment of the usefulness of several methods for identifying non-adherence to antihypertensive medication in a primary care setting.

Figure 4. Comparative usefulness of methods for identification of non-adherence to antihypertensives in a routine primary care setting

	Marks out of 5*			
	Reliability	Convenience	Cost	Total
Direct questioning / Patient self-reporting	4	4	5	13
Lack of therapeutic response	3	5	5	13
Doctor's perceptions	2	5	5	12
Attendance for follow-up appointments	3	3	3	9
Tablet counts	4	2	3	9
Prescription re-fills	3	3	3	9
Electronic monitoring	5	2	2	9
Monitoring side effects of the drug	1	3	2	6
Monitoring the concentration of the drug in urine or blood	4	0	1	5
Measuring of the concentration of a marker in urine or blood	3	0	1	4
*Author's subjective rating on scale of 1-5 where 0 = Not available,1=poor and 5=excellent				

This comparison was used when studying the options for developing and instrument for routine use at the health centres and one that could be used to study adherence in this thesis.

The reliability rating has been assigned after reviewing the work summarised above. It ranges from electronic monitoring (5) which is considered the "Gold standard" through to monitoring side effects (1), which is dose and individual dependent and ill suited to the modern tendency to use combinations of drugs at minimal doses. The convenience and low cost of relying on the doctor's perceptions or monitoring the therapeutic response are good reasons for using these to monitor adherence in clinical practice. However, the "low cost" fails to recognise the indirect cost of failing to minimise the long term morbidity due to hypertension or of continuing to prescribe medication to a person who does not need it. As adherence is probably responsible for around half of the failures to respond to sustained drug treatment, it will rarely be accurate in more than 75% of cases. The doctor's perceptions and the patient self-reporting should be equivalent as they have every opportunity to elicit a self-report from the patient. However, the method and structure of eliciting such a report seems to be the key to accurate self-reporting.

Therefore, a carefully designed, simple self-reporting measure is the best chance of improving the identification of adherence in routine clinical practice.

1.8 Factors determining adherence

1.8.1. Introduction

It has become almost routine practice for adherence studies to try to relate certain factors or characteristics to the adherence trait of the patient. Over 200 factors have been studied for their affect on adherence over the last 30 years. Over 30 of them are discussed in this section, with an emphasis, where possible, on adherence in hypertension. They are divided into three categories for ease of discussion.

- Patient factors
- Drug factors
- Environmental factors

Clearly, some factors are inter-related such as age and education, or education and socio-economic status; however, the association with adherence is inconsistent. Figure 7 provides a summary.

The practical use of these associations is discussed in 1.8.6.

1.8.2. Patient factors

Various "Patient factors" have been seen to have a bearing on adherence to chronic medications, including hypertension. These include: Gender; Age; Working or Retired; Socio-economic status; Smoking; Psychiatric and psychological factors and patient attitudes towards treatment and disease. They are discussed below.

1.8.2.1. Beliefs and regarding treatment and disease

The health beliefs (cognitions) of a patient regarding the treatment regime and the disease play a major role in determining adherence. Even in screening programs (pre-diagnosis) self-reported intentions and health beliefs could correctly distinguish between those who did and did not attend in 82% of cases[70]. In hypertension and other chronic diseases fears of addiction, side effects and fundamental misunderstandings about the nature of hypertension can result in low adherence. These are reviewed in 1.5 above. Many of these fears have been unspoken until solicited through structured interviews and this fact highlights the need for doctors and pharmacists to elicit the patient's cognitions about treatment.

It is important that any assumptions made by the professional are validated. Adherence to opiate analgesics in cancer patients is sometimes lower than expected. The common assumption is that this is because of the patients' fears of developing addiction. In a study of 65 adult cancer patients who were receiving opiate analgesics as outpatients, the patients kept a diary for 5 weeks. It was found that the most common reason for patients missing doses of opiate analgesics was the actual side effects that they experienced, not a fear of addiction, as many physicians believe. What's more, the main cause of the side effects was an inappropriately prescribed opiate regimen[71].

Patients who associate physical symptoms with their high blood pressure appear to be more likely to be non-adherent. In the vast majority of cases, there is no association between raised blood pressure and physical symptoms. However, many patients associate their blood pressure with headaches and feelings of "tension". The problem with this is that the absence of these "symptoms" may suggest to the patient that their blood pressure is now controlled and medication is not required, leading to low adherence. One study reports the results of interviews with 230 patients about hypertension[72]. Fifty of these patients were normotensive controls, of whom, 49% believed they could monitor their blood pressure by physical symptoms. This rose to 94% of 65 patients who had previously stopped treatment but re-started. Among the 180 treated hypertensives, if a patient mentioned "symptoms" of hypertension in their first appointment then they were more likely to dropout of treatment. It was also found that those patients who considered hypertension to be of a cyclical nature were more likely to dropout of treatment. The association of headache with blood pressure is discussed further in section 2.9.5 below.

Patient beliefs can change with time and are seen as an important target for interventions to improve adherence.

1.8.2.2. Gender

Studies have shown that men are less likely to be adherent with chronic medications. The reason has not been well described but one possible explanation is that many women are more practiced with taking chronic medication in the form of oral contraceptives[73].

1.8.2.3. Age

It is widely believed that older patients are less adherent than younger patients; however, the opposite has been found in many studies. Most studies compare

between patients aged below and over 60 years. This is an arbitrary breakpoint and sometime stems from the inclusion criteria in clinical trials. As the treatment of hypertension in the very old (more than 80 years) becomes more common, studies have started to report adherence rates for this group. Age cannot always be separated from other factors such as gender (women live longer) and working vs. retired (most older patients are retired). Some studies have found there to be no correlation between age and adherence. One study monitored attendance at follow-up appointments and tablet counts in over 10,000 patients aged 30-69 years, as part of the US Hypertension Detection and Follow-up Program (HDFP)[74]. In the SHEP study of the treatment of systolic hypertension in the elderly, high levels of adherence were found in patients after 3 months and 1 year of treatment with chlorthalidone or placebo using a mixture of tablet counts, self reporting and urinary chlorthalidone tests[75]. This included patients over 80 years of age. A longitudinal study of patients with chronic medical diseases (hypertension, diabetes, heart disease) was conducted to identify antecedents of adherence to medical recommendations in three US cities. Among other findings it was shown that patients who were younger and who relied upon avoidant coping strategies tended to be less likely to follow their doctor's specific recommendations[76]. The same observation was made in a cross-sectional study in 197 patients attending a specialized clinic for hypertension[77]. In a pilot study, the medication-taking behaviours of 48 adults diagnosed with hypertension, ranging in age from 35 to 87 years, were recorded for two months electronically [78]. It was found that the "oldest-old" (over 80 years) and middle-aged adults (under 60) were the most non-adherent, whereas the "young-old" (60-80 years) were more likely to adhere than the other age groups. It was not clear how many of the "oldest-old" might have had significant cognitive impairment. In a short-term study of adherence with a once daily ACE inhibitor in 2,173 French patients (aged 60±12 years) using MEMS monitors (see section 1.6.8), low adherence (taking less then 80% of doses) was found in 45% of those less than 60 years compared with only 30% of those over sixty years[73]. Higher levels of primary non-adherence may temper the higher levels of adherence among older people. A market research study from the USA found that among people over 60 years, up to 63% of prescriptions were not redeemed, compared with only 29% in younger patients[15]. The reasons for this were not apparent from the study but it was conducted in an environment where medication involved out of pocket expenses. Perhaps more elderly patients face financial difficulties than do younger people?

However, it is not so straightforward, as lower adherence has been seen in more wealthy older patients (see below1.8.2.5).

Apart from primary non-adherence, the general indication is that adherence in elderly patients is higher than in middle-aged patients and this has been shown amongst those taking antihypertensive medication.

1.8.2.4. Working or retired

Patients who work have been found to have lower adherence than retired patients do. Clearly, this isn't completely independent of age, as most people who are retired are over the age of sixty and this group has been shown to have higher levels of adherence (see 1.8.2.3). A translated abstract of a study of 174 hypertensive patients in primary care setting reports that low-adherence with scheduled visits was associated with being a housewife or with working activity[79]. A large, short term study [73], found that 43% of working patients missed more than 20% of doses, compared with only 29% of retired patients. Clearly it is likely that being too busy could explain the non-attendance or forgetting doses and highlights the reality that chronic medication regimes that fit conveniently into peoples lifestyle will encourage adherence.

1.8.2.5. Socio-economic status

Socio-economic status is difficult to define and measure. It is not a common feature of adherence studies, perhaps because it is not a truly independent factor. Higher socio-economic status is usually associated with having a job and higher education levels. Continuing access to healthcare and primary adherence generally improves with increasing socio-economic status; especially if out of pocket expenses are involved. A three-year prospective study of 1346 outpatient hypertensives found a drop out rate of 15.5% after the first year. Variables that were significantly related to increased drop out rates were low socio-economic status, along with male sex, young age, obesity at entry, cigarette smoking, direct referral to the clinic as a result of screening instead of referral by a general practitioner, absence of pre-existing antihypertensive treatment at the first visit, and moderate hypertension[48].

However, the effect of socio-economic status on adherence in patients who persist with treatment may be different. Interviews with 785 independently living adults aged 55 years and older (mean age 73.9 years) taking antihypertensive medication in the south-eastern United States, collected data on background characteristics, physical health, life satisfaction, psychological distress, and

medication compliance[80]. Overall, self reported adherence to medication was 79%. Non-adherence with prescribed medications was significantly associated with higher socio-economic status while age was not an independent-factor affecting adherence. Higher socio-economic status in older patients is expected to improve adherence by reducing the impact of out of pocket expenditure on drugs and hence, by reducing primary non-adherence; however, this would not have been detected as these patients were already "within the system" and by definition, were primarily adherent.

1.8.2.6. Smoking

Most hypertensives that smoke will be advised to stop smoking by their doctor; however, many continue to smoke. Smoking may therefore be an indicator of patient beliefs and attitudes towards the management of their hypertension and the patient's ability to modify their life-style to help reduce the blood pressure. Not many studies have been able to study the role of smoking as an independent factor in medication adherence. Cigarette smoking was an independent risk factor for low-adherence in the study by Degoulet *et al* (1983)[48]. In the study by Vaur *et al*[73], 49% of smokers were none adherent compared with 34% of non-smokers. Smoking and the inability to stop smoking are related to psychological stress among other things. It may be that in some patients, smoking is a marker of stress, and this may affect the patient's ability or decision to adhere to treatment. Both of these studies were performed in a European population, it is not clear how well the relationship between smoking, and non-adherence can be extrapolated to other ethnic groups. A study of 156 Indian hypertensives (mean age 55 years) attending a teaching hospital cardiology clinic used tablet counts to monitor adherence found that smoking was not significantly related to uncontrolled hypertension or non-adherence[81].

1.8.2.7. Psychiatric and psychological factors

Studies have shown that various psychiatric and psychological factors are related to decreased adherence, e.g. stress, anxiety and depression. In one US study of 1028 independent adults, higher psychological stress was identified as one of the independent factors associated with non-adherence[80]. Among hypertensives attending an Indian teaching hospital Cardiology department (median age 55 years), higher psychological stress (assessed by means of a Life Event Score calculated from interviews), was a factor associated with non-adherence to medication and uncontrolled hypertension[81] (see 1.8.2.1).

Anxiety and depression have been shown to be a characteristic of less adherent hypertensive patients. The adherence of 174 hypertensive patients receiving antihypertensive drugs in primary care was assessed by attendance for routine doctor appointments. Anxiety along with work activity and obesity were all characteristics of the non-adherent patient[79]. However, this information is gleaned from the translated abstract and detail of the definition and detection of anxiety is not available. A meta-analysis of the literature found the relationship between anxiety and non-adherence to be weak, but that depression can have a significant impact[82]. In this meta-analysis of 12 adherence studies about depression and 13 about anxiety, the associations between anxiety and non-adherence were variable, and their averages were small and not significant. However, the relationship between depression and non-adherence was substantial and significant, with an odds ratio of 3.03 (95% confidence interval, 1.96-4.89) i.e. depressed patients are three times more likely to be non-adherent. This is an important observation as clinical depression is generally under diagnosed, and in many ethnic groups, psychiatric conditions such as depression carry a substantial stigma. It could therefore be an unrecognised but common factor leading to low adherence, and conversely, non-adherence could be a marker for undiagnosed depression.

1.8.3. Drug factors

Various "Drug factors" have been shown to have a bearing on adherence to chronic medications including antihypertensive drugs. They include: Duration of therapy; Number of medications; Number of Daily Doses; Cost of Treatment and the type of antihypertensive drug.

1.8.3.1. Duration of therapy

Studies have reported that adherence is higher when the patient has been taking the medicine for longer. There is an unavoidable bias to this observation, as the least adherent patients will have probably dropped out from treatment completely within the first 6-12 months. The remaining patients may, have greater adherence. However, the relationship between duration of treatment and adherence is not consistent. Following interviews with 197 hypertensives to elicit self reported adherence, adherence was generally lower in those patients who had been taking the medication for longer[77]. However, the strongest relationship, which was between the patients' "barriers" to treatment (perceived "costs" of treatment) and the patients' barriers to adherence, remained constant, regardless

of the duration of treatment. In the large-scale study of adherence in 2173 patients using MEMS, the level of adherence (taking more than 80% doses correctly) was 60% in people diagnosed within the last 29 months, compared with 67% (p=0.001) in those who had been diagnosed more than 29 months ago[73]. However, this study also showed that while time since diagnosis could be shown to be an independent factor, it is closely related to the number of antihypertensive drugs (doctors usually prescribe in a step-wise manner over time).

1.8.3.2. Number of daily doses

In studies that report the impact of daily doses upon adherence to antihypertensive drugs, the number of daily doses often refers only to the number of antihypertensive drug doses i.e. how many times per day does the patient take the drug and does this affect the adherence? However, many hypertensives are taking a variety of medications for co-morbidities, both chronic and short-term, both prescription and over the counter. Therefore, the number of daily doses becomes difficult to separate from the number of drugs.

Following a systematic review of 76 studies (1986-2000) that used electronic monitoring to measure adherence, data was pooled to determine the mean adherence in patients taking once, twice, three times and four times daily drug regimen. These studies included a wide range of clinical situations, 22% of which involved hypertension medication[83]. The adherence data in terms of doses taken is shown in Figure 5. This was consistent with many studies that show an inverse relationship between frequency and adherence, but which fail to find a significant difference between once a day and twice a day. In hypertension, a difference has been shown between once and twice daily mono-therapy regimens.

Figure 5 Frequency of regime and average adherence

adapted from Claxton *et al* 2001[83]

Frequency of regime	No. Reports	% Adherence	SD (%)	Range (%)
1 dose / day	29	79[A]	14	35-97
2 doses / day	32	69[B]	15	38-90
3 doses / day	13	65[A]	16	40-91
4 doses / day	11	71[B]	17	34-97
All regimens	85*	71	17	34-97

[A] Once a day vs. three and four times a day were significantly different

[B] Twice a day vs. four times a day was significant

* Some studies reported for more than one frequency

In one of the reviewed studies, 105 patients received a single drug for their hypertension. Tablet counts did not show a difference between once and twice daily dosing but both produced adherence that was better then with three times daily dosing[84]. However, the electronic monitoring data indicated that adherence with once a day monotherapy was superior to twice daily regimen and that both were superior to three times daily regimes. Adherence was defined as the number of days on which the prescribed number of doses was removed from the electronic monitor.

Figure 6 Influence of dose regimen on adherence and effect of method used to measure adherence.

(adapted from Eisen *et al* 1987[85])

	Adherence (n=105)	
	Tablet counts	MEMS data
Once daily	96%	83.6%
Twice daily	93%	74.9%*
Three times daily	83.8%*	59.0%*

*Significantly different ($p<0.05$) from figure above

The number of daily doses is seen to influence the level of adherence; however, it may also affect the chances of the patient persisting with treatment. In the USA a retrospective analysis of the prescription records of a large pharmaceutical

benefits management organization studied the prescription refill behaviour of patients who had recently started outpatient antihypertensive therapy [86]. Persistence with treatment at 12 months after starting treatment was significantly lower with twice daily dosing (29%) than with once a day dosing (up to 56%, $p \leq 0.0001$).

1.8.3.3. Number of medications

The effect upon adherence of the number of medications is difficult to separate from the number of doses per day. However, it is becoming a more important consideration as the use of multiple drugs to treat modifiable risk factors becomes more common. The result is that patients with cardiovascular disease are being prescribed a large and increasing number of medications. A widely held and logical assumption is that as a regimen becomes more complex, the adherence will decrease. This has been supported by several studies among elderly patients[80] HIV patients[87] and, but some researchers have found the opposite[88-90]. Some of these discrepancies can be attributed to different methodology and, in particular, different methods of measuring adherence. An important consideration when studying the effect of the number of drugs is whether or not the patient perceives the number of drugs as a marker of their disease severity, and whether they are therefore more health benefit aware, and hence more adherent. Furthermore, within a complex regimen, medications taken for symptomatic conditions are more likely to be associated with better adherence e.g. ACE inhibitors for heart failure rather than statins for hypercholesterolaemia (or ACE inhibitors for hypertension). The adherence to ACE inhibitors and statins (assessed using retrospective refill data from the British Columbia prescription drug database) was found to increase as the number of prescribed drugs increased[90]. These findings cannot be easily applied to hypertension populations in general. Only 41% (n=367) of a group invited to participate in the study volunteered to do so. Only 48% of subjects had hypertension and over 55% had heart failure. Perhaps most notable was the high overall level of adherence, 91.7% of the subjects had more than 80% adherence, suggesting that this was perhaps a relatively adherent, non-representative population. However, the study serves as a reminder that widely held assumptions are not necessarily true for all patient groups.

1.8.3.4. Cost of treatment

Cost of treatment may reduce the chances of a patient continuing with treatment, primary non-adherence. There is no specific evidence on how this affects antihypertensive treatment. Primary adherence has been shown to be higher in patients who have to pay part of the cost of the prescription (see 1.4.3 above).

1.8.3.5. Type of antihypertensive

The choice of initial antihypertensive drug is the subject of wide debate. International guidelines continue to recommend diuretics or beta-blockers for uncomplicated hypertension. There is growing evidence that the choice of antihypertensive may affect persistence with treatment. This is discussed further in section 2.9.5 below.

1.8.4. Environmental factors

1.8.4.1. Physician characteristics

The influence of physicians' attributes and practice style on patients' adherence to treatment was examined in a 2-year longitudinal study of 186 physicians and their diabetes, hypertension, and heart disease patients[91]. General adherence and adherence to medication, exercise, and diet recommendations were examined. At 2 years, the strongest predictor of adherence was adherence at baseline; however, other predictors of higher adherence were physician job satisfaction, lower number of patients seen per week, the patient scheduling a follow-up appointment and specialist physician (as opposed to a generalist).

1.8.4.2. Location

Adherence may be higher when hypertension is managed in primary care. In a review of the 1980's literature[92], it was concluded that adherence among patients treated in primary health care, adherence was 81%, compared with 61% of those managed in hospital outpatients. This is similar to claims that the management of hypertension is more effective in primary care; however, it is difficult to allow for the fact that the more difficult cases will usually be referred for hospital management and these will include patients whose "resistant" hypertension is due to non-adherence. While many primary health care based patients may enjoy a more stable and productive relationship with their family physician, this may not be the case in all primary care settings due to increasing workload and manpower shortages.

1.8.4.3. Knowledge and support of the patient

Fifty adult hypertensive patients at a health maintenance organization completed questionnaires and participated in home interviews over a 10-week period[93]. Knowledge of medical regimens, information communication between the patient and the medical professionals, satisfaction with health-care providers, health locus of control, social support, and treatment disruption to life-style were assessed. Adherence was assessed through self-reporting, tablet counts, and the percentage of kept medical appointments. Higher levels of adherence were associated with a greater expectancy for internal control over health and hypertension, greater knowledge of the treatment regimen, and stronger social support. The higher levels of adherence were associated with greater levels of blood-pressure reduction. Perceptions of independence or high levels of social support are consistently linked to higher levels of adherence. In a logistic regression model derived from self reported adherence in 512 elderly patients admitted to hospital, those who perceived themselves as having greater independence were more adherent[94].

1.8.5. Physician-Patient relationship

The quality of the physician-patient relationship can have a major influence on health outcomes, including medication adherence. Communications between the doctor and patient are often criticized; however, the quality of the relationship depends not only on the doctor and patient being able to hear and understand what each other has to say, but on the health beliefs of the two and there ability to agree upon a treatment plan. Studies looking at the influence of the physician's health beliefs have not been performed, but the effect of the patient's health beliefs seems to be influenced by the quality of the relationship with the physician. A questionnaire study of 48 lithium outpatients (treated for manic depression) evaluated the relationships among lithium-related beliefs and attitudes, normative beliefs, behavioural intentions, and self-reported compliance to the lithium. The affect of these beliefs on the adherence was related to the patient's perceptions of the patient-physician relationship[95].

In many studies and reviews, it is assumed that doctor – patient communication is adequate and that the patient understands what is expected of them. However, patient understanding is rarely tested directly in adherence studies. Patients frequently complain that the doctor does not listen to them[96] and the ability of patients to recall what their doctor has told them about the diagnosis or

treatment is well known to be poor. When measured in terms of the patient's ability to recall doctor's instructions, patients fail to recall between one-third and one-half of the statements given to the by doctors[97]. However, this may over-exaggerate the problem as this type of method may fail to detect the patients' ability to get the general meaning of instructions despite not being able to give detailed recall of directions.

The recognition that doctor-patient communications are often poor has led to many undergraduate medical courses investing more time and effort in the teaching and practice of communication skills[98]. The effectiveness of the doctor-patient communication has been correlated with improvement in a wide range of patient health outcomes including blood pressure[99]; however, the correlation between adherence and improved outcomes is complex and not always easy to demonstrate[100]. The difficulty of the assessing the quality of the patient-doctor relationship can be judged by the doctor's difficult in identifying those patients that have good or poor adherence. There is good evidence from the Helsinki heart study that in the management of chronic conditions, doctors cannot accurately determine if their patients are adherent, especially if simple tablet counts are employed [44].

The quality of the relationship between a patient and doctor is, like any other relationship, a direct reflection of the quality of the communication. This can be undermined by many factors including language difficulties and the patient being attended by, consulting with several doctors. Even within a stable doctor-patient relationship there are many potential problems relating to both explanation and listening skills[101] .

Figure 7 Factors that have been shown to influence medication adherence.

Arranged by Patient factors, Drug factors, and Environmental factors

Factor	Effect on Adherence	Comment	Reference
Patient factors			
Male Gender	Decrease	Males more likely to miss and delay doses, 39% vs. 33% O.R 0.70	[73]
Age (30-69yr)	No Effect	HDFP study of stepped care and follow-up in 10,940 patients. Adherence assessed by attendance at follow-up appointments	[74]
Age >60 years	High adherence demonstrated	(SHEP) pilot study, 551 men and women over the age of 60 (mean age = 72 years), treated with chlorthalidone or placebo in a double-blind trial. Three measures of compliance to treatment protocol--pill count, self-report, and a urine assay-- high adherence in 80 to 90% of people at 3 months and 1 year including those >80 years.	[75]
Age (Younger)	Decreased	Young patients were less adherent, especially if they used "avoidant" strategies to deal with their diagnosis	[76]
Age (Younger)	Decreased	Adherence worse in younger patients especially if the "net barriers" were high (i.e. perceived benefits greatly outweighed by perceived disadvantages)	[77]
Age (Elderly)	Variable	60-80 year olds had better adherence than patients over 80 years and patients under 60 years	[78]
Age <60 years	Decrease	2173 patients using electronic monitors 45% of patients under 60 years vs 30% of patients over 60 years missed more than 20% of doses O.R. 1.80 (1.49-2.17)	[73]
Age (>60yr vs. younger)	Decreased	Primary non-adherence i.e. not presenting the prescription, 63% of prescriptions not redeemed vs. 26% in young adults	[15]

Factor	Effect on Adherence	Comment	Reference
Active (not retired)	Decreased	Reduced attendance with scheduled PHC visits. 174 hypertensive patients receiving treatment. Non-compliance with scheduled visits was assessed by review of the appointment book. One of the factors associated with non-attendance was being a housewife or having work ($p = 0.01$)	[79]
Active (not retired)	Decreased	Patients who were working were less adherent 43% vs. 29%	[73]
Higher socio-economic status	Decreased	Logistic regression model formed from self-reported adherence amongst 785 older patients taking a variety of medicines. The type of medicine was not a component of the model.	[80]
Smoking	Decrease	15.5% of hypertensive patients had dropped out of treatment (non-attendance) at 1 year. Smoking was an independent risk factor for non-attendance.	[48]
Smoking	Decrease	49% of smokers non-adherent vs. 34% of non-smokers	[73]
Higher psychological stress	Decrease	Logistic regression model formed from self-reported adherence amongst 785 older patients (>55yr) taking a variety of medicines. The type of medicine was not a component of the model. A 12-item questionnaire was used to measure psychological stress.	[80]
Stressful life events	Decrease	In a study of 139 Indian patients, a higher Life event score (LES) was associated with higher rates of non-adherence but the relationship could have been casual	[81]
Anxiety	Decreased	Reduced attendance with scheduled PHC visits. 174 hypertensive patients receiving treatment. Non-compliance with scheduled visits was assessed by review of the appointment book. One of the factors associated with non-attendance was anxiety ($p = 0.008$) **NB** The study below, did not find anxiety to be a factor in adherence to medication (all types not just hypertension).	[79]

Factor	Effect on Adherence	Comment	Reference
Depression	Decreased	In a review of the literature, concurrent depression was found to reduce adherence to all therapy O.R 3.03 (0.96-4.89)	[82]
Elderly patients taking medicines independently	Increase	In a logistic regression model derived from self reported adherence in 512 elderly patients admitted to hospital, those who perceived themselves as having greater independence were more adherent	[94]
Fear of addiction	Decreased	A fear of addiction was voiced in many hypertensive patients who were non-adherent	[33]
Fear of side-effects	Decreased	The fear of side-effects (not actual side-effects) has been reported to be more common in non-adherent patients in a wide range of disease states including hypertension	[20](epilepsy) [19](general) [29](Hypertension) [26](vaccination)
Patient associates HTN with symptoms	Decrease	If a patient mentioned "symptoms" of hypertension in their first appointment then they were more likely to drop-out of treatment	[72]
Patient considers HTN to have a cyclical nature	Decrease	Patients who considered hypertension to have a cyclical nature not a chronic nature were more likely to drop-out of treatment	
Stronger internal locus of control	Increase	Fifty, adult hypertensive patients. Adherence was assessed through self-report and pill-count ratio, percentage of kept medical appointments. Greater expectancy for internal control over health and hypertension was associated with higher adherence.	[93]
Greater knowledge about hypertension	Increase	As above	
Stronger internal locus of control	Increase	Among ambulatory hypertensive patients, the more internally oriented the patient, the greater the level of self-reported compliance behaviour.	[102]

Factor	Effect on Adherence	Comment	Reference
Drug Factors			
Early stage of treatment	Decreased	Non-adherence in the early stages of treatment was the strongest predictor of non-adherence at the 2 year follow-up	76
Early stage of treatment	Decreased	Non-adherence more common in early stages of treatment, especially if "net barriers" were high.	77
Short duration of treatment	Decreased	Patients who had been treated for less than 29 months were less adherent 40% vs. 33%	73
Number of medications	Decrease	In a study of 45 Canadians aged over 64, the adherence decreased as the number of medications (including antihypertensives) increased	103
Poly-pharmacy in the elderly	Decreased	"Brown Bag" Prescription Evaluation Program (USA)	104
More than one antihypertensive	Increased	Patients taking two antihypertensive drugs were more adherent than monotherapy patients 40% vs 31% O.R. 1.40 (1.14-1.72)	73
Number of daily doses per day, od vs. bd or tds	Increased	A study of 179 patients taking medication for type 2 diabetes. Low dose marker and tablet counts found od and bd better than tds but little difference between the od and bd.	105
Number of daily doses od vs. bd vs. tds	Increase	A study using electronic monitors in 105 patients receiving a single drug for their hypertension found adherence with once a day monotherapy to be 84%, 74.9% with twice a day and 59% in patients receiving three times a day monotherapy.	84

Factor	Effect on Adherence	Comment	Reference
Drug Factors *continued*			
Number of daily doses od vs. bd	Decreased	Once daily compared with twice daily. 24 patients studied for an average of 7 months each using electronic monitors. The % of doses taken was similar (89 vs 88%), but the once daily patients had twice as many dose free days as the twice-daily patients. The twice-daily patients were more likely to miss the evening dose.	[106]
Number of daily doses od vs. bd	Increase	A study of 31 patients taking Isosorbide Mononitrate for angina. Those on a once daily formulation had half the rate of angina attacks	[107]
Number of daily doses od vs. bd	Inconclusive	Data from a clinical trial comparing once daily amlodipine with twice daily diltiazem. No difference in total number of % doses taken but the adherence to the bd dosage was more erratic	[108]
Number of prescribed medications	Decreased	HIV patients taking complex antiretroviral regimes	[87]
Number of prescribed medications	Increased	Retrospective refill data and patient questionnaire in non-hospital patients taking statin or ACE inhibitor	[90]
Cost of treatment	Decreased	The Primary non-adherence rate in patients who were not-exempt from charges, were 33% - twice that seen in the exempt patients (UK)	[12]

Factor	Effect on Adherence	Comment	Reference
Environmental factors			
Initial antihypertensive drug used	Continuation highest with ACE inhibitors lowest with diuretics,	After 6 months, continuation with therapy was poor and differed according to the class of initial therapeutic agent highest for ACE inhibitors, lowest for diuretics.	109
		After 12 months continuation with therapy was highest for Angiotensin receptor antagonists and lowest for diuretics.	86
Diuretics	Increased	In a logistic regression model derived from self reported adherence in 512 elderly patients admitted to hospital, diuretics were "negatively associated with non-adherence" (along with bronchodilators and benzodiazepines)	94
Strong social support	Increase	Home interviews of 50 hypertensive patients found those with strong social support to be more adherent when measured by pill counts and clinic attendance	93
Quality of Physician-Patient relationship	Increase	A study of 48 outpatients taking lithium for mania.	95
Quality of Physician-Patient relationship	Increase	Clinical outcomes including blood pressure control were consistently related to specific aspects of physician-patient communication	110
Primary healthcare vs hospital outpatient care	Increased	In a review of the 1980's literature, it was found that adherence was reported in 81% of PHC hypertensive patients compared with 61% of those hypertensive patients managed in the hospital outpatients.	92
Physician Job Dissatisfaction	Decreased	Result of a 2 year longitudinal study	91
		Dissatisfied doctors more likely to have non-adherent patients	
Busy Physician	Decreased	The busier physicians (No. Patients / week) had less adherent patients	

1.8.6. Practical implications of factors affecting adherence

The above factors are often recommended as a screening tool for identifying patients who are at a higher risk of non-adherence. However, only rarely are these factors discussed in the context of whether they are modifiable and whether they should be the targets of interventions to improve adherence.

Equally important is the question of whether these factors are practical obstacles to adherence, e.g. patient cannot open the tablet container or cannot afford the medicine, or whether the factor is simply reinforcing or aggravating a set of health beliefs that make non-adherence more likely?

Health beliefs are a reflection of a person's cognitions, which in turn are affected by the views and experiences of each person and those around them. Therefore, it follows that any association between a characteristic and adherence seen within a population may not be true for other populations, other diseases. Furthermore, the presence and impact of some characteristics will be temporal and therefore may change with time. Figure 8 shows that most factors are related to Health Beliefs, are modifiable and are temporal. While this provides hope, that adherence can be modified through targeted interventions, any patient could have a range of factors and therefore the intervention will need to be tailored to the patient. This classification also emphasises the challenge presented by adherence to life-long therapy. Many of these factors could occur to greater or lesser degree at different points in the life-long care of a patient and adherence should therefore be formally reassessed at regular intervals. This largely explains the findings of a Cochrane Centre review of strategies to improve medication adherence in which the authors concluded that only complex, multi-faceted interventions had been shown to improve adherence in chronic therapy and even then, the improvement was modest[111]. Interventions to improve adherence cannot be one-off interventions and must concentrate on the health beliefs of individuals and be designed to address these specifically[21].

Figure 8 Factors associated with adherence; Related to Health Beliefs (HB), Modifiable by an Intervention and whether they are Temporal.

Description	Health Belief	Modifiable	Temporal
Patient factors			
Gender	Y	N	N
Age	Y	N	Y
Active (not retired)	Partly	N	Y
Higher socio-economic status	Partly	N	Y
Smoking	Y	Y	Y
Higher psychological stress	Y	N	Y
Stressful life events	Y	N	Y
Anxiety	Y	Y	Y
Depression	Y	Y	Y
Fear of addiction / side-effects	Y	Y	Y
Patient links BP with symptoms or cyclical nature	Y	Y	N
Greater knowledge about hypertension	Y	Y	Y
Stronger internal locus of control	Y	Y	N
Drug Factors			
Early stage of treatment	N	Y	Y
Number of medications	Partly	Y	Y
Poly-pharmacy in the elderly	Partly	Y	Y
Number of daily doses per day	Partly	Y	Y
Number of prescribed medications	Partly	Y	Y
Cost of treatment	Partly	Y	Y
Initial antihypertensive drug used	N	Y	N
Diuretics	N	Y	Y
Environmental factors			
Strong social support	Y	Y	Y
Quality of Physician-Patient relationship	Y	Y	Y
Primary care vs. hospital outpatient	N	N	Y
Physician's Job Dissatisfaction	N	Y	Y
Busy Physician	N	Y	Y
Non-specialist doctors	N	Y	Y

2. Hypertension

Contents

2.1 Introduction

Hypertension is a common clinical finding in older adults. Current theories suggest that it arises from a dysfunction in one or more of the various mechanisms that exert the homeostatic control of normal blood pressure. Modern drug treatments act upon these same mechanisms to compensate for the dysfunction. Failure to reduce a raised blood pressure increases the risk of cardiovascular morbidity and mortality. While there is strong clinical trial and epidemiological evidence for the effectiveness of these drugs, they must be taken so to have an effect on the blood pressure, all day and every day. Non-adherence to an antihypertensive regimen is a common reason for treatment failure and a waste of precious medical resources. Therefore, hypertension is an ideal model in which to study medication adherence in chronic disease as not only are cases common, but they are relatively easy to monitor and any positive outcomes from such research will benefit a large group of patients and prevent unnecessary waste of resources.

This is not a treatise on hypertension and it's management per se but focuses on the need to clearly define the diagnosis of hypertension, the threshold for treatment and the importance of describing and reaching the treatment target. It is assumed that the reader is familiar with the range of medications used to treat hypertension but the evidence to support treatment guidelines is discussed.

As a preface to this chapter, a "time-line" of hypertension provides some historical perspective on the understanding of hypertension. It spans almost 2,500 years and most of our current knowledge has been acquired in the last 50 years. A time-line of adherence awareness would also date from Hippocrates, but a methodological approach to the subject spans less than 40 years.

A Time-line of Arterial Hypertension[F]

400 BC

Hippocrates studies arteries and veins and teaches that veins carry air.

130-200 AD

Galen theorises that blood travels backward and forward in unconnected veins and arteries.

1616

William Harvey refutes Galen and introduces the concept of one-way circulation and the notion of capillaries.

1733

Stephen Hales investigates blood pressure by sacrificing his horse in his back yard and measuring the height of a column of blood (8 feet 3 inches!) extending from the carotid artery into a glass tube from the time of cannulation until the horses' death.

1816

René Laennec is credited with inventing the stethoscope, a convenience for physicians who preferred not to place their ears directly on the chest wall of an "unbathed or verminous" patient.

1880

Sphygmomanometer introduced to clinical practice, by Ritter von Basch, and enabled the measurement of human blood pressure without breaking the skin. Von Basch's sphygmomanometer was the forerunner of an ingenious device introduced by Scipione Riva-Rocci in 1896, which proved to be a prototype of the more refined instruments of today.

1905

Nicolai S. Korotkoff uses the stethoscope to study blood pressure while the blood pressure cuff was inflated. Not only did he get a more accurate blood pressure reading, but he also discovered that the pulse sound disappeared as the cuff pressure decreased, at a point roughly in consonance with the expanding of the heart. The term "Korotkoff sounds" came to be used

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[F] Adapted from 112. Hoel D, Howard R. Hypertension, Stalking the silent killer. *Postgraduate Medicine* 1997;101(Feb).

1945

With no treatment available, chronic hypertension kills President Franklin Delano Roosevelt, aged 63years, 2 months after the Yalta Conference.

1950-1990's

New drugs demonstrate great promise for managing high blood pressure. Oral diuretics, methyldopa and beta-blockers appear in the 1960's. Alpha-2 blockers appear in the 1970's and ACE inhibitors and the calcium channel blockers are introduced in the late 1970's and early 1980's. Angiotensin II (AT1) receptor antagonists appear during the 1990's.

1970-1989

US National hypertension education programs are instituted to reduce risks.

1990-1997

Mortality from heart attacks in the USA decreases by 50% since 1972, and stroke deaths drop by almost 60%.

1993

The JNC V report revolutionises the classification of hypertension by giving equal importance to the systolic blood pressure and by recognising that hypertension was a progressive disease and should classified by stage rather than class.

1997

The JNC 6 report maintains its position that beta-blockers and diuretics remain the first line treatment but acknowledges that other antihypertensive drugs may have favourable effects on co-morbidities, especially ACE inhibitors in diabetes mellitus with proteinuria and carvedilol or losartan in heart failure.

2000 and beyond

Results of long-term studies will be available to guide new therapy and new technology. Pharmacogenomics may revolutionise the screening for and treatment of hypertension

2.2 Defining hypertension

Hypertension is generally symptom-less and detected by chance during a routine health check-up. There is a continuous relationship between the level of blood pressure and the risk of cardiovascular events such as myocardial infarction and stroke so breakpoints are quite artificial. Treatment of a raised blood pressure is designed to reduce this risk; therefore, the actual blood pressure is an indirect measure of the therapeutic target, i.e. reduced cardiovascular risk. For each patient, the doctor has to decide at what point will an elevation of the arterial blood pressure lead to with an increased risk of cardiovascular disease.

The terms primary and secondary hypertension describe whether or not the diagnosing doctor has identified and clearly described the cause of the abnormal rise in the blood pressure. This definition helps the 2-4% of patients whose hypertension can be treated by addressing the original cause e.g. endocrine disturbances, reversible renal disease, and iatrogenic cases due to drug side effects.

The terms mild, moderate and severe hypertension are now discouraged. Not only do they introduce subjectivity in to an already difficult clinical area, but blood pressure is only one of several factors that determine the risk of cardiovascular disease. A "mild" increase in blood pressure can significantly raise the risk of cardiovascular disease in an individual who is diabetic and has a dyslipidaemia. The use of the terms such as mild and moderate can mislead patients (and doctors) in to thinking that the elevation in blood pressure is of mild or moderate importance and not therefore a serious risk to their health.

Within a population, there is a normal (Gaussian) distribution of arterial blood pressure. The WHO, International Society for Hypertension [113] and the Fifth US Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNCV) [114] agreed on a common definition. Hypertension (in adults), for the purposes of treatment, can be defined as; a Systolic Blood Pressure (SBP) of greater or equal to 140mmHg or a Diastolic Blood Pressure (DBP) of greater or equal to 90 mmHg (Figure 9 below). This has been refined in the follow up reports JNCVI[115] and WHO-ISH 1999[116].

Figure 9 Definitions and classification of hypertension by blood pressure levels mmHg.

Source JNCVI[115] and WHO-ISH[116]

Category	Systolic	Diastolic
Optimal	<120	<80
Normal	<130	<85
High Normal	130 – 139	85 - 89
Grade (Stage) 1 hypertension (mild)	140 – 150	90 - 99
Sub-group: Borderline [WHO]	140 – 149	90 - 94
Grade (Stage) 2 hypertension (moderate)	160 – 179	100 – 109
Grade (Stage) 3 hypertension (severe)	> or = 180	> or = 110
Isolated systolic hypertension	> 140	< 90
Sub-group Borderline [WHO]	140 - 149	< 90

The above values are for adults aged 18 and older, and who are NOT taking antihypertensive drugs and who are NOT acutely ill.

When a patient's systolic and diastolic blood pressure falls into different categories, the higher category should be used.

[WHO] These classifications are specific to the 1999 WHO-ISH guidelines

Having described "break-points" for hypertension one must also take in to account the fact that the blood pressure is quite variable from hour to hour and day-to-day as well as demonstrating a consistent circadian variation. This variability of blood pressure within individuals requires us to consider the blood pressure over a 24-hour period and this has important consequences for the diagnosis and the monitoring of treatment. Therefore, before labelling a patient as hypertensive and deciding to initiate treatment, it is necessary to confirm raised blood pressure by repeating measurements over periods of several weeks. Whenever a measurement indicates raised blood pressure then the patient should be followed up over three to six months. However, with more extreme elevations and multiple risk factors, a shorter period of observation is recommended before treatment.

2.3 Relative importance of systolic and diastolic hypertension

A high DBP has traditionally been used to define hypertension and has been the focus when evaluating hypertension as a risk factor cardiovascular disease. This approach has been perpetuated in clinical research and most clinical trials have used DBP to determine the inclusion criteria and as an end-point in studies of

antihypertensive drugs. In recent years large studies have been designed to address the question of what is the optimal blood pressure to provide protection against stroke and other complications. The Hypertension Optimal Treatment (HOT) study[117], involved almost 19,000 subjects aged 50 to 80 years and found that the optimal protection against a variety of major cardiovascular disease (actual events including stroke and myocardial infarction) was a SBP of 130-140mmHg and a DBP of 80-85mmHg.

However, over the last thirty years it has been repeatedly suggested that the SBP and the pulse pressure should play a bigger role when predicting the cardiovascular risk and that SBP should play a more dominant role in both the definition and management of hypertension. Framingham study data showed that SBP correlates strongly with cardiovascular risk [118]. Data from US prospective population studies on blood pressure [119] has shown that for middle-aged and older persons, SBP relates even more strongly to risk than DBP; at every DBP level, higher SBP results in a greater risk of cardiovascular disease and shorter life expectancy. Many studies have since confirmed that SBP and pulse pressure are better predictors of cardiovascular risk. Some intervention trials in mild hypertension have shown a closer correlation between adverse events and systolic, rather than diastolic pressure. In 2000, a clinical advisory statement from the US National High Blood Pressure Education Program, recommended that SBP should become the main criterion for diagnosis and management of hypertension, particularly in middle-aged and elderly Americans[120]. The United States Cardiovascular Health Study[121] reported that in older adults (65 years and older), SBP is a better predictor of the risk of major coronary and cerebrovascular events than is DBP. This was a large (5,888) prospective study over 10 years (average follow-up period 6.7 years) from recruitment between 1989 and 1990 at four US centres. The recruitment was more representative than most clinical trials (very few exclusion criteria) and the baseline assessment and follow-up was very thorough. Therefore, this study gave a good idea of the influence of SBP and DBP in every day clinical practice. Interestingly, even at the same SBP, the hazard ratio for myocardial infarction and stroke was less pronounced in those patients receiving treatment than in untreated patients. A cohort of 4,412 French men treated for hypertension in every day clinical practice were followed up after an average of 14 years[122]. The data showed SBP to be a far better predictor of cardiovascular disease and coronary heart disease in men with hypertension,

regardless of age (mean age was 52±11 years). The relative risk of cardiovascular disease mortality (adjusted for age and associated risk factors) was 2.5 times higher in men treated for hypertension with SBP over 160mmHg, compared with those with SBP under 140 mmHg. The predictive value SBP remained significant even after adjusting for DBP.

A reanalysis of the Framingham data has showed that there is an age and sex related increase in the SBP that is not linearly related to an increased cardiovascular risk and that the blanket application of JNCVI criteria may overestimate the risk of raised SBP in the elderly[123]. However, the current weight of evidence points to SBP as being the primary variable for the diagnosis and management of hypertension.

2.4 Isolated office ("white-coat") hypertension

In some patients, blood pressure measurements in the clinic (or "office" in North America) are persistently elevated whereas measurements at home or using continuous, ambulatory blood pressure monitoring (ABPM) show it is not elevated or the elevation is not as severe as in the clinic. This condition is widely known as "white coat" hypertension[124] but research has not always confirmed the link to physician-measured blood pressure, and the term could be a misnomer. An alternative of "isolated office" hypertension has been proposed[125]. However, the controversy is not so much in the descriptive term, but in the diagnosis and the prognostic value.

While several studies have suggested that the incidence of "white coat hypertension" to affect as many as 22-39% of hypertensives[126,127], true isolated office hypertension probably affects a small fraction of the hypertensive population. Repeated clinic measurements does not eliminate white coat hypertension[128] and some propose that the diagnosis should only be accepted after ABPM has confirmed that the blood pressure outside of the clinic is "normal" [129]. As for the prognosis of white-coat hypertension, there is still no evidence to dispel it as a risk factor. The WHO-ISH guidelines recommend close follow-up but that doctors should consider treatment if there is a particularly adverse risk factor profile or if there is evidence of target organ damage. As with all hypertension, accurate assessment is important and in this case, it can only be achieved reliably by the use of ambulatory blood pressure monitoring (ABPM).

2.5 Epidemiology of Hypertension

An overall prevalence of more than 20% of adults can be expected for most countries. The prevalence of hypertension varies according to age, sex and race and many international data do not distinguish clearly between these factors. Many surveys conducted over the past two decades have used different diagnostic criteria and different age break points, making it difficult to directly compare surveys

One in four adult Americans has hypertension[130]. This approximates to over 43 million men and women. In the 1976-80 survey the prevalence had been as high as 45% for men and 36% for women. However, there are important racial differences. People with lower educational and income levels tend to have higher levels of blood pressure. In the United States, the socio-economic status is closely related to race. Blacks and whites in the South-eastern United States have a greater prevalence of hypertension and higher death rates from stroke than in other regions of the country.

Despite progress in preventing and treating risk factors for stroke (e.g., increases in the use of antihypertensive therapy), the increasing prevalence of heart disease, diabetes, and obesity in the United States has increased the relative risk for stroke, particularly among blacks [131].

There is much less data regarding the prevalence of hypertension and associated cardiovascular risk factors in the UAE and surrounding Arab world. The UAE is a small but ethnically diverse country.

Most data from the region comes from the efforts of the WHO Eastern Mediterranean region office (EMRO) to co-ordinate data collection. The EMRO covers Bahrain, Cyprus, Egypt, Iran, Iraq, Jordan, Kuwait, Oman, Qatar and the United Arab Emirates (UAE) and extends to Pakistan and India[132]. The UAE has a majority (75%) expatriate population drawn mainly from the countries of the EMRO region.

Non-communicable diseases, in particular, cardiovascular disease, are emerging as a major health problem in the Eastern Mediterranean Region. The proportion of deaths from cardiovascular disease ranges from 25 to 45%. Coronary heart disease seems to be the predominant type of cardiac disease encountered in many countries, and hospital data indicate rising trends. Several countries including the UAE have experienced rapid socio-economic changes over the last two decades. Daily caloric intake has increased. Among Saudi Arabians aged 18

to 74 years, 51.5% of males and 65.4% of females were obese. A high prevalence of smoking (>70%) has been reported among patients having acute myocardial infarction. Hypertension is found in 22 to 47% of myocardial infarction cases and in more than 30% of cases of diabetes.

In the EMRO region the prevalence of hypertension is at least 20% of the adult population. Recent surveys have shown a prevalence of 26% in Egyptians and 23.6% in Omani adults. The prevalence of hypertension appears to be increasing in parallel with affluence. Under detection is also likely to be a problem. Low detection rates have been reported in some countries where, up to 60% of the people with hypertension were not aware of their high blood pressure.

In 1998, the UAE launched a national epidemiological survey of hypertension (NESH). This survey provides data on both Emirati nationals and on the majority of expatriate workers living in the country. Early data from this program indicates that the prevalence of hypertension is 25% of adults. The survey has also indicated that most of these people are under the age of 65 years, however, this is a skewed population where less than 2% of the 3 million population are aged over 65 years. A large proportion of the UAE expatriate population is from Pakistan and the Indian sub-continent. This is a diverse group, including both poor labourers and successful businessmen and professionals. The common factor for all these people is that most are exposed to a relatively more affluent lifestyle than what might be expected in their home country. The NESH data will be particularly interesting for this group, as worldwide studies have shown that the cardiovascular risk of people from developing countries rises when they move to a more affluent environment.

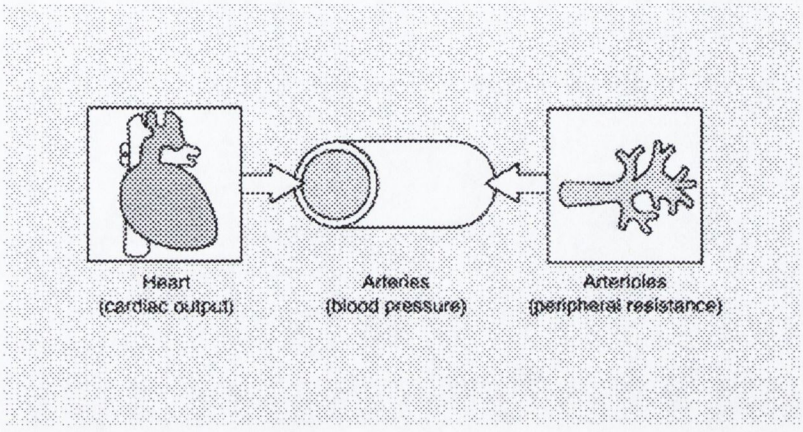
2.6 Pathophysiology of essential hypertension

Only between 2 and 5% of hypertensives are found to have an underlying renal or adrenal disease. The others are said to have "essential" hypertension. Attempts to explain the pathophysiology of essential hypertension have concentrated on the many inter-related physiological mechanisms that are involved in maintaining arterial blood pressure; the assumption being that there must be a defect in one or more of these systems. The work presented here includes some basic physiological theory and has been abstracted from several textbooks and reviews[115,133,134], but clinical research work is referred to where appropriate.

Arterial blood pressure is a product of the cardiac output and peripheral (arteriole) resistance.

Figure 10 Arterial pressure is the product of cardiac output and peripheral resistance

From Beevers *et al* 2001[135]



The cardiac output is a function of heart rate, and the end diastolic volume. These in turn are directly affected changes in the sympathetic nervous system and plasma volume. The peripheral resistance is affected by changes in sympathetic nervous activity, several other circulating and endothelial mediators and the physical response of the arteriole to auto regulatory stimuli.

It is expected that a defect in one of the physiological mechanisms controlling these factors will be responsible for essential hypertension. Research in to the pathophysiology of essential hypertension has focussed on several areas:

Sympathetic nervous system

Renin Angiotensin System

Salt intake

Arteriolar dysfunction

Genetic factors

2.6.1. Sympathetic nervous system

The sympathetic nervous system is a key control system for the short-term changes in blood pressure required in response to exercise and stress. It causes both the constriction and dilation of arterioles (depending on their location) and increases cardiac output; however, there is very little evidence that defects in the amount of circulating adrenaline or synaptic noradrenaline has a direct role in causing sustained elevations of blood pressure. It is more likely that the sympathetic system is involved in mediating the effects of the Renin Angiotensin System (RAS) and other hormones and it is also a useful target for drug therapy as drugs that block the sympathetic nervous system will lower blood pressure.

2.6.2. Renin Angiotensin System (RAS)

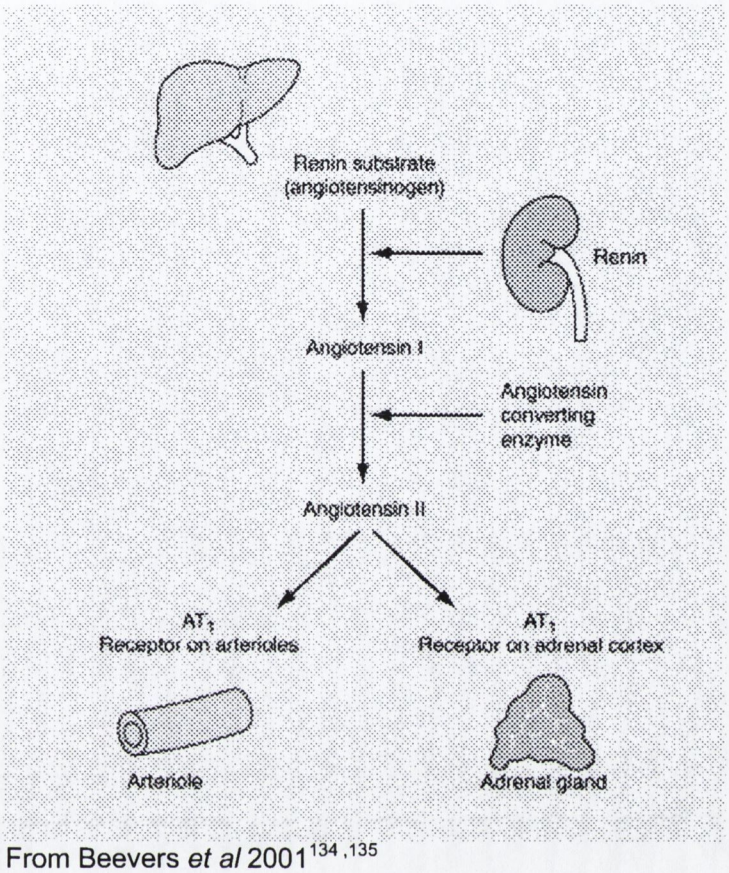
The RAS is the most important hormonal systems affecting the regulation of blood pressure. The traditional view of the RAS has been focussed on the renal source of Renin (see figure below).

Renin is secreted from the juxtaglomerular complex (or apparatus) of the kidney in response to a decrease in glomerular perfusion, a reduced plasma sodium or sympathetic stimulation. Angiotensinogen is produced in the liver and secreted into the blood at a constant rate. Renin converts angiotensinogen to Angiotensin I, which is rapidly converted to Angiotensin II by Angiotensin converting enzyme (ACE), mainly in the lungs.

Angiotensin II is a potent vasoconstrictor and acts via receptors (Angiotensin sub-type 1, receptors; AT_1) causing a rise in the blood pressure due to an increase in the peripheral resistance. Angiotensin II also stimulates the release of the mineral corticoid, aldosterone. Aldosterone increases sodium reabsorption in the kidney and the associated increased water reabsorption raises the plasma volume and increases the blood pressure.

Drugs that inhibit the ACE or block the Angiotensin II receptors are effective anti-hypertensives; however, an increase in the levels of circulating Angiotensin II does not appear to account for essential hypertension. Moreover, many hypertensives, especially the elderly and black hypertensives have low levels of Renin and Angiotensin and in these people, ACE inhibitors and Angiotensin receptor blockers are not as effective at reducing the blood pressure.

Figure 11 The Renin Angiotensin System



From Beevers *et al* 2001[134,135]

One possibility is that there are important non-circulating, "local" renin Angiotensin systems, which also control blood pressure. There are local RAS in the heart and brain, and it is possible that it a disturbance of these regional systems that leads to hypertension. They may also lead to some of the complications of hypertension. The heart has it's own Angiotensin converting enzyme which is not blocked by traditional ACE inhibitors. The myocardial RAS leads to an increase in myocardial contractility and hypertrophy of cardiac muscle cells. Left ventricular hypertrophy and cardiac failure are important examples of the target organ damage caused by hypertension.

2.6.3. Salt intake

The electrical and osmotic activities of various salts are responsible, at a cellular level, for all blood pressure regulation. It is a logical theory therefore that a disturbance of electrolyte intake, excretion or distribution could be a cause of essential hypertension. Getting the evidence is far more difficult. Most discussions of "salt intake" refer to sodium, but there is also data indicating a role

for potassium, calcium and even magnesium. It is a difficult area of research because there are so many confounding and inter-related factors. Evidence in support of the theory must show that a high or low dietary intake of the electrolyte is associated with essential hypertension (epidemiological data), and / or, that modifying the intake or loss of an electrolyte can ameliorate essential hypertension (intervention data). A diet that is low in sodium (100mmol or less per day[G]) and rich in potassium (90mmol or more per day), is recommended as part of the US national guidelines following evidence that it could reduce a raised blood pressure[115]. Some of this evidence is presented below. This of course, is not the same as identifying a pathological defect in the way the body handles an excess or deficit of an electrolyte and such hypotheses can only point to where researchers must look to find a root cause of essential hypertension.

2.6.3.1. Too much sodium may lead to hypertension

The INTERSALT Study was an international, collaborative, cross-sectional investigation of the relationship between blood pressure and dietary and other factors[136]. Analysis of the 24-hour urinary sodium excretion data found a strong relationship between higher excretion rates (result of higher sodium intake) and the systolic blood pressure, both across the sample population and between individuals[137].

Meta-analyses of intervention studies confirm the relationship between sodium intake and blood pressure; however, they disagree on the value of restricting sodium intake for the whole population. Public health authorities such as the US National Institute of Health interpret the epidemiological data as indicating a need for across the board reductions in sodium[138]. The National Heart, Lung and Blood Institute (NHLBI), a unit of the National Institute of Health, developed and evaluated the DASH diet and this was endorsed by the JNCVI guidelines. It is high in dietary fibre, potassium, calcium and magnesium; moderately high in protein and with a sodium content that was lower than the typical US diet. While evidence indicates benefits from reducing sodium in the diet of people with hypertension, independent meta analysis of intervention studies has been interpreted as indicating a reduction in dietary sodium for hypertensives (to below 100mmol per day), especially in elderly hypertensives but not for non-hypertensive people[139].

[G] 100mmol is the equivalent of 2.4g of sodium or 6g of sodium chloride

The exact mechanism by which excessive sodium intake leads to hypertension is not known but may be linked to natriuretic hormone. Natriuretic hormone is produced by the atria of the heart in response to a rise in plasma volume that follows a rise in plasma sodium and acts like a natural diuretic to promote urinary excretion of sodium and water. An excessively high dietary sodium intake could lead to a prolonged elevation in the levels of natriuretic hormone. Natriuretic hormone is also believed to block the transport of sodium out of arteriolar smooth muscle. If this was a sustained effect, it would increase the arteriolar tone and hence peripheral vascular resistance and blood pressure would rise. The fact that not all hypertensives respond to a restriction of salt intake suggests that this is not a simple environmental cause (high dietary sodium). More likely, there is an underlying, pathological variation in the way some individuals respond to excessive sodium intake and that this leads to essential hypertension.

2.6.3.2. Too little calcium may lead to hypertension

A defect in calcium homeostasis may also be involved in the pathogenesis of essential hypertension. The hypothesis is that a lack of calcium in the diet leads to a relative rise in intracellular calcium. This, together with an inter-related disturbance of sodium transport across the vascular smooth muscle cell wall, increases vascular tone and peripheral vascular resistance. This, in turn, raises the blood pressure. The hypothesis is supported by meta-analysis of epidemiological data that shows an inverse relationship between calcium intake and blood pressure. However, the studies have used heterogeneous populations and methods and the effect appears too weak to form the basis of public health policy or the basis for a large scale intervention study[140]. More recently, in the "Trial of Hypertension Prevention" (2182 adults, aged 35-54 year old, with diastolic blood pressure of 80-89 mm Hg), supplementation with calcium was one of seven interventions to lower blood pressure along with weight loss, sodium reduction, stress management, and supplementation with magnesium, potassium, and fish oil)[141]. After 18 months, there was no significant reduction in blood pressure attributable to Calcium supplementation, whereas weight loss and sodium reduction were well tolerated and produced significant decreases in systolic and diastolic blood pressures (-2.9mmHg SBP / -2.4mmHg DBP for weight loss and -2.1mmHg SBP / -1.2 mmHg DBP for sodium reduction, at 18 months).

2.6.3.3. Too little potassium may lead to hypertension

Both the INTERSALT study (see above) and meta-analysis of other studies that looked at oral potassium intake show that a low dietary potassium intake may lead to the development of essential hypertension[142]. The DASH diet (see above) is rich in potassium (more than 90mmol per day) and successfully lowers blood pressure. However, this does not mean that supplementing a "standard" diet with potassium will deliver the same benefits. The "Trial of Hypertension Prevention" (see above) found that after 18 months there was no significant reduction in blood pressure attributable to potassium supplementation. There are many confounding variables when trying to interpret potassium data. A diet rich in potassium, such as the DASH diet (see above) is usually rich in fruit and vegetables, which raises the fibre intake and tends to lower the overall fat intake and this is known to be associated with lower cardiovascular risks. Furthermore, some antihypertensives are potassium sparing, e.g. ACE inhibitors, and others increase potassium excretion, e.g. thiazide diuretics.

The mechanism by which a potassium deficiency could cause hypertension is not well described but it assumed that it could raise peripheral resistance in a similar manner to a calcium deficiency.

2.6.3.4. Magnesium is probably not associated with hypertension

A prospective follow-up study of the MRFIT study suggested an association between lower dietary magnesium intake and higher blood pressure[143]. However, there is no convincing intervention data to support the role of magnesium as having a role in the pathophysiology of essential hypertension. The "Trial of Hypertension Prevention"[141] found that after 18 months there was no significant reduction in blood pressure attributable to magnesium supplementation.

2.6.4. Arteriolar dysfunction

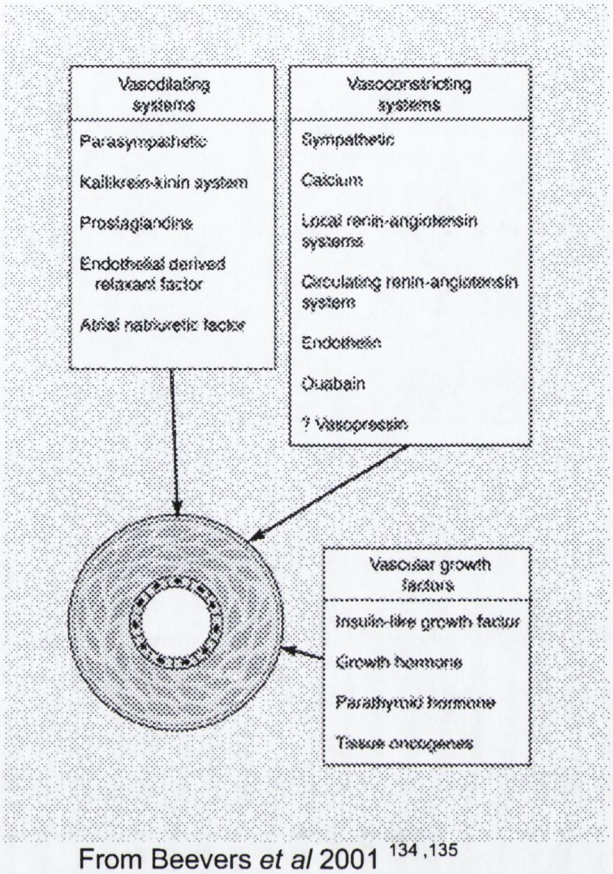
Peripheral arteriolar resistance, along with cardiac output is a direct determinant of arterial blood pressure (see Figure 10 above). Many stimuli affect arteriolar resistance and a pathophysiological defect in the way the arteriole responds to these stimuli could cause essential hypertension (see below).

The arteriolar endothelium is itself a source of a number of potent local vasoactive agents (Figure 12). These include the vasodilators; prostacyclin, bradykinin and nitric oxide (formerly known as endothelium derived relaxing factor) and the vasoconstrictors; Angiotensin II, endothelin-1. Bradykinin is a potent vasodilator and is inactivated by ACE. Consequently, ACE inhibitor drugs may exert some of their effect by blocking bradykinin inactivation.

Endothelin-1 is produced throughout the circulation, but especially in the pulmonary circulation. It has a complex pharmacology being both a potent vasoconstrictor via endothelin receptors (ET_A an ET_B) on the smooth muscle cells (implicated in pulmonary hypertension), and vasodilation via ET_B receptors on the vascular endothelium, triggering the production of prostacyclin and nitric oxide. Endothelin-1 may also directly, or indirectly, activate local RAS in arteries. It may therefore be involved in the rise in blood pressure associated with excessive salt intake.

The response of arterioles to a prolonged increase in cardiac output appears to be vasoconstriction, probably to prevent damage to the efferent tissues. This leads to an intimal fibroplasias and thickening of the vessel walls, which will be stimulated by a range of growth factors including Angiotensin II. An excessive response to growth factors could accelerate the development of essential hypertension. Several theories now focus on the dysfunction of this local cardiovascular regulatory system as being a cause of essential hypertension but therapeutic interventions aimed at this complex system are not yet developed. Effective treatment with any drug appears to normalise the nitric oxide production in the endothelium but the responsiveness of the endothelium to stimuli that should cause arteriolar relaxation remain impaired.

Figure 12 The control of peripheral arteriolar resistance



From Beevers *et al* 2001 [134,135]

This adds weight to the hypothesis that some type of arteriole smooth muscle or endothelial dysfunction is a pathophysiological defect in essential hypertension; and if it is not the primary defect, it becomes an irreversible secondary consequence of established hypertension.

2.6.5. Genetic factors

The hypothesis that there is a genetic basis to essential hypertension is supported by observations on inheritance, transplantation and that certain rare forms of hypertension can be explained by single gene defects.

Hypertension is about twice as common in people who have one or two hypertensive parents. Some epidemiological studies suggest that genetic factors account for approximately 30% of blood pressure variation. Although many family traits will be attributable to environmental and life style (dietary) factors, comparisons of parents with their twin children and adopted children support a genetic basis for essential hypertension.

The genetic variation is most likely to involve the kidney. Transplantation of a kidney from a hypertensive donor raises the blood pressure and increases the need for antihypertensive drugs in a recipient with no family history of hypertension. This is not seen when a donor with no history of hypertension donates the kidney. Specific gene mutations have been shown to be causes of hypertension through over expression of enzymes or receptor proteins, often part of a syndrome, but all are very rare. The inheritance of essential hypertension is probably depends upon multiple genes and additional environmental factors. Gene expression profiling is in very early stages and the practical utility for polygenic disorders such as hypertension is not clear[144].

2.7 Cardiovascular disease and the link to hypertension

Hypertension is a recognised risk factor for a wide range of cardiovascular diseases. Data from US prospective population studies on blood pressure has shown that the higher the blood pressure, the greater the risk of cardiovascular disease and a reduction in life expectancy [119]. A sustained high blood pressure will eventually lead to significant damage to the vascular system of critical organs such as the brain, heart, eyes and kidneys. This is the so-called "Target Organ Damage" and is a critical marker of the severity of the hypertension and risk of further cardiovascular events including stroke, coronary heart disease (CHD), left ventricular hypertrophy (LVH) and heart failure (HF). Damage to the renal and retinal vascular systems lead to two other major groups of complications; chronic renal failure (CRF) and retinopathy. The burden of cardiovascular disease is underestimated by the mortality statistics. Many coronary and cerebrovascular events are none fatal but may be sufficiently debilitating to seriously affect functional disability. Many others such as LVH, HF, renal disease and retinopathy are chronic, progressive diseases that reduce the quality of life, consume extensive medical resources and frequently lead to premature death.

2.7.1. Stroke (Cerebrovascular disease)

The most serious, acute cerebrovascular event is generally referred to as a stroke, although "brain attack" has become an increasingly popular term in North America. A stroke has been defined by the World Health Organization as a " *rapidly developing clinical, disturbance of cerebral function, with symptoms lasting 24 hours or longer, or leading to death, with no apparent cause other than of vascular origin".* Overall, about 25% of all stroke victims die in the first month and about 40% die within the first year. Up to 8% of those that survive one month

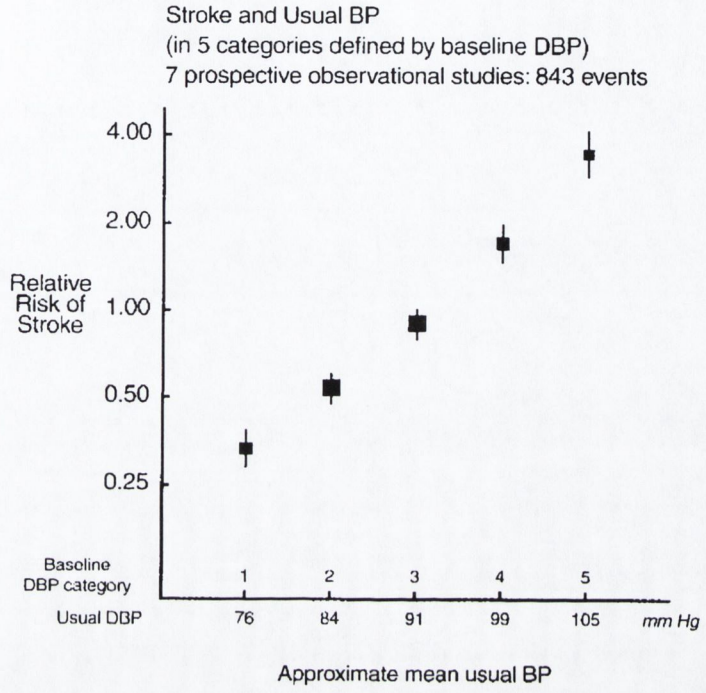
face a recurrent stroke and the risk of a recurrent stroke over five years is about 25%.

After a stroke, the victim will suffer a wide range of neurological deficits and these will get worse in 30% of patients. About half of all long-term survivors of stroke are physically disabled[145]. The financial implications are huge. In 1993, non-fatal stroke accounts for 4.4% of the entire UK National Health Service expenditure. The overall burden is difficult to assess in the absence of reliable morbidity data, but in developed countries, 25-30% of the cardiovascular disease burden arises from disabling sequelae of stroke or other forms of heart disease[130].

In the United Kingdom, it is estimated that 40% of all strokes are attributable to a SBP of 140mmHg or greater. After adjusting for age, men aged 40-59 years with SBP of 160mmHg to 180mmHg have about a four-fold higher risk of stroke during the next eight years than men who have a SBP of 140 to 159mmHg[146]. Stroke was found to be the cardiovascular event most closely associated with hypertension in a 1990 analysis of nine prospective longitudinal observational studies from North America and Europe[147]. It also showed a clear, continuous and almost linear relationship between mean DBP and the relative risk of the first stroke (Figure 13). This was as true for people with a mean DBP of 70-90mmgHg as it was for people conventionally considered hypertensive with a mean DBP greater than 90mmHg (up to 110mmHg). The data suggested that prolonged decreases in usual DBP of 5, 7.5, and 10 mm Hg were associated with at least 34%, 46%, and 56% less stroke.

Figure 13 Hypertension and the Relative risks of stroke

The solid squares represent risk of stroke in each category relative to the risk in the whole population; sizes of squares are proportional to the number of events in each diastolic blood pressure category, vertical lines show 95 per cent confidence intervals for estimates of relative risk[147]



These studies involved large, virtually untreated, middle-aged and pre-dominantly male (96%) populations with a total of 4.2 million person-years of observation and a mean 10-year follow-up. There was no "threshold" indicating an increased the risk of stroke. Neither was there any evidence that low blood pressure might be associated with an increased risk (the so called "J-curve" effect). The message was simple; the higher the blood pressure, the higher the risk of stroke. The same appears to be true also for women except that the relative risk is lower for women below the age of 55 years suggesting a protective effect of oestrogen against cardiovascular disease pre-menopause. The link between the recurrence of stroke and the level of blood pressure is not yet well established.

The observation of MacMahon *et al* of a continuous relationship between blood pressure and stroke means that only 25% of stroke occurs in people considered as being hypertensive. Therefore, a small reduction in the blood pressure, e.g. 9/5mmHg (systolic/diastolic), across the whole population would be expected to significantly cut the rate of fatal and non-fatal stroke.

In Figure 14 below the potential benefit of a population wide reduction is shown for France, America, Russia and China

Figure 14 Potential deaths from stroke prevented by a reduction of 9/5mmHg in SBP / DBP across a whole population

Country	Deaths prevented
France	20,000
USA	51,000
Russia	184, 000
China	476,000

Adapted from Chalmers *et al* 1997[148]

This would be even more pronounced for populations where the risk of stroke was more closely related to blood pressure. It has been estimated that in the Chinese and Japanese population a population-wide reduction of 3 mm Hg in DBP could eventually decrease the number of strokes in the by about a third[149].

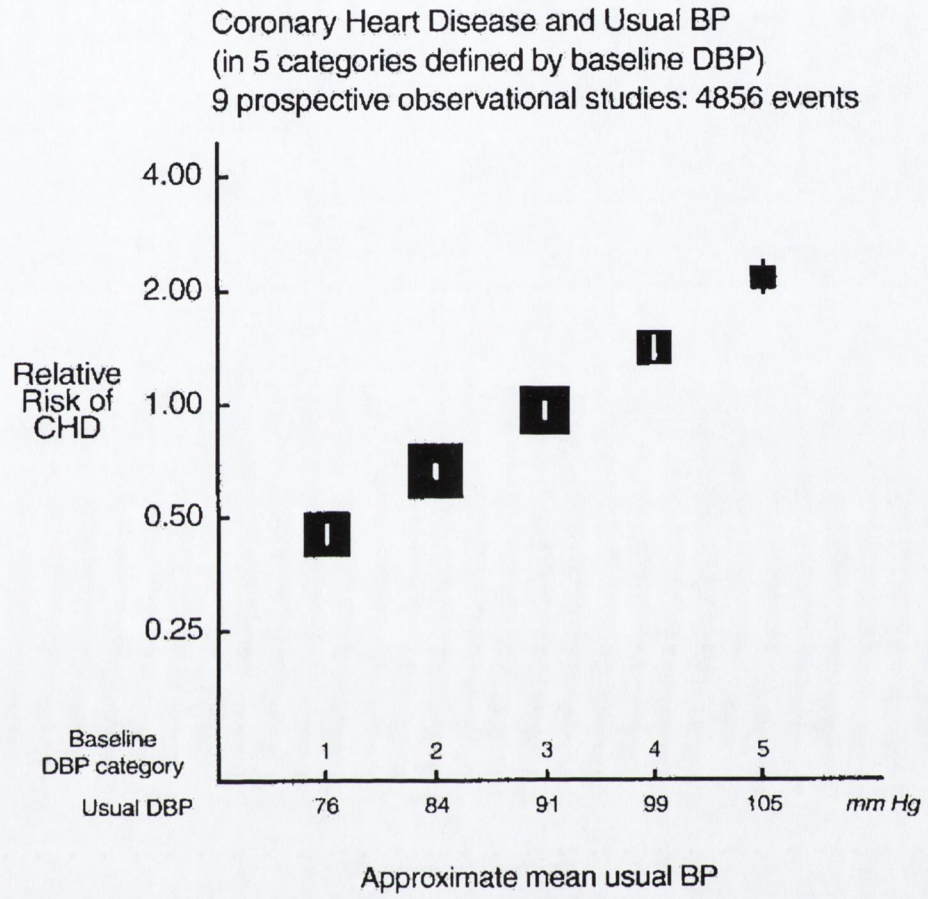
Data from the UAE is scarce and the numbers of deaths from stroke are relatively small due to the young population (there are less than 2% of the countries population over the age of 60 years). However, it generally agreed that the incidence of stroke is expected to rise rapidly over the next 20 years in line with the aging national population

2.7.2. Coronary heart disease

Fatal coronary heart disease (CHD) is seven times more common among hypertensives than stroke and, therefore, it is the major mortality among hypertensives. However, compared with stroke, it is less clear if this is a direct causal relationship. Hypertension may be independent risk factor for fatal myocardial infarction but it is very difficult to differentiate between the common risk factors amongst patients with hypertension and those suffering fatal CHD. This is borne out by the relative lack of intervention studies showing reduced CHD from treating hypertension.

Figure 15 Relative risks of CHD

Solid squares represent CHD risk in each category relative to risk in the whole study population; sizes of squares are proportional to number of MI's in each DBP category; vertical lines show 95% confidence levels for estimates of relative risk (MacMahon et al 1990)



The 1990 analysis by MacMahon *et al* demonstrated a clear, continuous and almost linear relationship between mean diastolic blood pressure and the relative risk of a coronary event (fatal and non-fatal heart attack, (Figure 16) [147]. As the blood pressure increased, so did the risk of stroke and coronary heart disease. The data suggested that a 5 to 6 mmHg reduction in the average level of DBP would result in a 20 to 25 per cent reduction in CHD.

The Multiple Risk Factor Intervention Trial (MRFIT) produced a huge amount of data regarding the link between blood pressure and CHD[150]. This was one of the coronary heart disease prevention trials recommended to the National Heart and Lung Institute in 1971 as an alternative to a national, single-factor dietary trial, which was judged not to be feasible. MRFIT was a randomised, primary prevention trial, conducted at 22 US clinical centres from 1973 to 1982 to test

whether lowering elevated serum cholesterol and diastolic blood pressure and ceasing cigarette smoking would reduce coronary heart disease mortality. Among the 356,222 men screened for the Multiple Risk Factor Intervention Trial aged from 35 to 57 years and who had no history of hospitalisation for heart attack at entry, more than 2,000 coronary deaths occurred during 6 years of follow-up. With this large data set, detailed cross- tabulations clearly show the strong graded relationship between blood pressure and CHD.

Figure 16 Relative risk (R.R.) of CHD increases along with the blood pressure

(adapted from Stamler *et al* 1989[150]

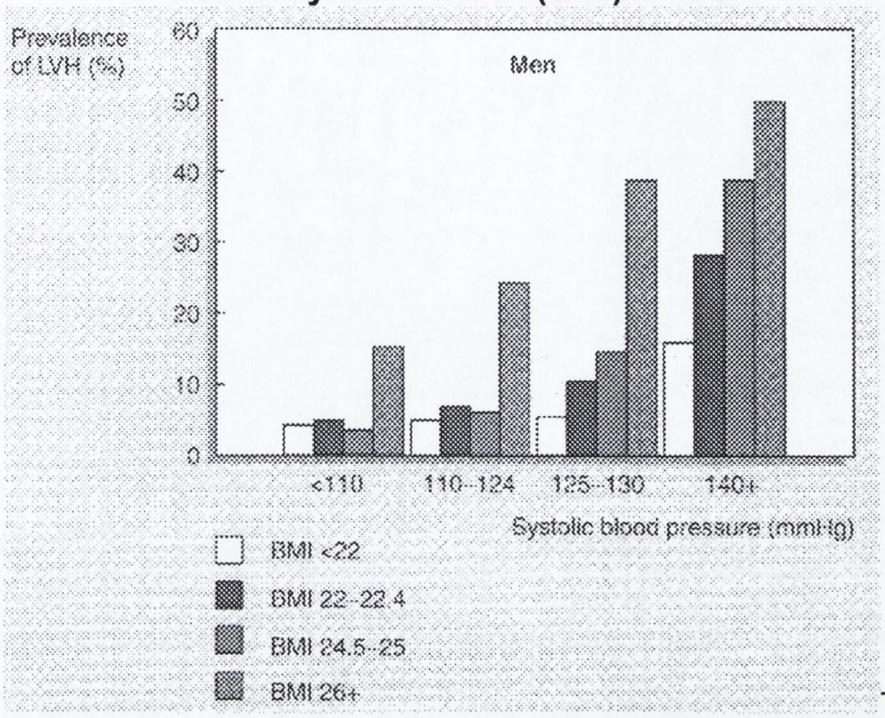
	Normal	IDH	ISH	HTN
SBP/DBP mmHg	**<120/<80**	**<120/>100**	**>160/<80**	**>160/>80**
R.R. of CHD	1.00	3.23	4.19	4.57

The data in Figure 16 shows that the relative risk of CHD increased progressively from 1.00 with optimum levels of blood pressure (SBP <120mmHg, DBP <80mmHg) to 3.23 in isolated diastolic hypertension (IDH = DBP >100mmHg, SBP <120mmHg). The relative risk was 4.19 in people with isolated systolic hypertension (ISH = SBP >160mmHg, DBP <80mmHg) and 4.57 in those with a combined increase of both SBP and DBP. This risk gradient was evident in each of five age groups. For middle-aged and older persons, SBP related even more strongly to risk of CHD than DBP at every DBP level. Higher SBP results in greater CHD risk and curtailment of life expectancy.

2.7.3. Left ventricular hypertrophy (LVH)

Hypertension is a well-established precursor of LVH[151]. It is an increase in the mass of the left ventricle and is an adaptive response to ventricular loading. It is not clear where the beneficial effects of hypertrophy ends and the pathological effects begin. In pathological hypertrophy, there is an increase in the number and size of cardiac muscle cells (myocytes), fibroblasts, vascular smooth muscle and collagen. The proliferation of non-myocytes appears to be a key factor leading to a pathological reduction in ventricular compliance and increased ischaemia in the increased muscle. The ventricular load is not the single factor leading to hypertrophy and it is dependent upon a number of growth factors including angiotensin-2 and mineral corticoids. The prevalence is directly linked to the SBP and to obesity (determined by the body mass index)[152].

Figure 17 Age adjusted prevalence of LVH according to SBP and Body Mass Index (BMI) in men



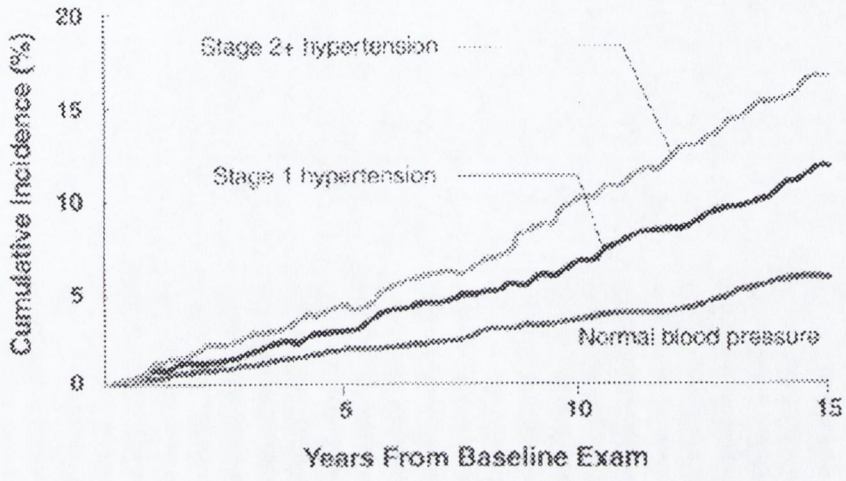
The association is similar for women but more pronounced for men. Long term follow up data from the Framingham study show that in patients with ECG proven left ventricular hypertrophy (LVH), there is a three fold risk of cardiovascular disease especially myocardial infarction, and congestive heart failure[118]. LVH increases all cause and cardiovascular mortality. The Framingham study has provided a wealth of data about the epidemiology of LVH. Age, obesity, and hypertension (especially the SBP for which the association is stronger for long-term data than for single measurements) are all risk factors for LVH. The prevalence increases progressively with age.

LVH is known to be a sequelae of hypertension and can be detected and measured using echocardiography, chest x-ray or ECG. The correlation between each method is modest and cannot be compared directly. In the Framingham study, 50% of men aged 70-74 years had radiographically confirmed LVH compared with 15.4% who had LVH when determined by ECG. Although cheaper and more accessible, the ECG is not as sensitive a method for detecting LVH, as is echocardiography. However, ECG detected LVH carries a worse prognosis as it is more severe and is more likely to be associated with ischaemia. ECG detected LVH is the most important risk factor for the later development of heart failure.

2.7.4. Heart failure

Data from the Framingham study showed that hypertension increased the cumulative risk of heart failure and that the higher the blood pressure, the greater the risk [153].

Figure 18 Effect of hypertension on the incidence of heart failure



Cumulative incidence of congestive heart failure in normotensive individuals and individuals with stage 1 and stage 2 hypertension as a function of time (in years) from baseline examination. Data from the Framingham Heart Study and National Heart, Lung, and Blood Institute, 1996.

The SBP was consistently and independently related to the risk of developing heart failure in both men and women and that the DBP was significantly and independently related to the risk of developing heart failure in women only. A person with a blood pressure of greater than 160/95mmHg had a six-fold higher incidence of heart failure than those with pressures <140/90mmHg[154]. Hypertension is the antecedent of 90% of cases of heart failure[153] . In the USA, heart failure is the leading cause of death, affecting 2-4 million people, with around 465,000 new cases diagnosed each year. Heart failure is one cardiovascular disease that has shown a marked increase in prevalence since the Framingham study. Data from the Framingham study showed that the annual incidence of heart failure among those aged 45-54 was 0.2%[154]. This was similar to the data gathered by the US National Health and Nutrition Examination Survey (NHANES) 1976-80. The NHANES data from 1988-91 showed a dramatic increase in the prevalence of heart failure, especially in those over 65 years. In the US, it is now the most common medical discharge diagnosis for patients over

the age of 65 years. Heart failure has a poor long-term prognosis. The diagnosis is associated with 50% mortality within 5 years[155].

2.7.5. Renal disease

The renal damage caused by hypertension is characterised by arteriosclerosis of the renal vasculature. In the early stages, there is glomerular hyperfiltration with intra-glomerular hypertension. The increased glomerular filtration is marked by microalbuminaemia and a gradual decline in the renal function, as glomeruli are lost. In severe cases, there can be atherosclerotic disease of the renal arteries and this can lead to renal artery stenosis and further progression of the hypertension. Hypertension is not a common cause of renal failure but it does aggravate the glomerular damage caused by diabetes mellitus, which affects up to 30% of people with high blood pressure.

2.7.6. Retinopathy

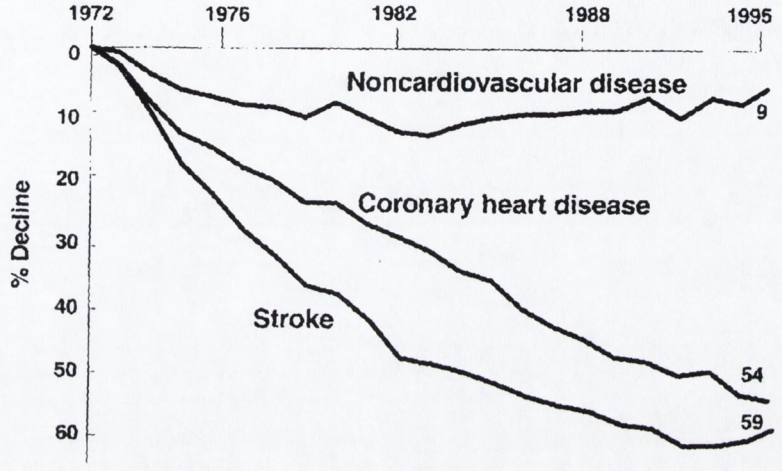
Various retinopathies are associated with hypertension and these can lead to significant loss of sight. They are caused by arteriosclerosis of the vessels serving the retina and optic nerve. In severe, uncontrolled hypertension, this leads to focal arteriolar narrowing, retinal infarcts and haemorrhages. Papilloedema is a swelling of the optic disc that is caused by a breakdown in autoregulation of capillary blood flow in the presence of high blood pressure

2.7.7. Global impact of cardiovascular disease.

Cardiovascular disease causes 12 million deaths in the world each year[156].

Figure 19 Percentage decline in age-adjusted mortality rates in the USA

For all individuals for stroke, coronary heart disease and non-cardiovascular disease for 1972-1995 (JNCVI)



Non-communicable diseases such as cardiovascular disease are recognised as the major emerging health problem in developing countries, rapidly replacing infection as the major cause of deaths in adults. In Africa, Western Asia and Southeast Asia, 15 to 20% of the estimated 20 million deaths are due to cardiovascular diseases. Overall, it is estimated that cardiovascular disease accounts for eight or nine million deaths in developing countries, or about 70% more than that for developed countries. By the year 2020, it is estimated that non-communicable diseases will account for 70% of all deaths in the developing regions[157]. A large part of this will be due to increases in the incidence of cardiovascular disease.

The international incidence figures conceal different trends in the rise and decline of death from cardiovascular disease in different countries. Many countries have reported significant decreases in mortality from cardiovascular disease as well as specific cardiovascular diseases over the last 20 years. In the USA, between 1972 and 1995, death from stroke decreased by 59% and death from coronary heart disease decreased by 54%. A decrease of 60% in male mortality has been reported in Japan and a decrease of 50% in Australia, Canada, France and the United States with similar figures for females. In other parts of Europe the decrease has been less in Scandinavia, Ireland, Portugal and Spain (20-25%).

The decrease in the death rate is a mixture of reduced incidence and improved treatment.

Amidst these, generally positive and optimistic statistics, there are a number of disturbing trends. As can be seen in figure 19 above, the rate of decline in age-adjusted mortality for stroke and CHD has been levelling off and may actually be increasing. It is also important to appreciate national statistics can hide significant variations within a country or region. A review of the US stroke mortality data (1968-96) shows wide racial and geographical variations in the death rate[158]. The contrast between Western Europe and Eastern Europe, the former Soviet Union, is particularly stark when one looks at premature death rates from cardiovascular disease. An ongoing WHO survey by the European regional office, the MONICA study has shown the incidence of cardiovascular events across 31 countries in Europe[159]. The data also suggests that since the break-up of the former Soviet Union there has been an increase in male cardiovascular mortality. This has been an increase of 40% in Hungary and the former Czechoslovakia, almost 60% in Poland and almost 80% in Bulgaria. Premature death rates from cardiovascular disease range from 40.5 per 100,000 in France to 248 per 100,000 in Latvia, a ratio of 1 to 6.

There are elaborate quality assurance procedures for the data collection in the MONICA study but some of these depressing results have been challenged. A prospective population study in the Ukraine showed that the incidence of stroke and the 30-day mortality data were much closer to the West European average than the MONICA data suggests[160]. This may reflect variation within the Ukraine or some other anomaly within the MONICA comparative data. Reanalysis of the MONICA data has shown that improvements in the acute care of cardiovascular events, especially coronary care and more rigorous secondary prevention is a strong factor behind the mortality improvements in some countries, rather than a decrease in the incidence per se[161]. Globally, premature death due to cardiovascular disease is 2.5 times higher in men than for women but this trend may also be reversing.

2.7.8. Hypertension defined according to the Cardiovascular Risk

A person's risk of suffering a serious cardiovascular event can be estimated from their exposure to certain risk factors Some risk factors cannot be modified, such as age, sex and family history; while others can be modified and include hypertension, smoking, obesity and a range of co-morbidity's including dyslipidaemia, diabetes and pre-existing cardiovascular disease (Figure 20). These risks are additive and can therefore greatly increase the risk of suffering a cardiovascular event.

Figure 20 Factors that will influence the definition of hypertension according to cardiovascular risk

Adapted from the WHO-ISH Guidelines 1999[116]

Risk Factors for Cardiovascular Diseases	Target Organ Damage	Associated Clinical Conditions
I. Used for risk stratification • Levels of systolic and diastolic blood pressure (Grade 1-3) • Men > 55 years • Women > 65 years • Smoking • Total cholesterol >6.5 mmol/L (250 mg/dL) • Diabetes • Family history of premature cardiovascular disease **II. Other factors adversely influencing prognosis** • Reduced HDL cholesterol • Raised LDL cholesterol • Microalbuminuria in diabetes • Impaired glucose tolerance • Obesity • Sedentary lifestyle • Raised fibrinogen • High risk ethnic group • High risk geographic region	• Left ventricular hypertrophy (ECG, echocardiogram or X-ray • Proteinuria and/or slight elevation of plasma creatinine concentration (1.2-2.0 mg/dL) • Ultrasound or X-ray evidence of atherosclerotic plaque (carotid, iliac and femoral arteries, aorta) • Generalised or focal narrowing of the retinal arteries	*Cerebrovascular disease* • Ischaemic stroke • Cerebral haemorrhage • Transient ischaemic attack *Heart disease* • Myocardial infarction • Angina • Coronary revascularisation • Congestive heart failure *Renal disease* • Diabetic nephropathy • Renal failure (plasma creatinine conc. >2 mg/dL) *Vascular disease* • Dissecting aneurysm • Symptomatic arterial disease *Advanced hypertensive retinopathy* • Haemorrhages or exudates • papilloedema

As can be seen in Figure 20, above, the same level of hypertension, defined in clinical and statistical terms, can be associated with a very wide range of risk of having a major cardiovascular event (stroke or myocardial infarction). A patient with a SBP of 145 mmHg could have a 10-year risk ranging from less than 15%

("Low risk") to about 20-30% depending upon the number of risk factors and co-morbidities.

Figure 21 Definition of Hypertension according to the Absolute Cardiovascular Risk

Adapted from the WHO-ISH Guidelines 1999[116]

Other risk Factors & Disease History	BLOOD PRESSURE (mmHg)		
	Grade 1 (mild hypertension) SBP 140-159 or DBP 90-99	Grade 2 (moderate hypertension) SBP 160-179 or DBP 100-109	Grade 3 (severe hypertension) SBP ≥ 180 or DBP ≥ 110
I. no other risk factors	LOW RISK	MED RISK	HIGH RISK
II. 1-2 risk factors	MED RISK	MED RISK	V HIGH RISK
III. 3 or more risk factors or TOD[A] or diabetes	HIGH RISK	HIGH RISK	V HIGH RISK
IV. ACC[B]	V HIGH RISK	V HIGH RISK	V HIGH RISK

Risk strata (typical 10 year risk of stroke or myocardial infarction): Low risk = less than 15%; medium risk = about 15-20% risk; high risk = about 20-30%; very high risk = 30% or more

[A]. TOD = Target Organ Damage (see above)

[B]. ACC = Associated Clinical Conditions, including cardiovascular disease or renal disease

2.8 Blood pressure measurement

Although the blood pressure is an indirect marker of the benefit of treatment, historical data is readily available in the medical record and it is measured at consultations relating to hypertension. However, if blood pressure data is to be used as a marker of adherence to medication it is important to understand the limitations and sources of error that affect clinic based blood pressure measurement.

2.8.1. Use of a Mercury sphygmomanometer

It is recommended that all blood pressure measuring devices should be validated and well maintained. The mercury, cuff sphygmomanometer is the instrument of choice. As concerns grow about the environmental dangers of mercury many anticipate that mercury sphygmomanometers will eventually disappear. Aneroid manometers are increasingly popular but inaccurate unless frequently

recalibrated. The most likely alternative is an electronic oscillometric device although very few are approved for clinical use now.

Detailed guidance has been provided by expert groups in an attempt to standardize this aspect of management e.g. The British Hypertension Society[162], The American Society of hypertension[163] and the American Heart Association[164]. The cuff must be appropriate to the arm circumference. The bladder within the cuff should encircle at least 80 percent of the arm (many obese adults and athletes require a large adult cuff). The patient should be seated comfortably (unless one is trying to exclude orthostatic hypotension e.g. in the elderly or diabetics when they should stand). The arm should be bared and supported at heart level, e.g. on a table. The systolic and diastolic pressures should be measured. The first appearance of sound (phase 1) is used to define systolic blood pressure. The disappearance of sound (phase 5) is used to define diastolic blood pressure. Two or more readings should be taken at least 2 minutes apart. The average of the two readings should be recorded. If the two readings vary by more than 5 mm Hg then further readings should be obtained.

Although the device itself is inherently accurate, several factors can reduce the accuracy of sphygmomanometers. Most of these can be avoided by proper technique on the part of the observer.

2.8.1.1. Systematic errors

Despite the important management decisions based upon it, blood pressure measurement is fraught with inaccuracy. The systematic method by which blood pressure is measured is an important source of variation. This is important either when comparing readings between patient visits or when comparing the effects of different blood pressure lowering interventions. . In the same way that many people are found to be hypertensive in the clinic, clinic measurements can also miss true hypertension. Research from Canada has found that clinic measurements can miss a sizeable portion of patients with high mean ambulatory blood pressure. This so-called "white coat normotension" has been estimated at between 14%[165] to 30% in elderly Japanese patients[166]. In a group of 319 healthy people who had repeated clinic blood pressure measurements, around 24% of these people were found to be hypertensive when they underwent 10-12 hour daytime ambulatory blood pressure monitoring, despite being normotensive according to the clinic measurements[167]. Not only is it of concern that so many people may miss detection, but these results confirmed earlier work[168] that many

with "white coat normotension" are older, male, past smokers who consumed more alcohol. All of which are themselves cardiovascular risk factors and make the diagnosis and treatment of hypertension important. In the Canadian study, "reasonable" diagnostic accuracy was achieved in the clinic only if the blood pressure was at least 20 points above or below the cut-off values for hypertension (140 / 90mmHg). The paper served as a timely reminder that there are many potential pitfalls when measuring blood pressure and frequent retraining of the observer is important.

2.8.1.2. Terminal digit preference

This refers to the tendency for observers to round off the blood pressure reading to a digit of their preference, often a zero. As the most common "break-points" between normal and raised blood pressure end in a zero, this can have important implications for studies that categorize blood pressure as "controlled / uncontrolled". It has the potential to reduce the power of statistical tests. Therefore, it was monitored in the research conducted in this thesis. It is discussed in Annex 6.

2.8.2. Ambulatory Blood Pressure Monitoring (ABPM)

Although developed as a research tool, a variety of commercially available monitors, which are reliable, convenient, easy to use and accurate are now available both in Europe[169] and the USA[170]. It is discussed here as an important development in the measurement of blood pressure and one that can be useful to differentiate between "white coat hypertension" and non-adherence.

These monitors typically are programmed to take readings every 15 to 30 minutes throughout the day and night while patients go about their normal daily activities. The readings can then be downloaded onto a personal computer for analysis. Normal blood pressure values taken by ambulatory measurement are lower than readings taken in the clinic (below 135/85mmHg) and even lower in patients who are sleeping (below 120/75mmHg). In the majority of individuals, blood pressure falls by 10 to 20 percent during the night. This corresponds more closely to patterns of sleep and wakefulness than to time of day, as illustrated by the blood pressure rhythm following the inverted cycle of activity in night shift workers[171].

Among persons with hypertension the ambulatory blood pressure correlates more closely to target organ damage than does the clinic measured blood pressure [172]. Prospective data relating ambulatory blood pressure to prognosis are limited to

two published studies which suggest that in patients in whom an elevated clinic pressure is the only abnormality, ambulatory monitoring may identify a group at relatively low risk of morbidity[173]

The American Society of Hypertension[174] has described the main uses of ambulatory blood pressure monitoring as:

most clinically helpful and most commonly used

- ✓ in patients with suspected "white-coat hypertension"

also helpful in patients with:

- ✓ apparent drug resistance (non-response)
- ✓ hypotensive symptoms with antihypertensive medication
- ✓ episodic hypertension
- ✓ autonomic dysfunction.

On a national level, the annual direct costs of ambulatory blood pressure monitoring could be as high as US$6 billion, if this technique were used routinely to diagnose and monitor hypertensive patients[172]. The extent to which direct costs would be offset by savings from less frequent or more efficient treatment for hypertension cannot be estimated reliably. This, together with several practical and technical issues also detracts from the potential usefulness of ambulatory devices. Ambulatory blood pressure monitoring is not yet recommended to for the routine evaluation and diagnosis of hypertension.

2.8.3. Self measurement of blood pressure

Measurement of blood pressure outside the clinic may provide valuable information for the initial evaluation of patients with hypertension and for monitoring the response to treatment. The American Society of Hypertension gives four general advantages for self-measurement[174].

Distinguishes sustained hypertension from "white-coat hypertension"

Assessing the response to medication and changes to medication

Improving medication adherence

Reducing the costs of management

It is important to note that all clinic based blood pressure measurements tend to be higher than those measured out of the clinic, therefore readings of 135/85mmHg or greater should be considered high[172 ,175]. The choice of appropriate monitor remains a point of discussion. While it is generally agreed that finger monitors are inaccurate[176] there are a variety of electronic and aneroid sphygmomanometers that have proven to comply with standard testing in both Europe[177] and the USA[170]. Most self measurements are slightly lower than those observed in the clinic; however, this should not change the management plan as the data from which management guidelines have been evolved is almost always derived from clinic based blood pressure measurements.

2.8.4. Variability in 24 hour blood pressure

In most cases, the diagnosis and monitoring of hypertension relies upon blood pressure measurements in the clinic. These measurements are a "snap-shot" at a particular time. Variation in blood pressure readings may occur due to patient factors or problems with the person taking the measurement (observer). This variation must be anticipated and controlled for if one is to objectively diagnose, treat and monitor hypertension. The main sources of variation lie in the diurnal variation, patient anxiety and the method of measurement. These factors are discussed below and will be referred to in subsequent sections discussing the management of hypertension.

2.8.5. Variation due to patient factors

In the course of a 24-hour period the normal, circadian rhythm will include a fall in blood pressure while asleep, and a rapid rise, at or just before the time of wakening and getting out of bed. On top of this will be the effect of physical exercise and emotional activity. Some patients only exhibit hypertension in presence of health professionals, especially doctors. This so-called "white coat hypertension" is controversial and is discussed in more detail in 2.4 above, definition of hypertension. It should be suspected in patients who show persistently raised blood pressure but have no sign of clinical sequelae or in patients who develop symptoms of hypotension even with small doses of antihypertensive drugs. White coat hypertension can be detected by encouraging patients to perform blood pressure measurements themselves with automated devices. To study the circadian variation researchers have developed 24-hour ambulatory blood pressure monitoring (ABPM) see 2.8.2 above.

The variability can become further complicated if patients are treated with once daily antihypertensive drugs. Concern has been voiced that these drugs may not be active for a full 24-hour period, or may achieve their effect by lowering the blood pressure excessively early in the 24-hour period, e.g. by giving an excessive dose. This concern for patient safety led the United States Food and Drug Administration (FDA) to introduce the concept of a Trough to Peak (T-P) ratio as part of their proposed guidelines for the clinical evaluation of new antihypertensive agents[178,179].

2.9 Clinical management of hypertension

Having discussed the need to lower a raised arterial pressure, this section will discuss the clinical management of hypertension.

Since 1997, there have been three major sets of guidelines published.

1997 – The sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNCVI)[115]

1999 – World Health Organization – International Society of Hypertension Guidelines for the Management of Hypertension[116]

1999 – Guidelines for the management of hypertension: report of the third working party of the British Hypertension Society[180]

Each has been written with different overall objectives and from a slightly different perspective but an important aim of each is to guide physicians on the optimal

management of mild to moderate hypertension and the significance of co-existing risk factors. As a result, these guidelines provide an outstanding summary of the existing evidence about the diagnosis and treatment of hypertension. The guidelines address the goals of treatment, lifestyle modification and drug therapy.

2.9.1. Goals of treatment

The goals of treating patients with hypertension have been summarised as follows[181]:

- Decrease the attendant cardiovascular risk from hypertension
- Decrease the attendant risk of co-existing cardiovascular factors
- Improve quality of life and encourage a healthy lifestyle
- Minimise adverse effects, inconveniences and ensure that there is a net benefit

While drugs play a large part in the management, lifestyle modifications can greatly improve the response to medication, and in some cases, avoid the need for medication.

2.9.2. Lifestyle modifications

Various, so-called lifestyle modifications have been proposed to prevent and control hypertension. They are summarised in Figure 22. These focus on exercise, diet and stopping smoking. They are designed to counter a range of known risk factors for hypertension, and cardiovascular disease in general.

Figure 22 Recommended lifestyle modifications

Adapted from JNCVI[115]

Lifestyle modifications for hypertension prevention and management
Lose weight if overweight
Limit alcohol intake to no more than 30mL of ethanol per day for men e.g. 720mL beer, 300mL of wine, and 60mL of whiskey. This should be no more than 15mL for women or lighter people
Increase aerobic activity (30 – 45 minutes per day)
Reduce sodium intake (not more than 100mmol per day)
Maintain adequate intake of dietary potassium (90mmol per day) and calcium and magnesium
Stop smoking and reduce dietary saturated fat and cholesterol intake

2.9.3. Drug management of hypertension

A modern antihypertensive drug regime will use one or more of the following drugs; Thiazide diuretics, Beta-blockers, Angiotensin Converting Enzyme Inhibitors (ACEI), Calcium Channel Blockers (CCB), Angiotensin II receptor antagonists (AIIA) and alpha-blockers. In clinical trials, any of these drugs can be shown to decrease the systolic and diastolic blood pressure by an average of 10-15mmHg / 5-10mmHg. This is often difficult to achieve in clinical practice and one reason for this will be non-adherence, especially as many of the trials exclude less adherent subjects. The challenge of adherence is made even greater by most hypertensive patients taking other chronic medicines. Up to thirty per cent of hypertensives are diabetics, many of who will be taking oral hypoglycaemic agents. Furthermore, a variety of other medicines may be taken to manage concomitant cardiovascular disease such as lipid lowering (statin) medicines and antiplatelet treatment. This is in addition to lifestyle changes. Other interventions range from dietary changes, modest alcohol intake and smoking cessation to. Some of these have been shown to be effective in large controlled studies e.g. antihypertensive drugs, statin therapy for primary and secondary coronary protection and anti-platelet treatment (aspirin) for primary and secondary protection, especially post myocardial infarction and in diabetes. The benefit of others is unclear e.g. dietary supplements of garlic and antioxidants; while some interventions are probably ineffective (Vitamin E) or even harmful e.g. short-acting calcium channel blockers. Figure 24 summarises the therapeutic options for people with hypertension and known cardiovascular disease.

Figure 23 Therapeutic options for people with hypertension and known cardiovascular disease

Adapted from Mulrow 2001[181]

Effective	Possibly effective	Unclear	Ineffective	Possibly harmful
Antihypertensive drug therapies	Mediterranean diet	Antioxidants	Vitamin E	Alpha-blockers
Statin therapy	Diabetes management	Vitamin C & flavanoids		Short-acting calcium channel blockers
Smoking cessation	Modest alcohol consumption	Garlic, Potassium, Calcium, Magnesium		Beta-carotene supplements
Physical activity	Fish oil			
Antiplatelet treatment				
Anticoagulant treatment				

The selection of a first-line drug for hypertension is a contentious subject. Consensus guidelines such as the JNCVI and WHO-ISH guidelines promote a low-dose thiazide diuretic or a beta-blocker as first line but also acknowledge that a variety of comorbid conditions may indicate the selection of an alternative first line drug. The main indications for tailoring the regime to individuals are comorbidities, especially diabetes, heart failure and coronary artery disease. The individualised approach may have more appeal to the UAE environment. While first line, low dose diuretics are most suitable for elderly patients; this group is a minority of the hypertensive patients in the UAE due to there being a very young population. Furthermore, at least 30% of hypertensive patients are diabetic.

The JNCVI guidelines provided an overview of the considerations for individualising antihypertensive drug therapy according to comorbidities and this is summarised in Figure 26 along with data that has been published since JNCVI.

Figure 24 Common indications for individualising antihypertensive drug therapy, unless contraindicated

Adapted from JNCVI[115] and Pignone et al[182]

Indication	Drug therapy
Angina	Beta blockers or long acting CCB
Diabetes (type 1) with proteinuria	ACE I
Diabetes (type 2)	ACE I or Beta blocker or Thiazide
Diabetes and Myocardial infarction	ACE I **and** Beta blocker
Heart failure	ACE I, with or without Thiazide
Heart failure from Left ventricular dysfunction	ACE I **and** diuretic Beta blocker in stable heart failure
Isolated systolic hypertension (older patients)	Diuretics (preferred), CCB (long acting DHP)
Myocardial infarction	Beta blockers (without ISA), ACE I (with systolic dysfunction)
Myocardial infarction and left systolic dysfunction	ACE I **and** Beta blocker **and** Thiazide
ACE I Angiotensin Converting Enzyme Inhibitor CCB Calcium Channel Blocker DHP Dihydropyridine	

This individualised care approach is supported by large controlled studies but at the time of the JNCVI guidelines, there was relatively less evidence to show the comparative efficacy of different first line drugs. One of the reasons for this is that the reduction in target organ damage seen with antihypertensive drugs does not appear to be directly related to the decrease in the blood pressure and although two drugs may have an equivalent effect upon the blood pressure, some may have a greater beneficial effect upon the cardiovascular risk[183]. As the blood pressure is an indirect outcome marker it follows that only well designed, large prospective studies can hope to provide answers regarding relative benefit from different drug classes. In recent years, this type of evidence has started to appear (summarised in Figure 25)

Figure 25 Summary of studies of first-line antihypertensive agents and their comparative effectiveness on overall cardiovascular disease

First line drugs	Overall conclusion	Study
ACEI or CCB vs. thiazide +/- beta blocker	No difference	STOP-2[184]
ACEI (Captopril) vs. thiazide +/- beta blocker	No difference except in diabetes	CAPPP[185]
CCB (Diltiazem) vs. thiazide +/- beta blocker	No difference	NORDIL[186]
CCB (Nifedipine) vs. thiazide	No difference in ESRD, CHD or stroke	INSIGHT[187]
ACEI vs. Beta blocker	No difference	UKPDS 39[188]
ACEI vs. CCB	Reduced vascular events with ACEI in type 2 diabetics	FACET[189]
Alpha blocker (doxazosin) vs. thiazide (chlorthalidone)	Excess cardiovascular events, especially heart failure, with doxazosin	ALLHAT[190]
Thiazide (chlorthalidone) vs. ACEI (lisinopril) vs. CCB (amlodipine)	No difference in primary endpoint	ALLHAT[191]

While there is little evidence from large studies of superiority of one class of drug over another, there is growing evidence that the choice of drug is important for diabetics and those at risk of heart failure. ACE inhibitors have clear benefits in patients with established heart failure[192] and it is expected that angiotensin receptor antagonists will confer the same benefits as ACE inhibitors[193], perhaps with fewer side effects[194] [195]. Furthermore, long-term negative effects are still being identified through carefully controlled studies e.g. use of the alpha-blocker doxazosin results in more cardiovascular events, especially congestive heart failure, compared with a diuretic (chlorthalidone) [190,196].

However, the main debate about the JNCVI guidelines is already moving on from the comparative first line efficacy of newer agents. Increasingly, the debate is about the first line use of multiple antihypertensive drugs in high risk

hypertensives[182], [197] and the need to promote persistence, and hence adherence to antihypertensive medication.

2.9.4. Relationship of non-adherence to therapeutic failure in hypertension

The corollary of effective therapies is that non-adherence will result in therapeutic failure. This assumes that therapeutic success is due to the medication, and that medication, if used properly, will always be successful.

Some adherence studies in hypertensives have found that 5-8% of "controlled hypertensives" have "low" levels of adherence. The Morisky study[39] found that after 18 months of treatment, 16% of the patients reported low adherence, of whom, almost half (47%) had "controlled" blood pressure (diastolic blood pressure <90-100mmHg depending upon the patients age). Vaur et al studied over 2000 patients taking a once daily ACE inhibitor for 6 weeks and measured adherence using an electronic monitor (MEMS)[73]. Six per cent (120/2173) of the patients had "very low adherence" (taking less than 50% of the doses at the correct time). In this group, 86 (71.7%) had a diastolic blood pressure of less than 90mmHg. This highlights the need to be aware of possible misdiagnosis or over-treatment of hypertension in a minority of patients.

Nuesch *et al* studied 103 consecutive hypertension patients in a specialist hypertension clinic at a University hospital and concluded that non-adherence was not a cause of "resistant" hypertension[198]. All patients were taking between two and four antihypertensive drugs and adherence was measured by dispensing two of the patient's antihypertensives in containers with electronic monitors (MEMS). Daytime ambulatory blood pressure measurement was used to assess control of blood pressure. They found no significant difference in the adherence of those patients whose blood pressure was controlled or not controlled. Approximately half the patients were controlled and in both groups, 82-85% of patients were taking over 80% of their monitored doses correctly. The authors concluded that this was evidence that non-adherence is not related to therapeutic failure in hypertension. This was an important challenge to the received wisdom that non-adherence is a major cause of treatment failure and therefore it is important to note several weaknesses in the study and difficulties extrapolating the conclusions to wider practice. The comparative groups were relatively small (54 vs. 49) and while the demographics appear to be well matched, there is no mention of the exact number of drugs taken by patients in the two groups or the

duration of treatment with that regimen. It is not clear, if all drugs were given as single formulations or if they included combination formulations. The overall level of adherence was over 80%, which is very good and much higher than expected for chronic therapy outside of a clinical trial, especially considering that some patients were taking four drugs! This was a specialist clinic and it may well be that patients with poor adherence are not referred for specialist opinion as frequently as in those who have other probable causes of uncontrolled hypertension. The conclusions of the study by Nuesch *et al* could equally be that the blood pressure treatment that had no impact on the control of blood pressure. Although this is an interesting study, it has weaknesses and it cannot be easily extrapolated to wider practice.

Non-adherence will result in a failure to reach the therapeutic goals in most patients. However, the degree of blood pressure control in patients with low-adherence will depend upon how closely the prescribed dose is to the minimal effective dose and the duration of action of the drug. Some drugs are prescribed in doses that are significantly above the minimally effective dose, and some have half-lives that are considerably longer than the dose interval. In both these cases the omission of one or two doses will have relatively little impact on the therapeutic effect of the drug. Such drugs have been described as being "forgiving" drugs[199] and could partly account for controlled blood pressure in people with low to moderate adherence.

2.9.5. Persistence with hypertensive medication

Persistence is the term used to describe continued treatment with a particular drug. Persistence is usually assessed retrospectively, often through the analysis of large databases of prescription dispensing or insurance claims. It is not entirely the same as adherence as the patient may simply switch to another agent; however, in many cases lack of persistence will become non-adherence and even when there is a regimen change, there will often be a disruption to treatment in the interim period.

Two large, industry sponsored studies have looked at the extent of antihypertensive discontinuation in the UK[200] and Canada[201]. The UK retrospective study of prescribing patterns in hypertensives used a database of 1.2 million general practice patients to identify 37,643 hypertensive patients. This included 10,222 patients who had started a new course of antihypertensive drugs during a one-year period in 1992-93. All these patients were prescribed a drug

from one of the four main groups, Diuretics, Beta-blockers, Calcium Channel Blockers or ACE inhibitors. Changes in or discontinuations of treatment were frequently observed, and by month six, continuation rates ranged between 40% to 50% for all four classes of drugs Although the study design could not determine the cause of this, side effects were considered by the authors to be the most likely cause along with lack of efficacy. In Canada, a cohort of 79,591 patients was identified through a state health database. Only 78% of newly treated patients continued with antihypertensive treatment beyond the first year compared with 97% of those with established hypertension. This study went on to highlight possibly better continuation with the more modern classes of antihypertensive medicines[109] such as ACE inhibitors.

Figure 26 Summary of studies of persistence to antihypertensive medication

Study	Country, Method & Finding
Jones, 1995[200]	UK: 37,643 patients from database review of 1.2million patients Persistence after 6 months was only 40-50% with all drugs but better for ACE inhibitors
Caro, 1997[202] & 1999[201]	Saskatchewan, Canada: Database review of prescriptions for newly diagnosed and established hypertensives After 6 months, persistence with therapy was poor and differed according to the class of initial therapeutic agent: 80% for diuretics, 85% for beta-blockers, 86% for CCB and 89% for ACEI ($p < 0.001$). Persistence was lower for newly diagnosed hypertensives (78% vs. 97%)
Bloom, 1998[86]	USA: Pharmaceutical Benefits database studied for recently diagnosed hypertensives At 12 months' follow-up, the percentage of patients continuing initial AIIA therapy was substantially higher (64%) than the percentage continuing therapy with ACEI (58%), CCB (50%), beta-blockers (43%), or thiazides (38%).
Degli-Esposti, 2002[203]	Italy: A 3 year retrospective analysis of information recorded in the drugs database of the Local Health Unit for 7312 subjects 57.9% of patients continued their initial treatment during the 3-year follow-up period, 34.5% discontinued the treatment, whilst 7.6% were restarted on a treatment in the third year. Persistence rate higher with AIIA, progressively lower with ACEI, beta-blockers, CCB's and thiazides.

Study	Country, Method & Finding
Gregoire, 2002[204 205]	Canada: A 3-month prospective cohort study through a network of 173 pharmacies to identify patients with hypertension who were newly prescribed mono-therapy with an AIIA, an ACEI, or a CCB. Individuals were interviewed by telephone 3 times over a 3-month period to determine perceived side effects of the antihypertensive medication prescribed. Among the 663 eligible individuals, the 3-month cumulative incidence of perceived side effects was 52.5% (42/80, AIIA), 60.2% (222/369, ACEI), and 69.6% (149/214, CCB). After adjustment, the odds of reporting a side effect compared with the AIIA were significantly higher among patients treated with an ACEI (odds ratio = 1.78: 95% CI, 1.02-3.12) or a CCB (odds ratio = 2.65; 95% CI, 1.47-4.78)
Marentette, 2002[206]	Saskatchewan, Canada: Retrospective review of the computer records of 46,458 people prescribed at least one antihypertensive therapy prescription during the study. Persistence was determined for four intervals: at 180, 360, 540 and 720 days. AIIA's had the highest persistence followed by ACEI, CCB's, beta-blockers and diuretics. Persistence decreased as the time interval increased. Females were significantly more persistent than males (P<0.005), and elderly patients were significantly more persistent than younger patients (P<0.001) at each of the four time intervals. For AIIA's, age and sex did not affect persistence.

Persistence is consistently shown to be better with angiotensin receptor antagonists and ACE inhibitors compared with other agents. The main reason put forward for this is the lower incidence of side effects, especially for angiotensin receptor antagonists.

Side effects undermine adherence, as they can be a barrier to continuing treatment and can influence the health beliefs of the patient and doctor so that the decision is taken to stop that agent. The association between the drug and the side effect may be spurious but it is the patient's perceptions of the side effect that will affect persistence. Gregoire et al[205] found that patient beliefs about the efficacy of a treatment and their perceptions were strongly related to treatment persistence. Those individuals who detected side effects from their antihypertensive medication were 1.91(C.I. 1.47-2.47) times more likely to discontinue their initial drug treatment; however, there was not enough statistical power to identify any difference in side effect among different drug classes. This was a study of new courses of antihypertensives, but not specifically newly diagnosed hypertensives. Indeed, while persistence has been shown to be lower among newly diagnosed hypertensives[201], this was not shown by Gregoire *et al.*

While persistence data continues to accumulate, it is possible that the beliefs of the doctor are being overlooked. Great efforts have been made by manufacturers to demonstrate to prescribers the low level of side effects with angiotensin receptor antagonists. Doctors are faced with frequent reports of often-spurious symptoms from hypertensive patients[207]. Perhaps doctors are being encouraged to be more discerning when attributing symptoms to angiotensin receptor antagonist side effects compared with diuretics or beta-blockers.

As shown in Figure 26, even for angiotensin receptor antagonists, persistence rates beyond one year are rarely higher than 60-70% and while this is considerably higher than that reported for diuretics and beta-blockers (around 40%). This is still a serious adherence failure. It is also clear that persistence is not the only marker of adherence and that erratic tablet taking patterns can still undermine the effectiveness of treatment. In a study of 5144 patient days using electronic monitoring, missed doses were most common at weekends[106]. This type of patient may still persist with treatment but fail to get the full benefit.

It is essential that the management of a patient's hypertension include an ongoing assessment of their adherence so that problems can be identified before

the patient discontinues treatment. The following sections present work that has produced a validated and effective Arabic language self-reporting measure of adherence and go on to describe how such a measure can be used to improve cardiovascular outcomes through improved assessment of adherence and to gain more knowledge about medication adherence in the UAE.

3. Method Development

Contents

3.1 Introduction

Little is known about patient and doctor perceptions of medication adherence in the UAE. The following method development and subsequent use of these research methods was performed to test the hypothesis that self-reported medication adherence is a clinically useful tool and can be used in the context of a busy clinical environment. More specifically, it was believed that an Arabic language, self-reported measure of adherence could be used to study the nature of medication adherence among patients receiving drug treatment for hypertension in Ministry of Health primary healthcare centres.

3.2 Healthcare sector in the UAE

The United Arab Emirates is a small, oil rich federation to the south of the Arabian Gulf. It became independent in December 1971 following many years as a British protectorate. It occupies around 83,000 sq kilometres of coastal and inland desert (20% larger than Ireland) and has a population of just over 3 million (20% smaller than Ireland). Less than 20% of the population are Arab, UAE nationals ("Emiraties" or "locals"). The country is Islamic (Sunni Muslim) and the law is administered according to Sharia principles; however, compared with some Muslim states, such as Saudi Arabia, the UAE is considered to be a very liberal environment. Among nationals, the social structure remains very traditional and tribal and family loyalties are very strong. The political system reflects the tribal traditions and the president of the UAE and ruler of Abu Dhabi has complete power and controls the "purse strings"; however, his wisdom and benevolence is admired throughout the region and among western leaders. While the system is not a democratic system, any UAE national has a right of access to their tribal and political leaders and they in turn are expected to attend to the needs of the individual. The majority of the population are expatriate workers and their dependents, although most workers are male, single status workers. This group of workers originate from many countries but the main sub-groups are from the Asian subcontinent, Egypt, Syria, Jordan, Palestine, Sudan and the Philippines. Although the per capita gross domestic product of the UAE is high (more than €21,000), many of the expatriate workers are on low salaries by western standards (€500 per month or less). There is no income tax but a growing number of sales and service related taxes are in place.

For non-nationals, a residence or visit visa is required to enter the country. Residence visas are only available for people who are employed and their dependents. Loss of employment usually results in loss of residence visa.

The age profile of the country is very unusual. Half of the UAE nationals are aged under 16 years and most expatriate workers retire and leave the UAE when they reach the age of sixty (rarely later than sixty five). As a result, less than 2% of the total population are over 60 years and the majority are aged between 30 and 50 years.

Healthcare is available through both the government and private sectors. There are around twenty-five federal government hospitals (25-460 beds) and twenty private hospitals (usually less than 100 beds). There are around 100 government health centres and over 3000 private sector doctors and dentists working in clinics. In addition to general practice, many offer specialist diagnostic, surgical and medical services. Government health services had been free to all residents; however, recent government reforms have introduced charges for health services to non-nationals. For non-nationals, there is a mandatory, annual "health card" costing €75 per adult and each non-emergency visit to a government doctor costs €12.50. There are also charges for government hospital accommodation and diagnostic and surgical procedures. However, the most significant change to government health services came in May 2001 when a decision was taken to stop the dispensing of medicines to non-national outpatients. The federal government plans to introduce a compulsory health insurance in 2004. In practice, UAE nationals have no significant out of pocket expenses for government health services. The UAE pharmaceutical market is estimated to be worth around €200 million per year, including government, private and over the counter sales. The federal Ministry of Health is the largest government healthcare provider, although the emirates of Abu Dhabi and Dubai have their own state-government health services and the armed forces and oil companies have their own hospitals and health centres. The Ministry of Health spends approximately €33 million on medicines each year; however, a historically accurate figure is difficult to find due to a blurring of federal and state government spending. Another important health care sector is treatment overseas. An undisclosed amount of money is spent directly by government and indirectly through private offices of the royal families, sending UAE nationals to centres of excellence around the world. One estimate is that more than €100 million may be spent each year. Several initiatives have been launched to try to reduce this expenditure.

Medicines and manufacturers are licensed in the UAE by the Ministry of Health and the standards of quality assurance are comparable to those in the West. There is a very competitive generic medicines market in the region and quality assurance of this

is very strict. However, despite this, the public confidence remains much stronger for innovator brand names. The health professions are controlled by the Ministry of Health and practitioners are licensed after passing a license exam and fulfilling various experience criteria. There is a UAE government funded UAE medical school and three private ones. There are two private pharmacy schools graduating pharmacists, and one government college graduating pharmacy "technologists" with a higher diploma. Less than fifty UAE nationals have graduated as pharmacists, most in Egyptian, Jordanian or Saudi universities. Most of these are women and around twenty-five nationals are working as pharmacists in the government sector. Subsequently, the model of pharmacy most commonly seen reflects that seen in Middle Eastern countries and India. It is supply orientated and there is very little clinical pharmacy or pharmaceutical care.

Clinical research is not common in the UAE. A lack of research students and almost no research money are the main reasons; however, a relatively transient workforce and a small number of national scientists add to the problem. The Ministry of Health is promoting clinical audit as a tool for quality improvement and this has lead to a growing appreciation of research projects that help to describe and improve common clinical problems. The research project reported in this thesis was conceived against this background.

3.3 Literature review

A comprehensive literature review was performed to support the background and focal theory behind this thesis. This research would not have been possible without extensive use of the Internet and the World Wide Web. There is one medical school library in the United Arab Emirates and it is a two-hour drive from Abu Dhabi (the city where the researcher lives). The UAE National Medical Library is well stocked but not resourced to support off campus / non-faculty research. Therefore, the principle search tool used for this literature review was Medline (1966-present). Medline was accessed via the Internet using the *Biomednet*[H] portal and *Pubmed*[I]. This was complemented by an ongoing review of relevant medical journals via their electronic contents pages on the Internet, electronic information services (*e.g. Medscape*[J]), re-print requests from contemporary authors and reprints downloaded direct from journal web pages. Where possible, past article reprints were obtained from the UAE National Medical Library and several; older or more specialised reprints were obtained from the British Library in Leamington Spa, UK.

If an article has been cited in this thesis, then at the very least, a copy of the abstract has been studied. However, if an article is of central importance to the subject under discussion then a copy of the complete paper will be on file. This is especially true for papers relating to the methodology of measuring adherence.

All references consulted during the construction of this thesis have been entered in a bibliographic database (EndNote version 5[K]). This database contains 652 references of which at least 65 are on file as full text (hard copy or electronic format). At the last count, this thesis cites over 250 articles from this accumulated database and includes most of those that are on file. The database does not include the hundreds of textbooks and web pages that have been consulted for background information or inspiration.

The overall search method could have been enhanced by access to databases such as PsychInfo®, Embase® and Sociological Abstracts® as this may have provided a greater social science angle and perhaps greater access to the growing body of adherence research performed by nurses, especially in North America. These databases were not readily available; however, this is partly compensated for by

[H] Biomednet www.bmn.com
[I] Pubmed www.ncbi.nlm.nih.gov
[J] Medscape www.medscape.com

carefully monitoring high quality social science journals such as Social Science and Medicine and by specifically searching for work by notable researchers who are active in social science and particularly, social pharmacy.

Overall, the introduction, method development and subsequent discussion is supported by a comprehensive literature review and appraisal of the subject of hypertension, drug management and adherence to medication.

3.4 Characteristics of an ideal self reporting measure in the UAE

The advantages and disadvantages of self-reporting measures of adherence are discussed in section 1.6 above. The settings for this research are busy, multicultural and multilingual primary healthcare centres. Many of the patients are UAE nationals and they are accustomed to receiving medical care with a minimum of delay and inconvenience. This type of research had not been performed before and it was important to get the support of the most senior Ministry of Health officials (in addition to the usual ethics committee approval) and to be able to show that the research was of a high quality and could benefit the patients.

The biggest challenge to developing a UAE self-reporting measure is the Arabic language as all the published measures have been developed in English. Most of the doctors are expatriate Arabs, and therefore are native Arabic speakers, or from India or Pakistan. All of the doctors speak Arabic and most are very comfortable with English. Most of the nurses speak Arabic and English, although for all nurses, English is a second language. Many of the nurses are from the Philippines and while Tagalog is their mother tongue, they are usually trained and fluent in English. However, being able to speak some Arabic does not mean that one can read Arabic and this would be impossible for some nurses. For the measure to be a consistent and valid tool, each question must be presented to the patient in a consistent way. Therefore, it is important that the person who is administering the self-reporting measure can read (and understand) the questions to a patient in a language which both are comfortable.

One option is to allow the patients to read the questions for themselves; however, this assumes a certain level of literacy. In the UAE literacy is highly variable and language specific. Even if one were to restrict ones research to UAE nationals, and concentrate on those who are literate in Arabic, literacy would depend upon age and sex. The majority of patients with hypertension will be over the age of 45. The UAE has existed as a country for only 30 years, there were very few schools 30-40 years

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[K] EndNote version 5 ©2001 ISI ResearchSoft, Berkeley, CA, 94710, USA, www.endnote.com

ago, and many nationals over the age of 40 have no formal schooling. This is especially true for the women who would have been expected to be busy with domestic duties even as young girls. For this reason, it was decided that any useful instrument would have to use questions that were read to the patient.

It is also important not to inconvenience the patients too far beyond the normal routine. This is undesirable from a service point of view and may affect the answers if they are given in a rushed, begrudging or resentful frame of mind. This is especially the case for the national men who usually expect to be seen very quickly and are quick to complain if they feel that they are being delayed unnecessarily.

In view of the clinical environment It was important to use a method that was simple and quick to use and easy to translate. For this work the ideal measure would be:

- Previously validated in a similar population
- Shown to be relevant to blood pressure management
- Simple to administer
- Quick to administer
- Easy to translate
- Easy to analyse

3.5 Development of an Arabic Self-reporting measure (SRM) for medication adherence

The Morisky self-reporting measureThe history and use of the self-reporting measure (SRM) from mid 1980's through to its use in recent years was described in 1.6.2 above. Professor Don Morisky and colleagues first described the most frequently cited self-reporting measure in 1986[39]. The original population studied by Morisky, Green and Levine consisted of 400 outpatients attending clinics affiliated to the Johns Hopkins Medical Institute in Baltimore, Maryland. They were mainly black (91%), mainly female (70%), had a median age of 54 years and a median of 8 years formal education. This was not a well-educated or socially sophisticated population and therefore indicated that the self-reporting measure might be easily adaptable to the study population in the UAE. The original 4-item self-reporting measure is shown in Figure 30.

The theory underlying the "Morisky" measure was that drug errors of omission can happen in any or all of several ways: forgetting, carelessness, stopping the drug when feeling better, or stopping when feeling worse. The four questions were phrased so that the answer was "Yes" or "No". A "Yes" corresponded with an admission to a behaviour that could lead to a drug omission. Rather than attempting to overcome the "Yes" saying bias, this approach used it to obtain disclosures of non-adherence. Each "Yes" answer scored one and the sum of "Yes" answers was considered to provide a composite measure of non-adherence. A score of zero was taken as "high adherence", one to two was "medium adherence" and three to four corresponded with "low adherence".

Figure 27 Original Morisky self-reporting measure

1. Do you ever forget to take your medicine?
2. Are you careless at times about taking your medicines?
3. When you feel better do you sometimes stop taking your medicine?
4. Sometimes if you feel worse when you take your medicine, do you stop taking it?

Each question has a "Yes" or "No" answer. Each "Yes"-answer scores one point.

A zero score indicates high adherence;

One to two points indicates medium adherence

Three to four points indicates low adherence

The Cronbach Alpha reliability coefficient of the scale was reported to be 0.61

Morisky et al 1986[39]

After five years, 290 patients were available for follow-up. Out of the 126 (43%) patients who scored high for adherence, 75% had controlled blood pressure, compared with only 47% of the 46 (16%) of patients who had low adherence scores. Criteria for blood pressure control was not as stringent as one would expect post JNCVI but was an age adjusted target agreed with the attending doctors (blood pressure was the average of 6 different measurements). The four-item measure had a relatively high internal consistency (Cronbach alpha = 0.61, see annex 5). With respect to blood pressure control at two years, the sensitivity was 0.81 and the specificity was 0.44. The low specificity indicates that the questionnaire is a poor predictor of blood pressure control but this is largely explained by the observations described in section 1.6.3 above whereby around half of non-adherent patients are found to have controlled blood pressure.

In personal communication with Professor Don Morisky of UCLA Public Health department (October 2000), he confirmed that the four-item scale had been further refined and expanded to nine-items. Unpublished data from a 24-month longitudinal study with hypertensive patients showed significant concurrent validity with blood pressure control and a higher internal consistency (Cronbach alpha 0.86). The design of a four-year longitudinal study of a patient education intervention to improve adherence has been reported and this will use the expanded nine-item scale to measure adherence[208] (described in 1.6.3 above and shown in figure 30 below).

Morisky's original four-item self-reported measure has been compared directly with electronic monitoring using the MEMS device (see 1.6.8 above) while measuring adherence to tricyclic antidepressants in chronically depressed patients[53]. Adherence was defined as taking 80% or more of the doses. Electronic monitoring correlated well with the self-reported adherence scores. It was found that a score of greater than zero using the four-item scale could identify low adherence (<80% of doses taken correctly) with a sensitivity of 72.2% and specificity of 74.1%, indicating a good level of agreement.

Figure 29 The amended Morisky self-reporting measure

1. Do you sometimes forget to take your blood pressure medicine?
2. People sometimes miss taking their medicines for reasons other than forgetting. Over the past two weeks, were there any days when you did not take your blood pressure medicine?
3. Have you ever cut back or stopped taking your blood pressure medicine without telling your doctor, because you felt worse when you took it?
4. When you travel or leave home, do you sometimes forget to bring along your blood pressure medication?
5. Did you take your blood pressure medicine yesterday?
6. Do you have a special routine or reminder system to help you to take your blood pressure medicines?
7. When you feel like your blood pressure is under control, do you sometimes stop taking your medicine?
8. Taking medicine everyday is a real inconvenience for some people. Do you ever feel hassled about sticking to your blood pressure treatment plan?
9. How often do you have difficulty remembering to take all of your blood pressure medicine? Never/Rarely, Once in a while, Sometimes, Usually and All the time
Items 1-8 have a "Yes" or "No" answer. A "Yes"-answer scores one point except for item 6, for which a "No" answer scores one point. Item 9 is answered using a Likert scale. "Never / Rarely" scores zero, through to "All the time" which scores 4. The Cronbach Alpha reliability coefficient of the scale was reported to be 0.84[209]

The amended Morisky scale was discussed with UAE colleagues and this produced suggestions ranging from asking the patients to give a quantitative assessment of their medication adherence / non-adherence through to asking more specifically about the shame or embarrassment that they feel when having to take daily medication. These are discussed below.

Item 1 - Quantitative estimate: The idea of introducing a Likert scale for the patient to quantify non-adherence in item 1 arose from an interest as to whether the patients could report the actual level of adherence in terms of missed doses. If they could, then this might enable one to investigate the validity of the widely accepted figure of 80% medication adherence (doses taken) as being the minimum requirement for blood pressure control. A similar approach had been used with some success in a study of adherence to asthma medication[45] and therefore seemed to be feasible and a worthwhile addition to the measure.

Item 5 – Change of "yesterday" to "to day": This change was made after considering the usual reasons for attending the UAE health centres. There is no appointment system in the health centres and the main prompt for a return to the centre is the need to get more medication. Therefore, taking the last remaining dose may be a common prompt to re-attend at the clinic. This, along with the observations that the majority of doses were taken in the morning and that more chronically sick patients attend the health centres in the afternoons, prompted the change of "yesterday" to "today" as it was felt more likely that it would be the morning dose on the day of attendance that would be missed.

Item 6 – Follow-up question: For many patients, the use of a reminder system is an important means of improving adherence. There is no information about what prompts are used by patients in the UAE to remind them. Therefore, patients who reported that, "Yes", they did have a reminder system, were asked to say what that system was. The most common prompts were noted during the pilot study and provided as a list of options following the pilot study. The investigators had no reason to believe that this additional component to the measure would in any way prejudice the answers to the following items.

Item 10 – Extra question: The doctors at the pilot site had reported that they felt that many of the patients, especially the men, were concerned that the taking of daily medication is a source of shame and embarrassment. They composed this item to elucidate this information. It was not intended to provide additional part of the self-

reporting measure and was therefore put at the end of the measure so not to affect the answers to the main items.

Figure 30 below, shows the UAE self-reporting measure that was used in the pilot study. Before this measure could be piloted on patients, the measure had to be translated.

Figure 30 Pilot study version of the UAE Self-reporting measure

1 Some people have difficulty remembering to take their medicines. Do you ever forget to take a dose of your blood pressure medicine?																				
If "Yes", on how many days per WEEK?							If "Yes", on how many days per MONTH?													
<1	1	2	3	4	5or more		<1	1	2	3	4	5	6	7	8	9	10	11	12	13
2 People sometimes miss taking their medicines for reasons other than forgetting. Over the past two weeks, were there any days when you did not take your blood pressure medicines?																				
3 Have you ever cut back or stopped taking your blood pressure medicines (without telling your doctor) because you felt worse when you took it?																				
4 When you travel or leave home, do you sometimes forget to bring along your blood pressure medication?																				
5 Did you take your blood pressure medicine today?																				
6 Do you have a special routine or reminder system to help you to take your blood pressure medicines? (if "yes", describe it)																				
7 When you feel like your blood pressure is under control, do you sometimes stop taking your medicine?																				
8 Some people find it very inconvenient to take their blood pressure medicine every day. Do you ever feel hassled about sticking to your blood pressure treatment?																				
9 How often do you have difficulty remembering to take all your blood pressure medicine? Never/ Rarely, Once in a while, Sometimes, Usually, All the time																				
10 Some people feel that it is embarrassing to take medication every day for their blood pressure. Do you ever feel embarrassed or ashamed that you have to take your blood pressure tablets?																				

Compared with the amended Morisky measure, the pilot self-reporting included two follow-up questions for items 1 and 6 and item number 5 was changed from "yesterday" to "to-day". The pilot measure also included an additional item (Item 10). The rationale behind these changes are explained above.

3.5.1. Translation of the English self-reporting measure into Arabic

The translation of English in to Arabic must be done most carefully if one is to retain the original meaning and nuances. Arabic is a very rich language but in common with some Western languages such as German, there is a common form of the language and a more formal, sophisticated, "classic" form and this is seen in most official media and forms the basis for most technical translations. It is not rare for two Arab pharmacists to disagree on the meaning of a classic Arabic medical term and it is not rare for an Arab to be unable to attain the demanding levels of written grammar required by the classical Arabic. Likewise, literal translation of English terms by none-technical translators can produce nonsense. It is easy for a non-native English speaker to lose some of the subtle but important idiomatic meaning during translation. Overall, the chances of mistranslation are enormous.

The translator chosen for this task was a highly experienced pharmacist (49 year old Arab) working as a Pharmacy consultant at the UAE Ministry of Health. He had been educated from primary to graduate level in English in his native country before living in the UK for three years to get a PhD at a leading English University. He is now domiciled in New Zealand. His work frequently involves the preparation of briefings and technical papers in both English and Arabic. The Arabic translation (Pilot study version) is shown in annex 4.

As there were only 10 main items to the self-reporting measure, it was felt that there was no need for an elaborate forward translation process. Therefore, to get a translation for validation, only one translator was used, followed by an informal review by some of the Arab doctors involved in the study.

3.6 Validation of the Self-reporting measure Arabic translation

3.6.1. Aims and objectives

The aim was to produce an Arabic translation of an English language self-reporting measure. The objective was;

To confirm the robustness of the translation by checking the back translation of the Arabic translation using a group who are representative of those people presenting the questions to the patients.

3.6.2. Description of the validation method

In this study, the method started with the Arabic translation of the items described above and shown in Figure 30. The translation was reviewed by some of the key medical doctors involved in the study to identify any obvious problems and was then validated through a process of back translation (from the Arabic in to English) by three selected groups. The back translated, English text had to be as close as possible to the original English text and not differ in its intention from the original, although minor changes to the words used would be acceptable. Only people who can communicate in both Arabic and English can do the back translation. Therefore, while it is not a direct validation, it is a validation of the Arabic translation's robustness and provides an indication of the accuracy of the translation's meaning to a third party.

3.6.3. Selection of back-translators (assessors)

Three groups performed the back translations.

- A group of Arab nurses (n=4) who were involved in reading the questions to the patients in Arabic.
- A group of Arab pharmacists (n=3) (i.e. native Arabic speakers with graduate level education).
- As a positive control, the original translator (English to Arabic) was asked to back-translate the text, 12 months after he had originally been asked to translate the English text in to Arabic.

The idea of using the positive control was that as he had not seen the English questions for a year, his ability to back translate his original translation would be a useful control for the pharmacist and nurse back translations.

Those providing back translations were asked to give written translations where possible, however, many Arabs can speak passable English but are not comfortable writing in English. In these cases, they gave verbal back-translations and these were recorded and transcribed by the main researcher (MF).

The three pharmacists (2 male, one female) had diverse backgrounds and experiences and were chosen to represent the many different ethnic and social backgrounds of Arabs living in the UAE (see figure 35 below). All three work in the Drug Control department at the Ministry of Health and were able to provide written back-translations. These were written without any discussion with each other or other colleagues.

Figure 31 The background of the pharmacists involved in the back-translation

Sex	Nationality	Age	Language of education
Male	Egyptian	60	Arabic, English
Male	Palestinian, born in UAE	29	Arabic, English, Hungarian
Female	Lebanese	32	Arabic, French, English

The nurses were considered an important group because at the second and largest study site, they were the ones conveying the questions to the patients. The nurses were all Arab expatriates and had worked as nurses in the UAE for over 5 years each. All four nurses gave a verbal back-translation, which was transcribed *verbatim* by the researcher (MF). If the nurses' back translation was incorrect or vague, the transcriber did not correct them.

3.6.4. Translation validation results

The results of the back-translation are presented on the following pages.

Each item is presented on a single page along with the back translations (verbatim). The information is presented as the original English text followed by the back translations of the positive control, Arab pharmacists and Nurses.

Item 1

Original English Text

Some people have difficulty remembering to take their medicines. Do you ever forget to take a dose of your blood pressure medicine?

Positive control

- Some people have difficulty in remembering to take their medicine. Have you ever forgot taking a dose of your anti-hypertension medicine?

Arab pharmacist back-translation

1. Some people find difficulties in remembering their medicines. Did you ever missed a dose of your hypertensive drug?
2. Some people find difficulty in taking their medicines regularly. Are you facing the same and forget one dose of your blood pressure medicine?
3. Some people find difficulty to remember taking their medicines. Did it ever happen that you forget to take a single dose from your hypertension medicines?

Nurse-Verbal back translation

1. Some people are getting difficulty to remember this medicine. Do you forget your Blood Pressure medicines?
2. Some people find difficulty to remember the medicine. Has this ever happened to you with your blood pressure medicines?
3. Some people have difficulty to remember medicines. Are you one of these people?
4. Some people find difficulty to remember. Does this sometimes happen to you?

Item 2

Original English Text

- People sometimes miss taking their medicines for reasons other than forgetting. Over the past two weeks, were there any days when you did not take your blood pressure medicines?

Positive control

- Some people skip taking their medicine because of reasons other than their weak memory. Have you faced that situation during the last 2 weeks with your antihypertension medicine?

Arab pharmacist back-translation

5. Some people don't forget to take their medicine but sometime they don't take it for some other reasons. Did that happened to you through the last two weeks with your blood pressure medicines?
6. Some people miss their medicines for reasons other than forgetting. Did it happen to you in the past 2 weeks concerning your hypertension medicines?
7. Some people miss their dose of hypertensive drug for other reasons than forgetting it. Did this happened to you last two weeks?

Nurse-Verbal back translation

1. Some people miss medicine for other reasons than forgetting. In the last 2 weeks have you stopped?
2. Some people forget to take their medicines for other reasons. In the last 2 weeks has this happened to you?
3. Some people have difficulty to take it for reasons other than memory. Has this ever happened to you?
4. Some people they are missing doses for many other reasons except forgetting. Have you not taken your medicines in the last 2 weeks?

Item 3

Original English Text

- Have you ever cut back or stopped taking your blood pressure medicines (without telling your doctor) because you felt worse when you took it?

Positive control

- Have you ever taken a lower dose or skipped on purpose taking your antihypertension medicine without your doctor's permission because you felt that you were better off without it?

Arab pharmacist back-translation

1. Did you ever reduce the dose or stop taking your hypertension medicine without having permission from your doctor because you condition became worse after you were taking it?
2. Did you ever stop or reduced the dose of your blood pressure medicine without a permission from your physician because you felt worst while taking that medicine?
3. Did you ever reduce or stop to take your hypertensive drug without consulting your doctor, because you did not feel well when you were taking it?

Nurse-Verbal back translation

1. Are you stopping your hypertension medications or reduce the dose because you are feeling something is wrong?
2. Do you reduce or stop the medicines for blood pressure without permission from doctor because you are worse?
3. Have you changes your dose because you feel that you are not doing well with the medicine?
4. If you feel worse with the medicine do you stop without excuse from the doctor?

Item 4

Original English Text

- When you travel or leave home, do you sometimes forget to bring along your blood pressure medication?

Positive control

- Do you forget sometimes to take your antihypertensive whenever you are travelling or when you are away from home?

Arab pharmacist back-translation

1. Do you sometimes forget to take the hypertension medicine when you are travelling and outside your house?
2. Did you forget sometimes to take your antihypertensive drug, especially when you are abroad or away from home?
3. Do you forget sometimes to take your blood pressure medicine while you are away from home or when you travel?

Nurse-Verbal back translation

1. When you are far away from your home do you take it?
2. If you are travelling far from your home do you forget to take your medicine?
3. You are forgetting to take your medicine when travelling or away from home?
4. When you leave home or country do you forget take it with you?

Item 5

Original English Text

- Did you take your blood pressure medicine today?

Positive control

- Have you taken your antihypertension medicine today?

Arab pharmacist back-translation

1. Did you receive your hypertensive drug today?
2. Did you take your medicine for hypertension today?
3. Did you take your blood pressure medicine today?

Nurse-Verbal back translation

1. Have you taken your hypertension medicine today?
2. Did you take your hypertension medicine today?
3. Have you taken it today?
4. Today have you taken your Blood Pressure medicines?

Item 6

Original English Text

Some people have a special routine or reminder system to help them take their blood pressure medication. What do you do?

Positive control

- Some people depend on a certain scheme or plan in reminding themselves to take their antihypertension medicine. What do you do to remind yourself?

Arab pharmacist back-translation

1. Some people rely on special ways and methods to remember the dose of their hypertensive drug. What you will do to remember?
2. Some people use a special / specific system to remind them that they have to take the antihypertensive medicine. What do you do to remember?
3. Some people follow a system to remember their blood pressure medicine. So what you do to remember?

Nurse-Verbal back translation

1. Some people they follow a way to help them to remember. Do you do this?
2. How do you remember to take your medicines?
3. Some people have system to remember medicines. What are you doing?
4. Some people have a reminder to take their medicines. What do you do?

Item 6.1

Original English Text

I do not have a special reminder

Positive control

- I do not depend on any scheme for reminding myself

Arab pharmacist back-translation

1. I do not rely on any method to remember
2. I don't follow any system
3. I do not rely on anyway

Nurse-Verbal back translation

1. No
2. No, I have no way
3. No I do not have a reminder
4. I do not use any way

Item 6.2

Original English Text

I take it with the same meal each day

Positive control

- I take it with the same meal every day

Arab pharmacist back-translation

1. I take it with meals
2. I take it daily with the same meal
3. I take it with meals every day

Nurse-Verbal back translation

1. With the meal
2. I take it with same meal everyday
3. I take it with meals
4. With the meals

Item 6.3

Original English Text

I take it as I wake up / go to bed

Positive control

- I take it before I sleep or when I wake up

Arab pharmacist back-translation

1. I take it when I get up or go to sleep
2. I take it as soon as I get up or when I go to bed
3. I take it when I wake up in the morning or before I go to bed

Nurse-Verbal back translation

1. I take it when I wake up or go to my sleep
2. As I wake up or go to sleep
3. I take it when I get up or before sleep
4. When I wake up or go to sleep

Item 6.4

Original English Text

My wife / husband reminds me

Positive control

- My wife/husband reminds me

Arab pharmacist back-translation

1. My wife / husband remind me to take it
2. My spouse reminds me
3. My partner reminds me

Nurse-Verbal back translation

1. I tell my wife/husband to remind me
2. My wife or husband remind me
3. My husband / wife
4. My husband / wife reminds me

Item 6.5

Original English Text

I take it at work

Positive control

- I take it during work

Arab pharmacist back-translation

1. I take it while I'm in duty
2. I take it when I am at work
3. I take it when I am at my work

Nurse-Verbal back translation

1. I take it at my work / duty
2. I take it at my work
3. At work
4. I take the medicine inside my work

Item 6.6

Original English Text

Other reminder system

Positive control

- Other options

Arab pharmacist back-translation

1. I follow a different system
2. Any other reason
3. Another way

Nurse-Verbal back translation

1. Other system
2. I do not have a way
3. Another way to remind me
4. I have another way

Item 7

Original English Text

When you feel like your blood pressure is under control, do you sometimes stop taking, or reduce the dose of your medicine?

Positive control

- Do you stop or cut sometimes your medicine dose whenever you feel that your hypertension is under control?

Arab pharmacist back-translation

1. Do you stop your blood pressure medicine or reduce it when you feel that your blood pressure is getting normal?
2. Do you sometimes stop or reduce the dose of your medication when you feel that your hypertension is stable?
3. Do you sometimes stop taking or reduce the dose of your antihypertensive medicines when you feel that the hypertension you have becomes normal?

Nurse-Verbal back translation

1. Did you stop the medicines when you feel that your BP is OK?
2. You reduce the dose when you are feeling that your BP is now reduced?
3. Did you ever stop or decrease the dose when you feel your blood pressure is under the control?
4. Do you reduce your medicines for hypertension if your hypertension has become regular?

Item 8

Original English Text

Some people find it very inconvenient to take their blood pressure medicine every day. Do you ever feel stressed about having to follow your blood pressure treatment?

Positive control

- Some people find it inappropriate to take a daily treatment for their hypertension. Have you ever felt that you are under the obligation to take treatment for hypertension?

Arab pharmacist back-translation

1. Some people feel that taking hypertensive drugs daily is not important. Did you ever felt that you are obliged to continue your hypertensive treatment?
2. Some people feel it is not good to take the antihypertensive medications daily. Did you ever have the feeling that you are under pressure to take your antihypertensive medicines?
3. Some people feel that it's not suitable to take the treatment of the blood pressure daily. Did you ever felt with a sensation that you are forced to take the blood pressure treatment?

Nurse-Verbal back translation

1. Some people feel they are suffering because they do not wish to take the medicine everyday. Do you feel that you are under pressure to take the medicine?
2. Some people they are feeling that they are taking this medicine everyday and it makes them depressed. Do you feel the same?
3. Some people feel stress because they take hypertension medicines everyday. Does this happen to you?
4. Some people feel that using this medicine is difficult because they do not want to be controlled by medicine. Do you ever feel this?

Item 9

Original English Text

How often do you have difficulty remembering to take all your blood pressure medicine?
All the time, Usually, Sometimes, Once in a while, Never

Positive control

- How can you rate the difficulty in remembering your antihypertension medicine?

Always, Usually, Sometimes, Once every now and then, Never

Arab pharmacist back-translation

1. What is the frequency of finding difficulty to remember to take your antihypertensive medication?

All the time, usually, sometimes, once in a while, never – **Same for all 3 pharmacists**

2. How difficult it is for you to remember your hypertensive treatment?
3. What is the difficulty rate to remember your blood pressure treatment?

Nurse-Verbal back translation

1. How difficult is it to remember your hypertension medicines:

All the time, usually, sometime, not often, never

2. What is the difficulty to remember to take your medicine?

All the time, usually, sometimes, less than once in a while, never

3. Some people forget to take their medicine. How often do you forget to take your medicine?

Always, habit, sometimes, once in a time, never

What is your difficulty in remembering?

Always, usual, sometimes, once in a while, never

Item 10

Original English Text

Some people feel unhappy that they have to take medication every day for their blood pressure e.g. some people are embarrassed or feel that it is a sign of weakness. Do you ever feel unhappy that you have to take your blood pressure tablets?

Positive control

- Some people feel uneasy when they are obliged to take daily treatment for their hypertension; in other words, some of them are annoyed or feel that it is a sign of weakness. Have you ever been sad that you have to take your antihypertension treatment?

Arab pharmacist back-translation

1. Some people who are suffering from blood pressure don't feel happy as they are forced to take their medicines daily. Some of them feel with empresses (sic) or as it's a weakness symptoms. Did you felt with sadness when you take your blood pressure medicine?
2. Some people feel not satisfied for being obliged to take their hypertensive medication daily. In other way, some feel shame . Do you ever feel unhappy that you have to take your blood pressure tablets?
3. Some people feel inconvenienced by being obliged to take the antihypertensive medicines. Some of them feel embarrassed or that it is a weakness. Did you ever feel "grieved" that you have to take your antihypertensive medications?

Nurse-Verbal back translation

4. Some people feel that they must take the medicines and feel distressed and that it is a weakness. Do you feel sad that you are taking medicine for blood pressure?
5. Some people feel shame / unhappy to take medication every day. It has happened to you?
6. Some people are not feeling good because of daily medicine for BP and feel it a sign of weakness. Do you feel sad to take the blood pressure medicines?
7. Some people are not happy taking the medicine and feel that this is a shame and they are not strong. Do you ever feel that feeling?

3.6.5. Review of translation

Positive control

For each item, the positive control was able to back translate the Arabic items to a form that closely resembled the original English text. Some potentially important differences were noted and are summarised in Figure 32. Item 4 asks about taking medicine when travelling. The translators interpretation of this was take, as in consume, and not take as in ones possession. The other differences were with item 8 where the used the words "inappropriate" in place of "very inconvenient" and "under the obligation" in place of "feel stressed", and Item 10 where he used the word "uneasy" in place of "unhappy" and "sad" in place of "unhappy".

Figure 32 Potentially important differences in the back-translations of the Positive Control and the Arab Pharmacist

Item	Differences
1	Pharmacist 1: Used the word "missed" for "forgot"
4	Positive Control & Pharmacists 1-3: Possible misunderstanding of "take" as in take the medicine with you versus "take" as in consume the medicine
6.2	Pharmacist 1 & 3: Not specific to the "same meal every day"
8	The positive control and pharmacists used different words in place of "very inconvenient" and "feel stressed" Positive control: "inappropriate" and "felt that you are under the obligation" Pharmacist 1: "inappropriate" and "felt that you are obliged" Pharmacist 2: "not good" and "feeling that you are under pressure" Pharmacist 3: "not suitable" and "felt with a sensation that you are forced"
10	The word "unhappy" was variously translated Positive control: "uneasy" and "sad" Pharmacist 1: "don't feel happy" and "with sadness" Pharmacist 2 "feel not satisfied" Pharmacist 3: "inconvenienced" and "grieved"

Arab pharmacists

Generally, the pharmacists were able to back translate each item to a form that was true to the meaning of the original English form. Some potentially important differences were noted and are described in Figure 32 above

Nurse verbal back translation

The Nurses were able to give an English verbal back translation for each item. The nurse back translation results are presented separately from the pharmacist data as the method used is not comparable and the data is intended to be complementary.

A key difference in the nurse back translation was noted if it failed to convey the key point of the original English text. These are noted in Figure 33

Figure 33 Potentially important differences in the Nurse back translations

Item	Potentially important differences in the Nurse back translations
1	Nurses 3 & 4: Not specific to blood pressure medicine
3	Nurse 1: "you are feeling something is wrong" in place of "you felt worse" Nurse 3: "you are not doing well with the medicine" in place of "you felt worse"
4	Nurses 1-3: Possible confusion about "take it with you" as opposed to take the medicine (orally).
6.2	Nurses 1,3 & 4: Not specific to the "same meal every day"
8	The nurses used different words in place of "very inconvenient" and "feel stressed" Nurse 1: "they are suffering" and "under pressure" Nurse 2: "makes them depressed" Nurse 3: "feel stress" Nurse 4: "using this medicine is difficult because they do not want to feel controlled"
10	The word "unhappy" was variously translated

3.6.6. Discussion of translation validation

The translation and back translation of a question is not easy, especially with English and Arabic, as the syntax for asking the question is quite different. Therefore, the validation of the translation has focussed on the meaning of each item and has tried to identify any incorrect translation and vagueness. In this way, any variation in the response to the item between patients will be due to a difference in the patient's experience, not a variation in the interpretation of the question. The differences highlighted in figures 32 and 33 have been termed "potentially important" as some of them are probably explained by factors relating to the level of Arabic / English fluency of the back translators and require closer study. As explained above, the pharmacist and nurse back translations were intended to complement each other. Therefore, it is those areas where both groups produced potentially important differences that require the closest attention. This includes items 1, 4, 6.2, 8 and 10.

The nurses were not given any warning of the request to back-translate the self-reporting measure and clearly found it a taxing exercise. It is important to remember that at work, these nurses mainly communicate in Arabic and get little English language practice, despite having trained largely in English. Therefore, It is important to focus on their ability to back translate the meaning of each item and not the exact words or syntax.

In item 1,there were minor differences seen in the back translations by both pharmacist 1 and Nurses 1 and 2.

Item 1: Some people have difficulty remembering to take their medicines. Do you ever forget to take a dose of your blood pressure medicine?

The pharmacist used the term "missed" instead of "forgot "; however, they had already correctly identified that the question was about remembering to take medicine and clearly took the term missed as referring to "missed" due to not remembering. Nurses 3 and 4 did not explicitly refer to blood pressure medicines, however, as their colleagues demonstrated, the question clearly refers to blood pressure medication. These differences are not considered to indicate a significant problem with the Arabic translation of the English original.

In item 4 there was a genuine misunderstanding regarding the "taking" of medicines when travelling.

Item 4: When you travel or leave home, do you sometimes forget to bring along your blood pressure medication?

The English original refers to the taking of the medicines along with the person when they travel. Some of the back translations have used "take" in place of "bring along", suggesting a minor misunderstanding. However, it was decided that this was due to the ambiguity of the term "take" in both languages and that this difference did not indicate a significant problem with the Arabic translation of the English original.

Item 8 has proven the most difficult question to translate.

Item 8: Some people find it very inconvenient to take their blood pressure medicine every day. Do you ever feel stressed about having to follow your blood pressure treatment?

The original English text provided by Professor Morisky used the word "hassled" in place of "stressed". This word was not familiar to most Arabic speaking colleagues and there did not appear to be an Arabic translation. Therefore, before the translation process started the word "hassled" was changed to "stressed". However, the difficulty has continued as there were several different back translations of the words "very inconvenient" and "feel stressed". This is partly explained due alternative meanings of the Arabic word used for "inconvenient". It is the correct Arabic word, but has alternative meanings including "inappropriate" and this explains the lack of precision in the back translations. Further discussions with the pharmacists and nurses have indicated that they are all agreed on what the item is asking; i.e. does the patient ever feel like they do not want to take their blood pressure medicines?

Item 10, is not part of the original or modified Morisky self-reporting measure.

Item 10: Some people feel unhappy that they have to take medication every day for their blood pressure e.g. some people are embarrassed or feel that it is a sign of weakness. Do you ever feel unhappy that you have to take your blood pressure tablets?

The translation of the word "unhappy" can be explained by important differences in the two languages. Whereas, in English we routinely talk about the absence of happiness, i.e. being unhappy, it is the nature of Arabs to describe a state of sadness. It was felt that these differences did not to indicate a significant problem with the Arabic translation of the English original.

In addition to the items where both pharmacists and nurses produced differences during back translation, there were differences in the back translation of Item 3 among the nurses.

Item 3: Have you ever cut back or stopped taking your blood pressure medicines (without telling your doctor) because you felt worse when you took it?

Two nurses used alternative phrases for "you felt worse". However, it was felt that these did not significantly change the meaning of the question and it was felt that these differences did not to indicate a significant problem with the Arabic translation of the English original.

3.6.7. Conclusion

The back translation indicated that the meaning expressed in the English original had been preserved in the Arabic translation of most items. For one of the items (item 4) the translated item provided a less ambiguous question and therefore, this were retained. One item (item 8) showed there to be some difficulty in translation of the item. However, the original translation was retained, as the overall meaning it conveyed appeared to be in the spirit of the original question

The translation of the English self-reporting measure has been performed successfully. This has been verified through an informal review by doctors involved with the study and through a formal process of back translation by Arab pharmacists and nurses.

The next step in the validation of this self-reporting measure was to administer the self-reporting measure among approximately 200 patients to determine the construct validity and internal reliability of the measure.

3.7 Development of a questionnaire regarding the doctors perceptions of medication adherence in their patients

3.7.1. Background

In the absence of objective evidence, doctors frequently overestimate the level of their patient's adherence to medication and other treatments.

There is little published work looking at what factors influence the doctor's perceptions of medication adherence in patients treated for hypertension. Therefore, it was decided to adapt the work of Goldberg et al[45] with asthma patients, to study this subject in doctor's treating patients for hypertension in the UAE.

3.7.2. Questionnaire development

The asthma study of Goldman et al used a 5-item questionnaire of which only the first item related to the doctor's perceptions of their patient's medication adherence (Figure 34).

Figure 34 Original 5-item questionnaire used by *Goldberg et al* to study doctor's perceptions of adherence in asthma patients

How would you describe the patient's level of compliance?

Choose from: High Medium Low

How would you describe the:

Quality of communication and openness with the patient?

Level of patient knowledge?

Effectiveness of patient treatment?

Choose from: High Medium Low

Evaluate the medical situation of the patient

Choose from:

Very good Good Medium Bad Very bad

It was decided to use this basic format but to add three more items relating to adherence to mirror the items in the patient self-reporting measure. Therefore, the first three items are additional items and relate directly to the doctor's perceptions of the patient's adherence using the same components of non-adherence used in the original four-item Morisky self-reporting measure: forgetting, stopping because they feel better, stopping because they feel worse.

The three questions asking about the medical treatment were retained.

The questionnaire was in English and was completed by the doctor after the patient had left the consulting room.

The structure and exact wording of the doctor's questionnaire was extensively discussed with doctors at the first health centre prior to the pilot data collection. From the original, concept version of the questionnaire, the version used for the pilot data collection period was the 4th version to be presented to the physicians and is shown below in Figure 35.

Figure 35 Doctor's questionnaire – Version 4 as used in Pilot Data Collection

After the consultation and after reviewing the file, please use this form to record your PERCEPTIONS

PLEASE DO NOT ASK THESE AS DIRECT QUESTIONS

1. Do you think that this patient ever **forgets** to take a dose of their blood pressure drugs? ☐ **Yes** ☐ **No**

If *yes*, on how many days per WEEK?

<1	1	2	3	4	5 or more

Circle your estimate

AND

If *yes*, on how many days per MONTH?

<1	1	2	3	4	5	6	7	8	9	10	11	12	13

2. Do you think that this patient sometimes stops taking their blood pressure drugs because they feel better or because they feel that their blood pressure is under control? ☐ **Yes** ☐ **No**

3. Do you think that this patient sometimes stops taking their blood pressure drugs because they feel worse, e.g. due to side effects? ☐ **Yes** ☐ **No**

Doctor Questionnaire Version 4

4. How do you rate the effectiveness of this patient's current antihypertensive medication?
(Scale 1 to 3, tick box)

☐ 1. Excellent ☐ 2 ☐ Poor

5. How do you rate the communication and openness between you and this patient?
(Scale 1 to 3, tick box)

☐ 1. Excellent ☐ 2 ☐ Poor

6. How do you rate this patient's knowledge of their hypertension and of their antihypertensive medication?
(Scale 1 to 3, tick box)

☐ 1. Excellent ☐ 2 ☐ Poor

7. How do you rate this patient's risk of suffering a major cardiovascular event in the next 5 years?
(Scale 1 = Low risk, to 3 = High Risk (tick box)

☐ 1. Low risk ☐ 2 ☐ 3. High Risk

The main evolutionary changes leading up to version 4 (above) arose from initial attempts to have the doctors quantify the level of non-adherence in terms of the number of days on which this happened. In the original version of the questionnaire, the doctor was asked to provide quantitative estimates for four aspects of non-adherence (see below). The doctors rejected this as too complex. As a compromise, the 4th version required the doctor to provide only one quantitative estimate, that of the level of non-adherence due to forgetting to take the medication (number of days). If the doctor felt that the patient did miss doses due to forgetting, they were asked to record how often they thought this happened according to a six point weekly scale and a 14-point monthly scale. The idea was that the two scales overlapped and that this provided the doctor with a scale that went from almost daily (5 or more times per week through to less than once per month).

The overlap provided a finer scale between 4 times a month, to 13 times a month and would also provide some degree of cross-validation.

Item 1: the doctor is asked to estimate the level of adherence of the patient: High (takes more than 80% of the doses as prescribed), medium (takes between 60 and 80% of the doses as prescribed) or low (takes less than 60% of doses as prescribed).

Item 2: the doctor is asked if the patient ever forgets to take a dose of their blood pressure drugs. The answer is Yes or No.

Item 3: the doctor is asked if the patients sometimes stops taking or reduces the dose of their blood pressure drugs because they feel better or because they feel that their blood pressure is under control. The answer is Yes or No.

Item 4: the doctor is asked if the patients sometimes stops taking or reduces the dose of their blood pressure drugs because they feel worse, e.g. due to side effects. The answer is Yes or No.

Item 5: the doctor is asked to describe the effectiveness of the patient's current antihypertensive medication: Good (Patient has reached their target blood pressure), Partial (some reduction in the blood pressure since starting but not enough) or Poor (no improvement in the blood pressure since starting the regime).

Item 6: the doctor is asked to rate the communication and openness between them and the patient according to a three-point scale: Excellent, OK or Poor.

Item 7: the doctor is asked to rate the patient's knowledge of their hypertension and of their blood pressure medication according to a three-point scale: Excellent, OK or Poor.

Item 8: the doctor is asked to rate the patient's risk of suffering a major cardiovascular event in the next 5 years according to a three-point scale: Unlikely, Increased risk or Greatly increased risk.

Item 9: If the doctor does not consider the blood pressure to be controlled, the doctor is asked to say why they think this is. They are given the options of Non-adherence, Non-ideal drug regime or to give another reason.

Item 10: The doctor is asked a) if they had changed the blood pressure medication at that consultation (Yes or No), and b) if "yes", why was this? They were asked to choose from "to improve control", "because of side effects" or "other reason".

It was with this version of the doctor questionnaire that was evaluated in the pilot study.

3.8 Pilot study. The Self-reported measure of medication adherence and the Doctor's perceptions of adherence.

3.8.1. Aims

The aims of the pilot study were to identify any problems with the recruitment method, use of the questionnaire and to ensure that the required data could be collected. It was estimated that 20–30 patients would be required for the pilot study.

3.8.2. Method

The pilot data collection was made at a MOH health centre close to the centre of Abu Dhabi city. It had a majority expatriate clientele. The doctors are Arab; mainly expatriates but there are some national interns who are studying for their Arab medical board qualifications. In 2000, this health centre reported an average of 1,700 patient consultations per month of which 259 were patients treated for hypertension.

The inclusion and exclusion criteria for the study are summarised in Figure 36.

The only exclusion criteria were if the patient had any disability that prevented them from answering the patient questionnaire. Hypothetical examples of exclusion criteria would be extreme deafness, or some mental incapacity that deprived them of independent decision-making.

Figure 36 A summary of the pilot study inclusion and exclusion criteria

Patient inclusion criteria
Registered with the health Centre for at least 3 months
Has a complete medical record (file) available at the health centre
Their hypertension is managed primarily at the health centre
Same antihypertensive drug regimen for last 2 months
Patient is aware of their diagnosis and can give the name of their high blood pressure medicine(s)
Patient consents verbally to completing the self reporting measure
Patient exclusion criteria
Any disability that would prevent them answering the patient questionnaire

Verbal consent was considered to be satisfactory as there was minimal change to the patient's normal consultation, perhaps some small delay while they were asked the self-reporting measure questions in the pharmacy. The MOH Department of Curative Medicines Ethics committee concurred with this view.

Three main pieces of data collected are:

- Patient Profile
- Doctor's perceptions
- Patient's Self-Reported Adherence.

It was agreed that the data collection would be as shown in figure 42 below. The decision to recruit a patient was taken by the doctor at the beginning of the consultation. The doctor explained that we were making a survey of patients with high blood pressure and how they take their tablets. As part of this survey, the pharmacist would ask them a few short questions while they were waiting for their tablets. If a patient consented to take part, the doctor attached a small red sticker to the prescription and the cover of the medical record. The red sticker on the prescription alerted the pharmacy to the arrival of a recruited patient and made it easier to identify the prescriptions of these patients when checking the data provided by the doctor. The red sticker on the cover of the medical record would help to recognise the files of patients in the study at a future date.

Figure 37 Pilot data collection plan following recruitment by the doctor

Data collection	Stage of consultation	Collected by?
Patient profile	During consultation with the doctor	Doctor & Researcher
Doctors perceptions	After consultation with doctor	Doctor
Patient's Self- Reported Adherence	While waiting for prescription to be dispensed	Pharmacist
History of treatment and last 3 BP readings	Within 24 hours of the consultation	Researcher (MF)

3.8.3. Patient profile

The patient profile was designed to ensure identification of the patient and to, record the potentially relevant demographic and medical details. These are listed below .

Figure 38 Summary of recorded patient parameters

Parameter	
Today's date	Date of last attendance
Is today's attendance a "Walk in" / Appointment	Was previous attendance a "Walk in" or by appointment
File number	First treated for HTN
Height	BP at start of treatment
Weight	BP at today's attendance
Date of Birth	Two previous BP measurements
Sex	Pulse at today's attendance
Health card number	Current BP medication & start date
Nationality	Previous BP medication
Family in the UAE for >6 month of year?	Number of BP drugs
PO Box number	Number of BP drug dose per day
Home tel no.	Other medicines including OTC drugs
Mobile phone no.	Number of non BP drugs per day
Years of education	Number of doses of non-BP drugs per day
Smoker?	Number of chronic diseases requiring regular medication
Household income	List of other chronic diseases requiring medication
Mother tongue	
Second language	

This data was entered in to a Microsoft Excel 2000 spreadsheet and analysed using both Excel and SPSS 10. A detailed description of each patient parameter is presented in Annex 2.

3.8.4. Pilot of Self-reporting measure and Doctor's perceptions

The self reported medication adherence measure was the one described above as version 4. The doctor's perceptions were recorded using the questionnaire developed above.

Before the start of the pilot data collection a meeting was held for all health centre staff to introduce the study and the researcher (MF) and one to one meetings were held between the researcher (MF) and the four doctors and the three pharmacists at the health centre to further explain the patient profile, doctors questionnaire and self reporting measure.

To help distinguish between the three different data collection forms, the patient profile was printed on blue paper, the doctor's questionnaire on red paper and the self-reporting measure on yellow paper.

Pilot data collection started 11th November 2000 and was scheduled to finish fifteen days later on 25th November, which was the day before the start of the Holy month of Ramadan, or when twenty patients data sets had been collected, whichever happened first. Data was entered into a Microsoft Excel 2000® workbook.

3.8.5. Results

By the end of the fifteenth day (11 working days), 23 patients had been recruited. Out of the 23 patients, one woman had been treated for only one month. The study inclusion criteria require patients to be treated for at least two months so she was excluded from hypertension and adherence analysis. This is summarised below. Descriptive statistics are used but no inferential statistical tests were performed as the sample was small and this was not an aim of this pilot study.

3.8.5.1. Pilot Patient Characteristics

Twenty-three (23) patients were recruited, sixteen (17) male and six (6) female. Two of the patients (both women) were attending prearranged appointments; the rest had walked in without appointment.

The age of five men and one woman could not be found. The average age of the men was 52 (range 40-64, 5 not known). The average age of the women was 45 (range 38-55, 1 not known).

The Body Mass Index (BMI, Body weight in Kg divided by the Height in metres squared) was calculated. For men the average BMI was 28 (range 21-35) and for women it was 32 (range 26-36).

There were ten different nationalities of patient in this pilot study (Table 1).

Table 1 Nationality of patient according to sex

	Male	Female	Total	%
Algerian		1	**1**	4%
Bangladeshi	2		**2**	9%
Egyptian	3	2	**5**	22%
Indian	6		**6**	26%
Jordanian	1		**1**	4%
Lebanese	1		**1**	4%
Filipino		1	**1**	4%
Somali		1	**1**	4%
Sudanese	3	1	**4**	17%
UAE	1		**1**	4%
Total	**17**	**6**	**23**	

The majority of the patients were Indian (n=6, 26%), Egyptian (n=5, 22%), and Sudanese (n=4, 17%). Thirteen of the patients were native Arabic speakers (57%). Fourteen (61%) of the patients reported English as their second language. Only one patient was a UAE national. All patients had Arabic as a first language or English as a second or third language.

Thirteen (57%) of patients, including all the women, live in the UAE with their families for at least 6 months of the year.

Data on the educational level attained by each patient was available for 17 and is summarised in Table 2).

Table 2 Educational level of the pilot data set (n=17)

Sex	None	Primary	Secondary	Graduate	Postgraduate	Subtotal
M	0	1	2	3	4	10
F	0	1	2	0	4	7

The median income of the households was between Dh 4000 and Dh 8000.

Two of the men reported that they smoked. None of the women smoked.

The time since the last attendance at the City Health Centre ranged from 2 days to 31 days (n=15). The clinic attendance data was not available for eight patients.

3.8.5.2. **Blood pressure data**

Data to calculate the average blood pressure was available for twenty-one (21) patients, fifteen (15) men and six (6) women. One patient (male) did not have historical data available regarding the time of diagnosis of hypertension. This data is

required for calculating blood pressure control and to ensure that treatment has stabilized. Therefore, this patient could not be included when analysing the change in blood pressure since the start of treatment. However, where practical, they have been included for the evaluation of the pilot study.

For men, the median duration of treatment was 5.08 years (range 0.94-12.78) and for women, the median duration was 3.85 (range 1.85-8.48).

The average blood pressure data for the pilot group as a whole is shown in Table 3, below. .

Table 3 Blood pressure control among the pilot data set

BP. Control criteria	Number at target BP	% (n=22,)	Controlled	
			Male (% of m)	Female (% of f)
≤140/90 mmHg and ≤130/85 in diabetics	8	36%	4 (25%)	4 (67%)

Five of the patients (n=23, 22%) were diagnosed as having type 2 diabetes (4 men, 1 women), none of which met the criteria for blood pressure control.

3.8.5.3. Medication Review

Medication data was available for all twenty-three patients (including the recently diagnosed patient) and is summarised in Table 4.

Table 4 Number of patients on monotherapy and the drugs used

ACE Inhibitors		Beta blocker		CCB			
Captopril	1	Atenolol	2	Amlodipine	1		
Enalapril	2						
Lisinopril	6						
subtotal	9	*subtotal*	2	*subtotal*	1	12	Total

Of the eleven patients taking two antihypertensive drugs eight patients were taking an ACE inhibitor with a Beta-blocker, two were taking a Beta-blocker with a diuretic and one was taking and ACE inhibitor with a diuretic.

Data on other drugs was available for twenty-three patients. Five of the twenty-three patients (22%) were receiving medication for type 2 diabetes and four patients (17%) were taking NSAIDs regularly. Other regular medications included lipid lowering (1), vitamins (2), dyspepsia medication (3), salbutamol inhaler (1), allopurinol (1), nitrates (1) and diazepam (1).

3.8.5.4. Self-reporting measure

All twenty-three patients answered the ten-item self-reporting measure. A "yes" answer indicates that they are admitting to a potentially non-adherent behaviour and scores one. There are two exceptions to this. In items five and six, a "yes" answer

indicates good compliance, i.e. they have taken their medication that day (or in the preceding twenty-four hours) and they do have a routine to remind them of their need to take medication. For analysis purposes, for these two items, a "no" answer is scored as one, i.e. there is a possible adherence problem. If the response to question one was "yes" then the patient had to give an estimate of the non-adherence frequency; weekly (item 1w) and monthly (item 1w).

Twenty-one patients (91%) answered "yes" to at least one question showing that 91% of patients reported to behaviour that indicated non-adherence.

Table 5 Number of patients who indicated non-adherent behaviour in response to each item

(n=23, *=see notes above)

	Q1	Q2	Q3	Q4	Q5*	Q6*	Q7	Q8	Q9	Q10
"Yes"	7	3	1	4	2*	18	3	1	2	1

Item six; "Do you have a routine to help you to remember your blood pressure medicines" was answered as "No" by eighteen patients (Equivalent to a "Yes" answer to other questions). However, as this question showed such a low ability to discriminate between the pilot patients it was excluded from further pilot data analysis. Five items (items 3,5,8,9 & 10) were answered by less than 10% of the patients. Items three, eight and ten were answered "yes" by only one patient each and questions five and nine were answered "yes" by only two patients each.

In accordance with the original Morisky scale, one can create a scale of adherence e.g. 0 = high, 1-4=medium adherence, >4=low adherence), a score of 1 is given for each "yes" answer (table 6). The scale presented below was used for illustrative purposes only as only a larger, validated sample could be relied upon to devise a scale of adherence. Items 6 and 10 were excluded as 6 appeared to be unreliable at this stage and item 10 was a supplementary question that was not a part of the Morisky scale.

Table 6 Distribution of the pilot study patients' self-reported non-adherence score: 8 item raw score after excluding item six and ten (n=23)

Patient Self reported score	Number of patients (%) Raw Score		Adherence	
0	13	57%	57%	High
1	4	17%	34%	Medium
2	3	13%		
3	1	4.4%		
4	0	0%		
5	1	4.4%	9%	Low
6	1	4.4%		
7	0	0%		
	23	100%		

3.8.5.5. **Pilot Doctor Questionnaire**

Data was available for twenty-three patients but for two patients items four to seven were not available. All twenty-three of the pilot patients were included in this analysis as the aim was simply to study the ease and comprehensiveness data collection

The doctor's perceptions of the patient's adherence to medication were to be determined from items 1-3. A "Yes" answer to one of questions 1-3 is assigned a score of 1 (see below).

Table 7 Number of "yes" responses to the three doctor items (n=23)

	Question text	Yes
Q 1	Do you think that this patient ever forgets to take a dose of their blood pressure drugs?	10
Q 2	Do you think that this patient sometimes stops taking their blood pressure drugs?	5
Q 3	Do you think that this patient sometimes stops taking their blood pressure drugs because they feel worse, e.g. due to side effects	6

In all ten cases, the doctor answered "Yes" to question 1. In four cases this was the only question answered "yes" and in five cases they answered "yes" to all three questions. To create a scale of adherence (0 = high adherence, 3=low adherence), a score of 1 was given for each "yes" answer. A "zero" score indicates that the doctor answered "No" to each question and therefore, did not perceive an adherence problem (Table 8).

Table 8 Distribution of the patient Non-adherence score as assessed by the doctor (n=23)

Dr score	Number of patients		Dr.'s assessment of Adherence	
0	13	57%	57%	High
1	4	17%	21%	Medium
2	1	4%		
3	5	22%	22%	Low
	23	100%		

A comparison to the patient questionnaire data and the clinical data was not performed for the pilot data.

The secondary questions, items 1w and 1m were not analysed at this stage.

3.8.5.6. **Pilot - Doctor's clinical impressions**

Following the consultation with the patient, the doctor was asked to give their clinical impression of the patient and quality of their communication, items 4-7). Data was available for twenty-one out of the twenty-three patients. The data omission was because two of the doctor's questionnaires had a page missing. The response to the clinical impressions items is shown below in Table 9.

Table 9 Doctors response to Items 4-7 for the pilot data set (n=21)

	Number of patients		
Items	**Excellent**	**Average**	**Poor**
4.How do you rate the effectiveness of this patient's current anti-hypertensive medication?	9	9	3
5. How do you rate the communication and openness between you and this patient?	15	6	0
6. How do you rate this patient's knowledge of their hypertension and of their antihypertensive medication?	6	12	3
	Low Risk	Medium Risk	High Risk
7. How do you rate this patient's risk of suffering a major cardiovascular event in the next 5 years?	7	9	5

3.8.6. Discussion of the pilot study

The aim of the pilot study was to identify any problems with the recruitment method, use of the questionnaire and to ensure that the required data could be collected. Each of these is discussed below.

This pilot study showed that the recruitment rate was lower than might be expected by the historical clinic data. The average attendance data had suggested one might expect around 130 hypertensive patients to attend the health centre in a 15-day period. The inclusion criteria are quite wide and therefore the recruitment of 23 patients over a 15-day period is much lower than expected. Following discussion with the doctors, it was decided that this was due to a variety of factors. Firstly, the average clinic figures conceal a wide seasonal variation with low attendance during the summer months (many people on vacation) and higher attendance pre summer as people get their "summer supplies" before travelling, often making more than one attendance. Secondly, the number of people who declined to participate was not known. Thirdly, if the doctor were busy then they would sometimes not ask the patient to participate. Therefore, it was decided that during future data collection, a number of steps had to be taken to improve the quality of data collection and these are listed in Figure 39 below

Figure 39 Improving the quality of patient recruitment

Steps taken after the pilot study to improve recruitment
Find a data collection method that was less intrusive on the doctor's time
Encourage doctors to collect data
Ensure that a record was kept of those patients who declined to give consent
Arrange for at least one other centre for data collection

3.8.6.1. Discussion of the Pilot Patient Profile

Most of the patient profile data could be collected from the medical record. The age of the patient was often only recorded as the year. This is a reflection of the poor availability of records from 50 years ago and the fact that in the practice of Islam, the celebration of birthdays is not encouraged. To ensure that this was recorded in the database in a consistent manner, a decision was taken that when only the year of birth (YY) was available, it was to be entered in to the database as 1st July YY.

The doctors successfully completed the parts that required direct questioning of the patient such as location of family, education level, household income and language spoken. The data about walk-in consultations versus appointment soon ceased to be

relevant as the plans to introduce an appointment system were abandoned for a variety of reasons.

3.8.6.2. Discussion of the Self-reporting measure

The pharmacists were able to deliver the self-reporting measure in Arabic or English. A review of the data and discussions with the pharmacists highlighted two problem areas.

Items 1w & 1m: Their inclusion was mainly for comparison with alternative quantitative methods of measuring adherence e.g. electronic monitors. The doctors commented throughout the pilot study that they found it very difficult to quantify their suspicions of non-adherence. The pharmacists reported that patients found the Likert scale for quantifying the frequency of non-adherence very difficult to use. The scale was far more complex than those used in other studies. In a study of adherence to asthma medication[45], four categories were provided for patients unlike the six point weekly ("1w") and fourteen point monthly ("1m") scales used in the pilot. Following further discussion with the doctors and pharmacists involved with the study it was felt that there were several problems with trying to quantify self-reported adherence, including:

It was not part of the previously validated Morisky scale

It would be difficult to ensure that these estimates would not in some way influence how the patient responded to subsequent items

It was difficult to find a simple descriptive phrase for a level of non-adherence equivalent to less than 20%, i.e. the level below which blood pressure control is considered achievable, e.g. 5 days out of 28.

Therefore, it was decided to not have any estimation of frequency in the self-reporting measure and to retain the simple dichotomous response ("Yes" or "No" for items 1-5.

Item 6: In the latest Morisky questionnaire a "No" answer to this question scores one, as it has been associated with a reduced likelihood of adherence. Although there had been no statistical item analysis, this item showed very little ability to discriminate between patients. The translation was not a problem so it was possible that the item was not being explained or presented properly to the patients. It was decided to explain this item carefully to the pharmacists presenting the question and to encourage them to ask patients to think carefully before answering a simple "I do not have a system", perhaps encouraging the use of "Other reminder system".

Meanwhile, item 6 would be kept in the measure, as it was a part of the amended Morisky measure.

3.8.6.3. Discussion of the Doctor Questionnaire

The attempt to get the doctor to make a quantitative estimate of adherence was unpopular with the doctors. The doctors said that this was very difficult to apply, and therefore, not something that was likely to have any specific value. This item was simplified and split into two questions; items 1 and 2 of version 6 of the final questionnaire (Figure 40 below).

Other, minor changes were made to four items asking the doctor about the patient's treatment (these are items 5-8 of the version 6). Each of these questions has three options and these were clarified by providing descriptions or explanations for each option.

Following the pilot study, it was decided to add three more items (Items 9, 10a & 10b, *see version 6*). These items were introduced to allow the doctor an opportunity to show that they recognized sub-optimal blood pressure control and had responded to it.

New Item 9: It is recognised that failure to control blood pressure may be due to a number of factors and that some contributing factors may worsen with time. Therefore, if the doctor said that the blood pressure was not controlled, the doctor was prompted to say why.

New items 10a and 10b: If the doctor changed the drug treatment at that consultation, they were asked why they had made the change. This was added because it was felt that the study might prompt the doctor to review the blood pressure treatment. A change of treatment during the consultation is not an exclusion criteria and it would be useful to correlate the doctor's motives to their overall perceptions of the patient and their treatment.

Following further discussions and minor redrafting, Version 6, was agreed and became the version preferred by the doctors. This is presented on the following pages (Figure 40) .

Figure 40Doctor's questionnaire – Version 6, Final

After the consultation and after reviewing the file, please use this form to record your PERCEPTIONS

1. Please give your estimate of this patient's adherence to their blood pressure medication

High adherence	Takes more than 80% of the doses as prescribed	☐
Medium Adherence	Takes between 60 and 80% of the doses as prescribed	☐
Low Adherence	Takes less than 60% of doses as prescribed	☐

tick one

2. Do you think that this patient ever **forgets** to take a dose of their blood pressure drugs? ☐ **Yes** ☐ **No**

3. Do you think that this patient sometimes stops taking or reduces the dose of their blood pressure drugs **because they feel better or because they feel that their blood pressure is under control?** ☐ **Yes** ☐ **No**

4. Do you think that this patient sometimes stops taking or reduces the dose of their blood pressure drugs **because they feel worse, e.g. due to side effects?** ☐ **Yes** ☐ **No**

Version 6 (Final)

5. How would you describe the effectiveness of this patient's current antihypertensive medication? **(tick one box)**

☐ **Good -**Patient has reached their target BP ☐ **Partial** - Some reduction in the BP since starting but not enough ☐ **Poor** - No improvement in the BP since starting this regime

6. How do you rate the communication and openness between you and this patient? **(tick one box)**

☐ Excellent ☐ OK ☐ Poor

7. How do you rate this patient's knowledge of their hypertension and of their BP medication? **(tick one box)**

☐ Excellent ☐ OK ☐ Poor

8. After considering the patient's age and sex, how do you rate this patient's risk of suffering a major cardiovascular event in the next 5 years? **(tick one box)**

☐ Unlikely ☐ Increased risk ☐ Greatly increased risk

9. If the patient's BP is **NOT** controlled, what do you think is the main reason? **(tick one box)**

☐ **Non-adherence** ☐ **Non-ideal drug regime** ☐ **Other reason e.g.** worsening pathology

10. a) Have you changed the blood pressure regime today? **(tick one box)** ☐ **Yes** ☐ **No**

10. b) If "**Yes**", why? **(tick one box)** □ **To improve control** □ **Because of side effects** □ **Other reason**

3.9 Method Development and Pilot Study Conclusions

A self-reported adherence measure was developed, based upon a previously published instrument and following discussions among primary health doctors. This instrument was translated in to Arabic and the translation was found to have good validity when studied using a process of back-translation. In addition to an Arabic language self-reporting measure of adherence, a questionnaire was developed to record the doctor's perception of medication adherence and other factors relating to the patient, their condition and their relationship with the doctor.

A pilot study was performed and showed that both the Arabic self-reporting measure and the doctor's questionnaire can be easily administered in a normal clinical setting of a ministry of health centre. The pilot study had been a useful exercise for all those involved in the data collection and had identified several areas for refinement before full data collection.

3.10 Next steps

A top priority was to get approval from the Ministry of Health to use a second health centre for data collection to ensure a reasonable rate of recruitment. A second centre would need more hypertensive patients and ideally, should have a higher proportion of UAE nationals attending the centre so to better reflect the target population of the Ministry of Health. However, it was not practical to operate two centres concurrently. None of the required changes reduced the validity of the data collected in this pilot study, with the possible exception of responses to item 6 of the self-reporting measure. Therefore, it was decided to include the pilot data in an analysis of the complete data unless statistics showed it to be too heterogeneous.

This pilot study had fulfilled the objectives and had identified a small number of important and unforeseen problems with the recruitment method and data collection. All of these problems could be easily rectified allowing the study to go into the next stage of full data collection.

The main experimental work is described in the following chapters.

4. Concurrent validity of an Arabic / English self-reported measure of medication adherence

4.1 Aims and objectives

One aim of this PhD thesis was to devise and evaluate an Arabic / English instrument for the self-reporting of medication adherence in patients attending primary healthcare centres for the management of hypertension. The objectives of this part of the study were as follows:

- To use the method described above to collect self-reported medication adherence data for approximately 200 patients taking medication for high blood pressure at primary health care centres
- To perform factor analysis and determine the internal reliability of the self-reported data in order to determine the construct validity of the Arabic / English self-reporting measure

4.2 Method

The study was performed in two Ministry of Health (MOH) health centres in Abu Dhabi city. The inclusion and exclusion criteria were the same as in the pilot study. One of the centres was the centre described in the pilot study and the second health centre was a UAE nationals-only health centre. At the first centre there was no change to the protocol beyond the pilot study. However, the second health centre was much more busy and included a busy dental and maternal and child health facility resulting in 11,346 attendances per month and with an estimated 500 adult hypertensives registered as receiving their hypertension care at the centre. The busier workload necessitated a review of the best method to collect the data at the second centre. The clinic staff were very keen to participate but they were concerned that the original data collection process could take too much time from the doctors and pharmacists, especially during the peak attendance periods. The solution was to make use of the time prior to the doctor's consultation. There are no appointments, so patients join a queue. On arrival, the medical record is retrieved from the registration section and while they wait to see the doctor, the nurse measures the blood pressure, pulse, body weight etc. The standard of nursing staff is higher than average at the second health centre and there is a very efficient and highly motivated nurse in charge. Therefore, it was decided that at the second health centre, the nurse would be in a good position to gather the patient profile data, recruit the patient into the study and deliver the self-reported adherence measure. The nurse then attached a red sticker to the medical record folder and placed a blank copy of the doctor's questionnaire in to the medical record to prompt the doctor to

complete their questionnaire after the consultation. Consequently, at the second health centre, the doctor had only to complete his questionnaire at the end of the consultation and pharmacy were not involved with the data collection. All the staff members at the second health centre were introduced to the study protocol and the nurses and doctors were coached individually about the correct way to complete the data collection.

It was estimated that approximately 200 patients would be required for the results to be statistically valid. This was based upon several rules of thumb when performing factor analysis and these are described in Annex 2. It was agreed with a statistician at the local medical faculty that 200 patients would be comfortably "mid-range" as well as practical, considering the uncertain rate of recruitment and that this would also leave some room to discard "outliers" later in the analysis.

Recruitment continued at the first centre after the pilot study following the end of the Holy month of Ramadan and the Eid festivities in January 2001 and continued at the first centre until mid April. At this point recruitment started at the second health centre and continued until June 2001, a time when many staff and patients are leaving for their summer vacation.

Data analysis

Data analysis was performed using SPSS (version 10) and Microsoft Excel 2000. Data was entered into an Excel spreadsheet as in the pilot study and imported in to SPSS 10 as required. The statistical analysis involved descriptive statistics for each item on the patient profile and each item of the self-reporting measure. Factor analysis in the form of Principal component analysis (PCA) was used to identify the dimensionality of the measure and the internal reliability of the adherence measure was calculated using the Cronbach alpha. The Cronbach alpha ranges from 0 (*no internal reliability*) to 1 (*perfect internal reliability*). A description of Internal reliability and Factor analysis is provided in Annex 5.

4.3 Results

A total of 203 patients were recruited to the study (22 from the pilot study, a further 25 from the first centre and 156 patients from the second centre). The patient profile was recorded as described in the pilot study and is summarised below.

4.3.1. Self-reported adherence measure

A comparison of the response frequencies from the first health centre (47 patients) and second health centre (156 patients) is shown in Table 10, below. This table compares the percentage of patients who had responded to each item. Using the percentage response frequency makes it easier to compare the responses from the

different sized populations. The table shows that most items were responded to with a "Yes" at least 9% of the time in the total population and in the population at the second health centre. When comparing the response frequencies of all 203 patients with the first and second health centre samples; at the first health centre, there appears to be a much lower response frequency to items 3, 8, 9 and 10, and a relatively low response to item 7. This was studied further to determine if it was a type 2 error arsing from the small sample.

Table 10 Percentage response frequency to the 10 item Arabic / English self-reporting measure

		% Responding "Yes" to each item									
Sample	n	1	2	3	4	5	6	7	8	9	10
All	203	16	16	12	11	9	41	17	16	26	14
PHC1	47	20	13	**2**	13	7	52	11	**7**	13	**7**
PHC2	156	15	17	15	11	10	38	19	19	30	17
PHC2r1	47	17	21	19	13	13	41	24	19	34	17
PHC2r2	47	15	19	11	**2**	15	36	15	13	26	17
PHC2r3	47	15	**9**	13	11	13	30	21	17	32	**6**

To investigate further the influence of sample size upon the response frequency, Table 10 presents the response frequencies for three different random samples of 47 patients selected from the second health centre sample of 156 patients (PHC2r 1-3). This selection was done using the data selection function in SPSS 10 (Tool bar; Data, Select cases, Random Sample of Cases and choosing 47 out of the "first" 156). This shows occasional, low response frequencies among the three random samples e.g. items-2, 4 and 10.

4.3.2. Internal reliability and Principal component analysis (PCA) of the Self reported adherence measure

Principal component analysis (explained in Annex 2) was used to determine the extent to which the 10 items measured a common construct or measured two or more clusters of variables that represent different dimensions of adherence.

The Cronbach alpha for all ten items was 0.67 showing a moderate internal consistency (recommended minimum is 0.6 but less than 0.8 is common in social science measures such as the self reported medication measure). In PCA, the KMO statistic is first used to predict if the sample is adequate and likely to factor well, see Table 11. The overall KMO statistic for the ten items was 0.74, comfortably above the 0.60 often considered the minimum for factor analysis to proceed. The KMO for item six was 0.475, the lowest in the set. The pilot study indicated that items 5 and 6 might reduce the internal reliability of the self-reporting measure. The individual KMO statistic for these two items was among the lowest along with item 10. This indicates that these items are amongst the least likely to show strong correlations as part of an overall Principle Component Analysis.

Table 11 The KMO statistics for all ten items (n=203)

Item	KMO Statistic*
Overall	0.74
1	0.72
2	0.81
3	0.82
4	0.74
5	0.66
6	0.48
7	0.79
8	0.67
9	0.81
10	0.65
*Kaiser-Meyer-Olkin statistic *see Annex 2*	

As shown in Table 12 below, a PCA of the responses to all 10 items showed that there were three main factors (Eigenvalues greater than 1, i.e. a three-dimensional model:). These three factors accounted for 53.812% of the variation in response to the ten items while a further seven, minor factors (dimensions) explained the remaining variation.

Table 12 Total Variance shown by PCA of all ten items

Factor	Eigenvalue	% Variation	Cumulative % variation
1	3.047	30.468	
2	1.250	12.497	42.965
3	1.085	10.847	53.812
4	0.976	9.758	63.570
5	0.859	8.595	72.164
6	0.755	7.554	79.718
7	0.614	6.143	85.861
8	0.545	5.454	91.315
9	0.469	4.695	96.009
10	0.399	3.991	100.000

In order to study the contribution of each item, the items were combined and studied in a stepwise manner to determine which combination gave the optimal internal consistency and reliability.

As shown in Table 13, each item showed a distinct correlation to a single factor. For dichotomous data, a factor loading is considered a strong correlation if it is 0.45 or greater. In this case, the strongest factor loading ranged from 0.495 (item 5, Factor 1) to 0.818 (item10, Factor 2). Items 1,2,3,7 and 9 correlated most strongly with factor 1. Items 8 and 10 correlated most strongly with factor 2 and items 4 and 6 correlated strongly with factor 3. Item one was unusual in that it also showed a moderate to weak correlation to factor 3; however, the loading of 0.441 for factor 3 is considered as "weak" when analysing dichotomous data and was therefore disregarded.

Table 13 Principal Component Analysis of all 10 items showing the "factor loading" of each item to each factor

Item under analysis		3 factors (dimensions)		
		Intentional 1	Emotional stress 2	Lack of planning 3
1	Some people have difficulty remembering to take their medicines. Do you ever forget to take a dose of your blood pressure medicine?	0.608	0.080	0.441
2	People sometimes miss taking their medicines for reasons other than forgetting. Over the past two weeks, were there any days when you did not take your blood pressure medicines?	0.554	0.351	0.201
3	Have you ever cut back or stopped taking your blood pressure medicines (without telling your doctor) because you felt worse when you took it?	0.627	0.207	0.128
4	When you travel or leave home, do you sometimes forget to bring along your blood pressure medication?	0.283	0.316	0.631
5	Did you take your blood pressure medicine today?	0.495	-0.088	-0.246
6	Do you have a special routine or reminder system to help you to take your blood pressure medicines? (if "yes", describe it)	-0.162	-0.227	0.697
7	When you feel like your blood pressure is under control, do you sometimes stop taking your medicine?	0.748	0.041	0.040

8	Some people find it very inconvenient to take their blood pressure medicine every day. Do you ever feel hassled about sticking to your blood pressure treatment?	0.140	**0.808**	-0.0027
9	How often do you have difficulty remembering to take all your blood pressure medicine? Never/ Rarely, Once in a while, Sometimes, Usually, All the time	**0.590**	0.367	-0.200
10	Some people feel that it is embarrassing to take medication every day for their blood pressure. Do you ever feel embarrassed or ashamed that you have to take your blood pressure tablets?	0.067	**0.818**	0.0073

The shaded cells show the highest factor loading (correlation) for each item

Table 14 Assigning a description to the 3 main factors

Factor	**Description** (trait leading to non-adherence)	Items with a strong correlation to this factor
1	Forgetting & Intentional	1, 2, 3, 5, 7 and 9
2	Emotional stress	8 and 10
3	Lack of planning or organisation	4 and 6

It can be seen from Table 14 that there is a common theme to the questions that correlate most strongly to the same dimension.

The items that contribute most to the first factor (1,2,3,5,7 & 9), all address the non-adherence arising from forgetfulness or intentional non-adherence. Items 8 and 10 both address emotional stress as a cause of non-adherence and items 4 and 6 relate to non-adherence arising from a lack of planning or routine organisation in the way that the patient manages their medicines.

The effect of various combinations of items on the internal consistency and reliability of the scale was studied in a stepwise manner and is summarised in Table 15.

Step 1 Analysis of the complete 10 items produced a Cronbach alpha of 0.67, a KMO statistic of 0.74 but three factors with an Eigenvalue of more than 1. These three factors accounted for over 53% of the variation.

Step 2 The determination of the ideal combination of items started with those six items (1, 2, 3, 5, 7 and 9) that showed the strongest correlation to factor 1 (forgetting and intentional non-adherence). When analysed alone, these six items had a Cronbach alpha of 0.70, a KMO statistic of 0.73 and provided two major factors (dimensions), which accounted for 50.86% of the variation. Item five was the weakest of these items (correlation was 0.495) and therefore, item five was omitted before reanalysis.

Step 3 Omitting item five increased the Cronbach alpha to 0.72 and reduced the number of factors to one, a single dimension accounting for 41.44% of the variation. Item five was rejected.

Step 4 Item 10, the strongest component of factor two (Emotional stress) was then added to the analysis. These six items (1, 2, 3, 7, 9 and 10) had a Cronbach alpha of 0.72 and produced a single factor accounting for 42.32% of the variation.

Step 5 Item eight, was also a strong contributor to factor two and when this was substituted in place of item ten (analysis of items 1, 2, 3, 7, 8 and 9), the results were almost identical, with the same Cronbach alpha, a single factor but a slightly higher KMO statistic and slightly higher variance associated with the single factor.

Step 6 However, addition of item 10 and item 8 produced a two dimensional model as might be expected due to the extra loading on factor two. Item ten was therefore rejected.

Step 7 Item six was the strongest component of factor three (Lack of planning or organisation) and was included in the analysis next. The Cronbach alpha for this set of items was the lowest of all at 0.59 and it produced two factors, due partly to the strong factor loading for factor 3 and a negative factor loading of item 6 on factors 1 and 2. Item 6 was rejected.

Step 8 Item 4 was the second component of factor 3 and this was analysed along with the two previous six-item scales. The best combination was with items 1, 2, 3, 7, 8, and 9. This seven-item scale produced a Cronbach alpha of 0.76 and a single factor accounting for almost 40% of the variation.

Table 15 Determining the optimal internal consistency and reliability

Step	No. Items	Items analysed	Cronbach alpha	KMO statistic	No. Factors Eigenvalue >1	Total No. Factors	% Variation from the main factor(s)
1	10	All 10 items	0.67	0.74	3	10	53.81%
2	6	1, 2, 3, 5, 7 & 9	0.70	0.73	2	7	50.86%
3	5	1, 2, 3, 7 & 9	0.72	0.75	1	6	41.44%
4	6	1, 2, 3, 7, 9 & 10	0.72	0.78	1	6	42.32%
5	6	1, 2, 3, 7, 9 & 8	0.72	0.79	1	6	42.62%
6	7	1, 2, 3, 7, 8, 9 & 10	0.74	0.76	2	7	55.97%
7	7	1, 2, 3, 7, 9 & 8 & 6	0.59	0.78	2	7	52.57%
8	7	1, 2, 3, 7, 9 & 10 & 4	0.74	0.79	1	7	39.04%
	7	1, 2, 3, 4, 7, 8 & 9	0.76	0.79	1	7	39.69%

4.3.3. Result summary

As shown by internal reliability analysis and principal component analysis, the optimal combination of items in a self reported measure of adherence is shown above (shaded). It combines seven items (1,2,3,4,7,8 and 9) and relates three key types of non-adherent behaviour in to a single dimension with a high internal consistency, Cronbach Alpha of 0.76. Items 5, 6 and 10 were rejected from the scale used for the self-reporting measure of adherence but would be studied separately for the relationship to adherence.

The frequency distribution of the seven-item self reported adherence scores is shown in Table 16

Table 16 Distribution of the patient's self-reported non-adherence measure after excluding questions 5,6 & 10 from the analysis

Patient' Self eported score	Number of patients (%)	Adherence *n* (%)
0	106 (52.2)	High 106 (52%)
1	39 (19.2)	Medium 87 (43%)
2	21 (10.3)	
3	12 (5.9)	
4	15 (7.4)	
5	5 (2.5)	Low 10 (5%)
6	3 (1.5)	
7	2 (1.0)	
	203	

Studying the relationship of the adherence score to the blood pressure control can further assess the concurrent validity of this adherence measure. This is shown in Table 17 and figure 47 below.

4.3.4. Quality assessment of blood pressure data

The quality of the blood pressure data was studied to identify the extent of the measurement error due to systematic error, terminal digit preference and observer bias. Three blood pressure measurements were available for most patients and for 86 patients; three more were available from the follow-up period. The data was also evaluated to identify any differences between the two health centres. This data is presented in Annex 4. There was no evidence of any major systematic error. There was a strong preference for recording blood pressures that ended in zero. Overall, around 91% of all systolic pressure measurements ended with a zero and around 5%

ended with a five. For diastolic pressure readings, around 82% of readings ended with a zero and 11% ended with a five. There was little difference between the two health centres in the terminal preference of systolic measurements. However, at health centre 1, the incidence of diastolic pressure records ending in a zero was somewhat lower that at health centre 2, at around 76%. Although high, the rate of terminal digit preference was comparable with that reported in international studies. Analysis of observer bias suggested that it was not common but that up to seven percent of patients were misreported as not being hypertensive.

4.3.5. Relationship of Self-Reported Medication Adherence to Blood Pressure

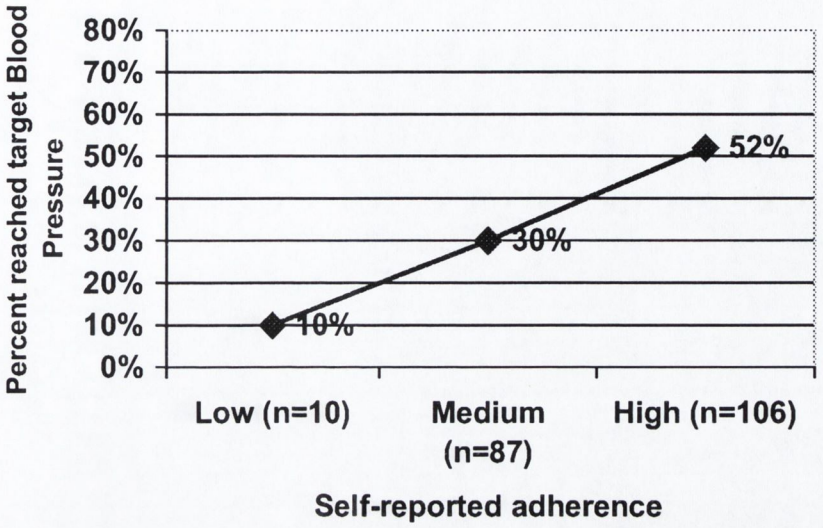
Among the 203 patients, 40% of patients had reached target blood pressure; however, 52% of those patients scoring zero on the seven-item scale (high adherence) had reached target blood pressure compared with 30% of those scoring between one and four and 10% of those scoring five or more (Table 17). The difference in blood pressure control between the high, medium and low groups was highly significant (*p>>0.001* Chi square = 12.584, 2df, one-tailed) and therefore showed a strong association between self-reported adherence and blood pressure control (figure 47).

Table 17 Number of patients reaching target blood pressure according to JNCVI at different levels of Self reported adherence (n=203)

Patient' Self eported score	Target Blood Pressure No		Yes		Adherence n (%) controlled	
	n	*row %*	*n*	*row %*		
0	51	48.1%	55	51.9%	High 55* *(52%)*	
1	28	71.8%	11	28.2%	Medium 26* *(30%)*	Medium to Low 27 *(28%)*
2	17	81.0%	4	19.0%		
3	7	58.3%	5	41.7%		
4	9	60.0%	6	40.0%		
5	4	80.0%	1	20.0%	Low 1* *(10%)*	
6	3	100%	0			
7	2	100%	0			
Total with target BP			82	40%		

* p > >0.001, 2df

Figure 41 Percent reaching target blood pressure control by self-reported adherence (n=203)



Analysis of the 202 patients for whom at least 3 months blood pressure data was available showed that both the average systolic and diastolic blood pressure was significantly correlated to the score on the self-reported adherence scale Table 18.

Table 18 Correlation of blood pressure with the Self-reported Adherence Scale Score

	Spearman's Rho	1 tailed significance (p)	n
SBP	0.111	0.018*	202
DBP	0.232	0.0004**	202
d. SBP	0.185	0.006**	184
d. DBP	0.076	0.153 ns	184

SBP & DBP: Systolic (SBP) and Diastolic (DBP) blood pressure. The average of the last 3 clinic measurements

d. SBP & d. DBP: The change in systolic (d. SBP) and diastolic (d. DBP) pressure

* = significant at >0.05; ** = significant at >0.01;

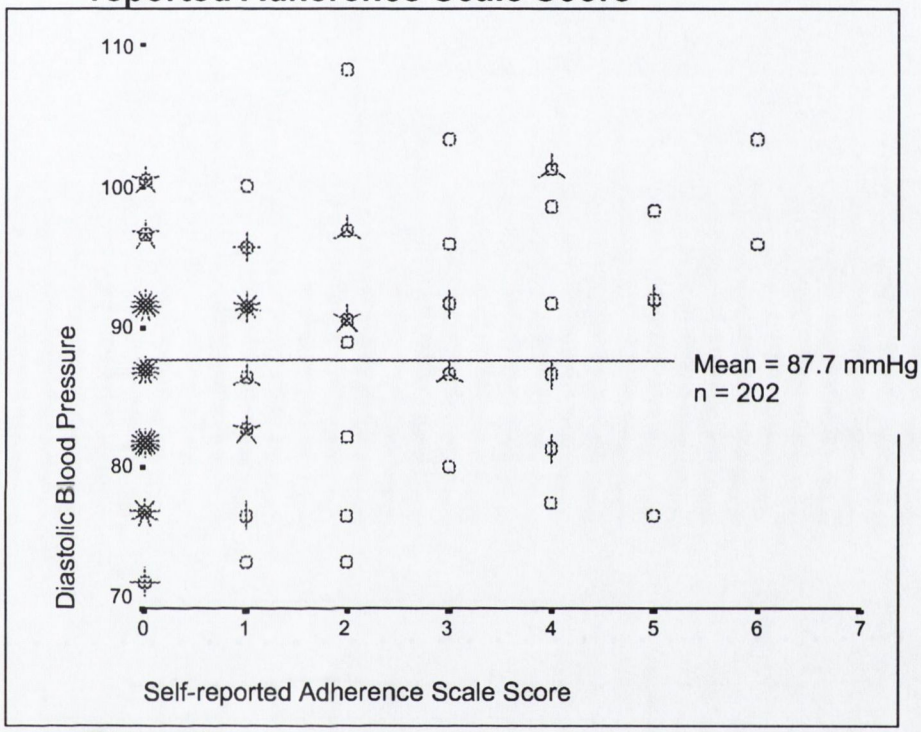
ns = not significant

Data on the change in the blood pressure since the start of drug treatment was available for 184 patients. The correlation between the self-reported adherence scale score and the change in the systolic blood pressure was significant. However,

the change in the diastolic blood pressure was not significantly correlated with the score.

This is illustrated by a scatter plot of diastolic blood pressure versus score is shown Figure 42 below. The SPSS "sunflower" notation is used whereby each point is portrayed as a single point e.g. or as a "sunflower" in which the number of "petals" indicates the number of cases represented by the at point, e.g. would represent 4 case points and many case points.

Figure 42 Scatter plot to show Diastolic Blood Pressure by Self-reported Adherence Scale Score



4.4 Discussion

Both samples (health centres 1 and 2) were representative of the type of patient attending at the PHC centres in terms of age, sex and medication. The patient demographics were typical for the health centre profile but it is worth noting that the first centre had a higher proportion of males attending but this was expected and reflects the predominantly male expatriate work force, whereas the second health centre was a "nationals only" health centre. Therefore, the two most likely differences between the two health centres were patient gender and nationality. Neither of these has been shown to influence the validity of self-reported adherence. During the design of the method, it was assumed that there is no intrinsic difference between the nationals and non-nationals (Arab and Non-Arab) in terms of their answers to the self-reporting scale. However, table 10 suggested that the response frequencies could be different at centre one compared with centre two, especially for

items 3, 8, 9 and 10. These differences are most likely to be due to the smaller sample size at centre one. Annex 5 describes the importance of having an adequate sample size when studying responses to a scale using reliability and factor analysis. The minimum sample for a scale such as this would be 50; therefore, the sample from health centre one is smaller than one needs if one was to study it in isolation. The response frequencies of the three smaller (n=47), random samples drawn from the second centre also showed that with small samples, unusually low response frequencies can be found when compared with larger samples. This was a major reason behind the decision to combine the two populations for the purpose of developing a self-reported adherence scale and performing internal reliability and factor analysis. The pilot self-reporting scale had included two supplementary items for item 1. These were disregarded in the initial, validation study

The original four-item "Morisky" self-reporting scale was one-dimensional and the subsequent nine-item Morisky scale is reported to be one-dimensional. In this study, variation in response to a ten-item scale could be explained according to three factors. This is also described as a "three dimensional model". This means that the variance in the responses to the questions is distributed according to three major factors. For the scale to be used as a specific and sensitive scale of adherence, the overall variance in response should be due to a single factor with an Eigenvalue of one or greater (see Annex 5), and be related, in a linear fashion, to the level of medication adherence. As shown in Table 14, one can relate the three factors to behavioural traits. These are in accordance with Morisky's initial model but forgetting and intentional non-adherence is combined. All three traits are important contributory causes of non-adherence. Through a step-wise process of iteration, items were omitted and combined from the ten-item scale until the variation in responses was attributable to a single factor. This process has been criticised by Pratt *et al* who compared different self-reporting scales in people with HIV infection [210]. Their main concern is that by eliminating items until a single dominant factor is achieved, one weakens the model and chooses to overlook the importance of individual traits that lead to adherence, or non-adherence. Among the concerns of Pratt *et al* was that a one-dimensional self-reporting scale might have a reduced sensitivity because it combines facets of intentional and non-intentional non-adherent behaviour. In addition, Pratt *et al* found that in patients taking complex anti-retroviral drug regimens, some patient characteristics were more closely related to some traits than others. However, these concerns also highlight the importance of validating self-reporting scales in specific patient groups. The criticism of Pratt *et al* goes on to

make some assumptions that are not well supported in the literature. The scales studied in the Pratt study included the original four-item Morisky scale and a scale developed among patients with end stage renal disease[211]. While both of these scales have been used in populations with a variety of chronic diseases, few are as complex and critical as adherence to the modern anti-retroviral therapy that they studied. Perhaps more important is the assumption that the level of non-adherence and the behavioural trait leading to non-adherence remain constant. On the contrary, early work and subsequent work using electronic monitoring has reported that adherence varies with time and that there is not a specific "non-adherent" personality[212]. Adherence is a dynamic characteristic that reflects the patient's health beliefs; therefore, both the extent and nature of non-adherence may vary over time. Furthermore, the distinction between intentional and non-intentional adherence has little clinical relevance except in terms of how one may try to improve it. Forgetting may be considered non-intentional, but it is also a reflection of the relative importance of taking medication in that patients' life. One is less likely to forget tasks and commitments that are personally important. As the patient gets the opportunity to admit to one or more of the most common non-adherent traits, their response reflects those that they identify most closely with at that time, or in the recent past. The time frame is not exact but patients will naturally have a recall bias towards recent events. This is not a problem and may enhance the accuracy of the report as research into self-reported adherence in HIV patients has shown that self-reporting adherence to HIV regimen is most accurate when it relates to the previous one month[213]. Therefore, while identifying specific traits may help to select the most appropriate strategy for improving adherence in an individual, any one of those traits will reduce adherence and reduce the chances of reaching target blood pressure.

The selection of breakpoints on the scale, demarcating high adherence from medium or low adherence was done in the spirit of the original Morisky scale and reflected a similar distribution of adherence as reported in many large adherence study populations involving hypertension. The scale breakpoints would need to be re-evaluated if more items were included in the scale, as this would increase the likelihood of higher scores. The same breakpoints were studied during the pilot study, where eight items were used, but this was on to give an indication of the way the scale would be used. The correlation with achieving target blood pressure was striking. The observation that 52% of those reporting high adherence had achieved target blood pressure is a strong reminder of the "rule of halves" whereby numerous studies in hypertension has found that in the general population, only half of those

taking antihypertensive therapy will achieve their target blood pressure. Patients reporting medium or low adherence were almost twice as likely to be above their target blood pressure and therefore be at significantly increased risk of target organ damage due to sustained hypertension. Figure 47 implies a linear relationship between the reported adherence and blood pressure control in this population, but this may over simplify the level of blood pressure control in the medium range of adherence scores. As shown in Table 17, for scores of one to four, the percentage reaching target blood pressure varied between 19% and 41.7%; however, this is probably due to the decreasing number of patients with each score exaggerating the level of control when expressed as a percentage.

The concurrent validity of the self-reported adherence scale was further emphasized by the positive correlation between the average systolic and diastolic blood pressure, the scale score as well as the change in systolic blood pressure and scale score. The lack of correlation between adherence scale score and the change in the diastolic blood pressure is probably due both to the smaller absolute change in the diastolic blood pressure and the smaller sample size (n=184 instead of 202) arising from incomplete data for starting blood pressure for some patients, i.e. a type 2 error.

4.5 Conclusion

A seven-item Arabic / English scale for self-reported adherence was developed. The reliability and internal reliability of this scale was well within acceptable limits for an instrument of this kind.

The patient's score on the self-reporting scale correlated with the change in systolic blood pressure, diastolic blood pressure and the change in systolic blood pressure since the start of drug treatment. Those categorized as having high adherence were twice as likely to have reached their target blood pressure than patients who had reported medium or low adherence.

The statistical validity is only part of the concurrent validity. An important challenge for this self-reporting scale is whether the scale correlates with future blood pressure control (predictive validity) or whether the scale helps to improve the doctor's chances of identifying non-adherent patients. These are addressed in Chapters 5 and 6 respectively.

5. Predictive validity of an Arabic / English self-reported measure of medication adherence

Chapter contents

5.1 Introduction

The original Morisky four-item scale was a very inefficient predictor of blood pressure control over a 42-month period. The authors attributed this to the high proportion of medium adherence scores and the lack of blood pressure data for the "drop-put" patients. However, in that study the self-reported adherence was not reassessed and changes to antihypertensive medication prior to follow-up were not taken in to account. The predictive validity can be assessed by means of following-up the group to compare the reaching of the target blood pressure with the original self-reported adherence. If the Arabic self-reported adherence measure has predictive validity one would expect that those subjects reporting a higher adherence in the first study would continue to have better blood pressure control than those who reported medium or low adherence. In this follow-up, by repeating the self-reported adherence measure it was possible to see how adherence changes with time and see how much of the improvement in blood pressure control is explained by changes in the drug regimen.

5.2 Aim

The aim of the follow-up study was to determine if the self-report of adherence was reproducible and to study the concurrent and predictive validity of the self-reported adherence with respect to achieving the target blood pressure and changes to the blood pressure medication regimen.

5.3 Selection of the follow-up period

A three and a half-year follow-up period as reported by Morisky *et al* was impractical within the scope of this PhD thesis. It was decided to perform a follow-up after at least six months from the beginning of data collection at the second health centre. At that point, a period of eight weeks was available for data collection that was not interrupted by public and religious holidays.

5.4 Selection of the follow-up sample

A follow-up of the exact same population was not possible. After May 2001, the expatriates had effectively been excluded form the primary health care system because of the introduction of a Ministry of Health ban on providing medicines to expatriate outpatients. Therefore, the follow-up would be of a sample of the UAE nationals from the second health centre.

Based upon the recruitment rate during the original study, a follow-up period of around 6 weeks was expected to capture 80%-90% of the original population from the second health centre, approximately 125-140 patients.

5.5 Method

Patients from the initial study were identified during routine attendance at the health centre and asked by the nurse to provide a self-report of adherence using the self-reporting measure. They were able to identify patients from the original study by a red sticker that had been affixed to the medical record during that study. The nurse, as in the original study, completed the patient data collection and this included a record of the patient's previous blood pressure recordings. To determine if the patient had reached their target blood pressure, the average of these three readings was compared with the JNCVI maximum blood pressure target (as in the original data collection). Nurses were asked to keep a record of those patients who declined to participate in the follow-up study. The self-reported medication adherence assessment was performed and a score calculated using the seven-item scale described above in chapter 4. The main researcher (MF) reviewed the medical record to identify any changes to the patients' condition or situation. There was no data collected by the doctor in the follow-up study.

5.6 Results

The follow-up data collection was scheduled to be between Saturday, 29th December 2001 and Wednesday, 12th February 2002 (seven working weeks plus two days; 37 working days). At the end of this period, 86 patients had consented to participate in a repeat of the self-reported adherence assessment. The recruitment rate is shown in Table 19.

Table 19 Recruitment rate in the Follow-up period compared with the original data collection at the second health centre.

	Original	Follow-up
Week 1	28	4*
Week 2	23	28
Week 3	29	12
Week 4	16	13
Week 5	14	14
Week 6	18	12
Week 7	6	3
Week 8	9	Eid Al Adha marked the end of follow-up
Week 9	6	
Week 10	7	
Total	**156**	**86**
*Only 2 working days in follow-up		

5.6.1. **Validity of the follow-up sample**

To determine if the follow-up sample was representative of the initial 156 patients at the second health centre, the characteristics were compared; including age, gender, Body Mass Index (BMI), Appointment Gap, those reaching the target blood pressure, the median blood pressure and the proportion who were diabetic (Table 20).

Table 20 Comparison of the two samples (values are for that characteristic during the INITIAL data collection)

	Initial sample (n=203 unless stated)	**Follow-up sample** (n=86)
Age, mean (s.d)	**52** (± 8.9) n=197	**53** (± 10)
Male (%total)	90 (**58%**)	51 (**60%**)
BMI (mean ±s.d.)	**31** ± 6.5	**32** ± 6
Appointment Gap (n, % ≤ 35 days)	122 (**61%**)	50 (**58%**)
Reaching target BP (%total)	82 (**40%**)	34 (**40%**)
Median SBP ±s.d.	**140.0** ± 17	**141.4** ± 14
Mean DBP ±s.d.	**88** ± 10	**86.7** ± 7.8
Diabetic (% total)	61 (**30%**)	26 (**30%**)
Antihypertensive treatment (%)		
Monotherapy	62%	62%
Dual therapy	33%	33%
Three or more drugs	5%	6%

A review of the above parameters shows that the follow-up sample was highly representative of the initial sample used to validate the self-reporting measure.

The time between the two data collection periods varied between 5.8 months and 9.1 months, the average follow-up period being 7.6 months.

5.6.2. Validity of the blood pressure recordings

The validity of the blood pressure data is presented in Annex 4. The zero terminal digit preference in the follow-up study was slightly higher than seen at the second health centre during the initial study.

5.6.3. Follow-up Self reported adherence

A comparison of the self reported adherence in the follow-up sample compared with the initial study population is shown in Table 21.

Table 21 A comparison of the self-reported adherence (SRA) in the follow-up sample compared with the initial study population

	% of total (Number reporting each level of adherence)		
SRA	At Follow-up	Initial Sample	Initial total population
Low	**5%** (4)	**5%** (4)	**5%** (10)
Medium	**40%** (34)	**44%** (38)	**43%** (87)
High	**56%** (48)	**51%** (44)	**53%** (105)
	(n=86)	(n=86)	(n=202)

When the self-reported adherence measure was repeated at follow-up the proportion reporting high adherence increased to 56% (+4 subjects) and the number reporting medium adherence decreased from 44% to 40% (-4 subjects). Although the overall change appeared quite modest, it is the net result of significant intra-patient changes (see Table 22). Out of the 86 patients, forty one percent ($^{17}/_{42}$) of those initially reporting medium to low adherence reported high adherence at follow-up while thirty percent ($^{13}/_{44}$) of those initially reporting high adherence, reported medium to low adherence at follow-up.

Table 22 Self reported adherence (SRA) in initial study versus follow-up for 86 subjects

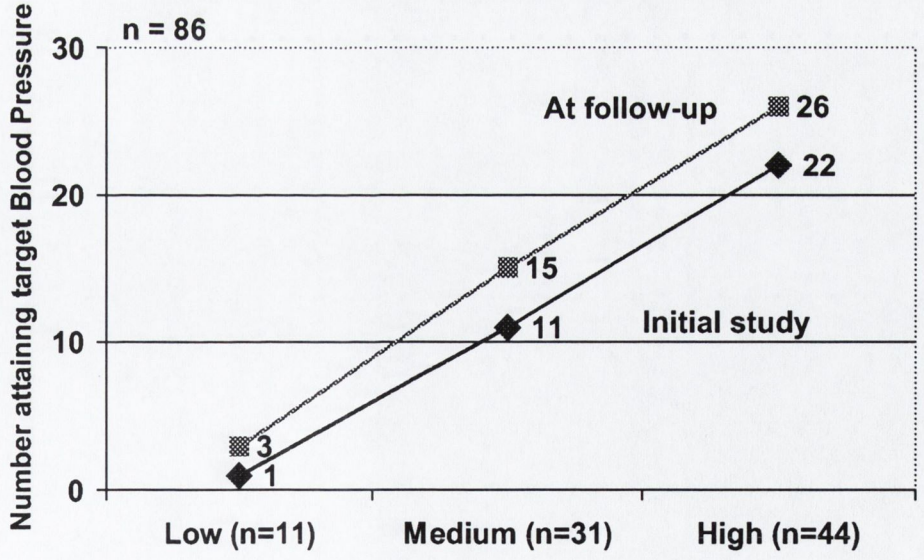
		SRA in follow-up study		
		Med-low	High	
SRA in initial study	Med-Low	25	17	42
	High	13	31	44
	Total	38	48	86
Chi square = 7.381, p > 0.01, two-tailed				

For the validation of this scale it is important to determine, if these changes in self-reported adherence are associated with changes in therapeutic effect of the anti-hypertensive drugs i.e. the reaching of target blood pressure. If this is the case, then these large changes in the self-reported adherence emphasise the dynamic nature of adherence over the medium term, in this case, an average of seven and a half months.

5.6.4. Relationship of the initial self-reported adherence score to the attainment of target blood pressure at follow-up

The relationship between the self-reported adherence during the initial study and the reaching of target blood pressure at the initial data collection and at follow-up is shown below.

Figure 43 Attainment of target blood pressure according to the initial self-reported adherence (SRA)



This chart shows the overall net increase in blood pressure control at follow-up and that this effect was seen at all levels of self-reported adherence with no particular

difference seen in the level of control seen at follow-up in those who reported high adherence compared to those who reported medium or low adherence.

The relationship between the self-reported adherence and the reaching of target blood pressure at the initial data collection and at follow-up is shown in more detail below. The 86 patients studied at follow-up are compared with the entire sample of 202 UAE national patients studied at the two health centres. In the initial study, the overall percentage that had reached their target blood pressure was 40% in the total group and 40% in the sample who were later studied in the follow-up. When reassessed at follow-up, this was higher at 51% (*not significant*).

Table 23 Self reported adherence and the proportion reaching target blood pressure

Number who reported that level of adherence and
(% of that adherence group who reached target BP)

	Follow-up data		Initial data for Follow-up sample		Initial population	Total
Low	4 (50%)	38 (32%)	4 (25%)	42 (29%)	10 (10%)	97 (28%)
Medium	34 (29%)		38 (29%)		87 (30%)	
High	48 (67%*)		44 (50%)		105 (51%)	
Total	86 (**51%****)		86 (**40%**)		202 (**40%**)	

* $X^2 = 0.105$ not significant, calculated on raw data, not percentage

** $X^2 = 1.900$ not significant, calculated on raw data, not percentage

At follow-up, of those reporting high adherence, 67% has reached their target blood pressure. When combining the low and medium adherence groups the percentage of patients reaching target blood pressure was slightly higher than in the initial study at 32% (*neither were significant using a Chi square test*). Any percentage differences seen in the low adherence group are exaggerated and attributable to the low number of subjects involved.

In summary, an improvement was seen in the rate of treatment success between the initial study and at follow-up. This was mainly due to the group reporting high adherence, among which, at follow-up, 67% had reached their target blood pressure. However, this did not reach statistical significance.

5.6.5. Sensitivity and specificity of the Self-reported adherence in relation to attaining target blood pressure

The predictive value of this self-reporting scale can be estimated by calculating the sensitivity and specificity. This can be calculated using the data presented in Table 24. Using only the high adherence scores reported in the initial study, the predictive

value (PV+), when positive (showing high adherence), was 0.57. This indicates at follow-up around 40% of patients failed to remain at or attain the target blood pressure despite having reported high adherence in the initial study.

Table 24 Sensitivity and specificity of the self-reporting scale

(Initial self report vs. BP at follow-up) Number achieving Target BP at follow-up			
	Not at target	At target	Total
Predicted to have Medium-Low adherence	24	18	42
Predicted to have high adherence	18	26	44
Total	42	44	86
Sensitivity	57.1%	*24/42 = 0.571*	
Specificity	59.1%	*26/44 = 0.591*	
PV+	0.57	*24/(24+18)=0.57*	
PV-	0.59	*26/(18+26)=0.59*	
PV	0.58	*(24+26)/86 = 0.58*	

The predictive value if negative (PV-), that is using only the reports of medium to low adherence, was 0.59, i.e. at follow-up, around 40% of patients attained the target blood pressure despite reporting low to medium adherence in the initial study. The sensitivity and specificity of the measure were 57.1% and 59.1% respectively.

The data presented in Table 27 and Table 26 presents a detailed picture of the changes in self-reported adherence and how they relate to the control of blood pressure. Thirty-four (40%)of the patients had changed their adherence report at follow-up. Of these changed reports, 20 were reporting a higher level of adherence at follow-up and 14 were reporting lower adherence at follow-up.

Table 25 Comparison of adherence and blood pressure data between the initial and follow-up studies

Self reported Adherence and the reaching of target BP (No, Yes)		Follow-up data									
		High			Medium			Low			Grand Total
Initial data		No	Yes	Sub Total	No	Yes	Sub Total	No	Yes	Sub Total	
High	No	10	**8**	*18*	3		*3*	1		*1*	22
	Yes		13	*13*	**4**	4	*8*		1	*1*	22
	Sub total	10	21	***31***	7	4	***11***	1	1	***2***	**44**
Medium	No	6	**5**	*11*	14	**1**	*15*	1		*1*	27
	Yes		6	*6*	**2**	3	*5*				11
	Sub total	6	11	***17***	16	4	***20***	1		***1***	**38**
Low	No				1	**1**	*2*		**1**	*1*	3
	Yes					1	*1*				1
	Sub total				1	2	***3***		1	***1***	**4**
Grand Total		16	32	**48**	24	10	**34**	2	2	**4**	86

In the initial study there were 44 patients who reported high adherence; however, at the follow-up study eleven of these had changed their reports to medium adherence and two had changed their report to low adherence. Of the 31 who continued to report high adherence, 21(68%) had attained the target blood pressure at follow-up, including eight patients who had not initially been at target blood pressure. Only four (9%) of the 44 patients who had initially reported high adherence had lost control of their blood pressure at follow-up and each one was reporting a lower level of adherence.

There were 38 patients who initially reported medium adherence; at the follow-up 17 reported high adherence and one reported a drop in adherence. Of the patients whose adherence had increased, eleven (65%) had reached target blood pressure including five who had not been under control at the initial study. Of the twenty patients who continued to report medium adherence, there was a net loss of blood pressure control with one patient gaining control and two losing control. The two patients who reported lower adherence did not achieve the target blood pressure.

Out of the four patients who initially reported low adherence, three reported medium adherence at follow-up. Two of these patients had reached the target blood pressure at follow-up, including one patient who had initially been above the target pressure.

As shown in Table 26, among the 52 subjects who reported the same level of adherence, the blood pressure control improved in 15% ($^{(10-2)}/_{52}$). The 20 subjects who reported an increase in their adherence saw target blood pressure achieved in 30% ($^{6}/_{20}$) of cases. In the 14 subjects who reported a decreased adherence, the target blood pressure was achieved in 29% less patients ($^{4}/_{14}$) than at the initial study.

Table 26 Summary of the changes in adherence and blood pressure control at follow-up (numbers of subjects)

Adherence at follow-up	BP control at follow-up				
	Gained	Lost	Unchanged	Net BP Change	Total
Unchanged	10	2	40	+8 (15%)	52
Increased	6	0	14	+6 (30%)	20
Decreased	0	4	10	-4 (-29%)	14
Total	16	6	64		86

The relationship between the blood pressure, adherence and regime changes at follow-up is shown in Table 27 and Figure 44. A regime change was classified as the addition, discontinuation or substitution to the antihypertensive drug regimen prescribed at the initial study. Twenty nine percent ($^{25}/_{86}$) of the subjects had a regime change during the follow-up period. Antihypertensive regime changes since the initial study was more common in patients with medium to low adherence at follow-up. However, this did not reach statistical significance Table 27.

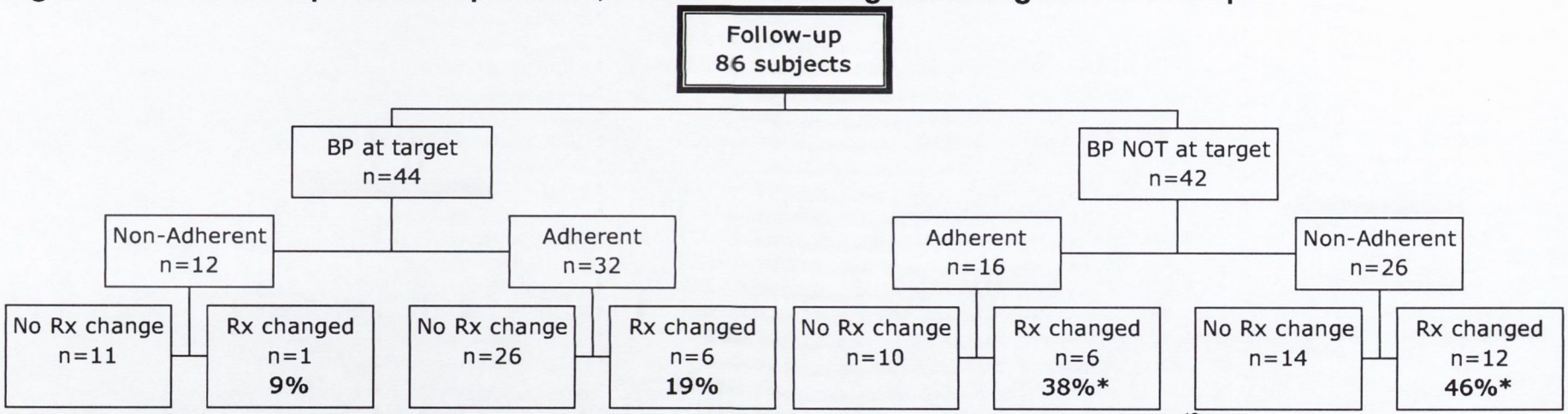
Table 27 Association of regime change with non-adherence

	High Adherence	Medium or low adherence	
Rx changed	12	13	25
No Rx change	36	25	61
	48	38	86

$X^2 = 0.483$ not significant

As shown in Figure 44, while regime change was most common in those who had not reached the target blood pressure (43%, $^{18}/_{42}$), within this group, regime change was equally likely among those reporting high or medium-low adherence.

Figure 44 Relationship of Blood pressure, adherence and regime changes at follow-up



% Figures are the percentage of all that adherence sub-set; e.g. 46% of Non-adherent, Non controlled patients ($^{12}/_{26}$)

* not significantly different (Chi square)

Key

BP at target	The average of the last three readings according to JNCVI criteria. The third pressure reading was the blood pressure measured at the follow-up appointment
Adherent	Self reported High adherence (scale score = 0)
Non-adherent	Self reported medium or low adherence (scale score >0)
Rx change	The addition, discontinuation or substitution to the antihypertensive regimen that was prescribed at the initial study. Dose changes were not included.

Prescription changes since the initial study were 2.7 times more common in those who were not at target blood pressure (43%, $^{18}/_{42}$) compared with those who had achieved target blood pressure (16%, $^{7}/_{44}$).

Table 28 Association of prescription change since the initial study and achieving target blood pressure at follow-up

	At Target BP	Not at Target BP	
Rx changed	7	18	61
No Rx change	37	24	25
	44	42	86

$X^2 = 6.3176$, $p > 0.05$, two tailed

5.7 Discussion

The key aspects of the follow-up study for discussions are:

5.7.1 Validity of the follow-up sample,

5.7.2 Predictive validity of the self-reported adherence

5.7.3 Changes in self-reported adherence in relation to attaining target blood pressure.

5.7.4 The relative effects of changes in self reported adherence and changes in blood pressure medication upon blood pressure control.

5.7.1. Validity of the follow-up sample

The number of subjects involved in the follow-up was less than anticipated but adequate. As with the initial study, the recruitment pattern at follow up showed a sharp drop after week three and four, as by then, many of the patients had already visited the health centre within the previous month. The main reason for the lower number of subjects is most likely to be the slow start to recruitment by the nurses (Table 20) in the first week. However, there are other possible causes.

In the follow-up study, the nurses did not keep an exact record of those patients who did not consent to repeat their self-reported adherence. The lack of a database of patient visits to the health centre means that only a search of each hypertensive file could have determined if the reduced recruitment reflected "drop-outs" from treatment / attendance or inefficient recruitment at the start of the follow-up. These two factors make it difficult to determine whether the lower number of patients reflected a reduced consent rate, a seasonal decrease in attendance or patients dropping out of treatment.

Dropout from treatment with cardiovascular drugs in general and antihypertensive drugs in particular is a common problem (2.9.5 above). While this cannot be ruled out, as shown in Table 20, the follow-up group was very similar to the initial study group at the second health centre. In addition to basic demographic characteristics, blood pressure control, adherence

and clinic attendance were all similar and therefore, treatment dropouts were unlikely to be the main cause of reduced recruitment.

As discussed in annex 6, the terminal digit preference for zero in the blood pressure readings used to calculate the "current" blood pressure at follow-up was marginally higher; however, this does not undermine the validity of the data. Furthermore, there was no evidence of observer bias in the follow-up data.

5.7.2. Predictive validity of the self-reported adherence

In the 6-9 month follow-up performed in this study, the seven-item Arabic / English self-reporting scale was an inefficient predictor of blood pressure control. Improvements in blood pressure were seen in patients who reported all levels of adherence in the initial study. This was only partly similar to Morisky's original report using a four-item scale in 290 patients.

Morisky found that after an average of 42 months, the original 4-item scale was an inefficient predictor of blood pressure control. The scale had a predictive value of 0.69 (sensitivity 81%, specificity 44%) when using only the high and low adherence reports. Combining the low and medium results reduced the predictive value of the scale down to 0.60, similar to the UAE study. In addition, as in the UAE study, the level of "control" (reaching target blood pressure) was higher for each adherence group. However, unlike the UAE study, Morisky's subjects who initially reported high adherence showed a 21% increase in the attainment of target blood pressure compared with only a 5% improvement in those reporting low or medium adherence. Seventy five percent of those initially reporting high adherence had attained their target blood pressure compared with 47% who had reported low or medium adherence. This was not consistent with the UAE study and may be due to differences in the context of the two studies.

The comparison of this study with the Morisky follow-up is fair but not exact. Not only was Morisky's cohort of 290 patients larger and therefore statistically more robust, but also it was from an original sample of 400. A prior analysis of the 110 (28%) dropouts reported them to have no demographic differences but they had lower adherence scores and more elevated blood pressure[214]. Therefore, the recruitment of 290 patients for follow up may have unintentionally selected a more adherent sample. Furthermore, the Morisky cohort had been involved in an educational intervention to promote adherence. Although it was almost three years earlier, perhaps the adherent patients had preferentially benefited from the intervention.

Although the assessment of predictive validity was an important part of comparing the Arabic / English instrument to a widely used instrument, the failure to show predictive validity should not be surprising. A key assumption in the assessment of predictive validity is that the adherence remains constant over time. There is very little evidence to support the concept

of predictive validity of adherence measures. Most psychological models used to explain adherence support the idea that adherence will vary with time as the patient's experiences and concerns change. This was underlined in this study by the significant intra-patient variation in self-reported adherence over the seven-month follow-up period and is discussed below.

5.7.3. Changes in self-reported adherence

At follow-up, 40% of patients reported a different level of adherence 6-9 months after their first report. These were clearly not random changes in the self-reported adherence. Strong concurrent validity was demonstrated by both the strong association between these increases and decreases in reported adherence and the increased and decreased rates of attaining target blood pressure. Subjects who reported high adherence at follow-up were more than twice as likely (67% vs. 31%) to have reached or exceeded their target blood pressure than those reporting medium or low adherence.

The results of studies looking at adherence over time have been inconsistent. The "Medical Outcomes Study" examined medication adherence over a two year period in 1198 subjects with a chronic disease[76]. The study used the health belief model to fashion a measure of adherence. None adherence at the initial study was the strongest predictor of non-adherence after two years. This was widely interpreted as evidence that early interventions to improve adherence will have long-term benefits. While this would be true for those people with very low adherence (any deterioration would be withdrawal from therapy), it does not provide any clues about the majority of patients.

Predictive validity promotes the idea that non-adherent behaviour, once identified, will characterise future adherence and future benefit from drug therapy. On the contrary, as discussed in 1.8.2 above, early work and subsequent work using electronic monitoring has reported that adherence varies with time[212] and that there is not a specific "non-adherent" personality. Several social cognition models support the idea that adherence is a dynamic characteristic that reflects the patient's health beliefs and experiences and that the result of those beliefs will depend upon the patient's circumstances and experiences. Therefore, that the type of non-adherent behaviour and the degree of non-adherence may vary over time.

Only one of the original eleven subjects initially reporting low adherence, reported low adherence at follow-up. This reduction in the number of reports of low adherence could have been due to a reduction in the number of frivolously negative responses. However, more than half of these patients had now attained target blood pressure, suggesting that this was a real increase in adherence and that they were deriving greater benefit from a real increase in the adherence to their prescribed medication.

In self-reporting, the patient will invariably have a recall bias and will be reporting their perceptions and recollections from the recent past. Item two of the scale referred specifically to the preceding two weeks but the other items did not refer to any time frame. Research into self-reported adherence in HIV patients has shown that self-reporting adherence to HIV regimen is most accurate when it relates to the previous one month [213].

For most of the follow-up patients (over 70%), the preceding month had been the Hijri month of Ramadan, a time when the structure of the day and especially, meal times are ceremoniously assigned to certain hours and minutes of the day and this may help to improve adherence to once and twice daily medication. Ramadan is also a period of contemplation and reflection and this may have focussed the attention of these subjects upon their need to adhere to both the medication and the diet and life-style changes recommended to them. This would have the effect of optimising the adherence (reducing the number of low adherers) and enhancing the response to the drug therapy (increasing the number of subjects who attained target blood pressure). Both phenomena were seen. While this remains speculative, this could be a fruitful area for future research.

5.7.4. Relative influence of adherence and medication changes upon blood pressure control

Prescription changes could have been one of the factors accounting for better blood pressure control in the adherent patients. It was important to determine how much of the improvement in blood pressure control could be attributed to changes in the anti-hypertensive drug regimens. Although changes in hypertensive drug regimen are common, most changes occur within the first 12 months of treatment with up to half the patients stopping their medication within the first six months[200]. In this study, only 4% of the patients had been treated for hypertension for less than one year, (median 5.16 years, ± s.d.4.67) so one would expect changes to be infrequent. In the time between the initial study and the follow up, 29% ($^{25}/_{86}$) had changes made to their regime. A change was defined as the discontinuation or initiation of an anti-hypertensive drug.

During the initial study, prior changes to the antihypertensive regime were noted but these changes were not limited to the previous 6-9 months. Since the start of drug treatment for their hypertension, regime changes had been made in 28% of subjects. The importance of this data had not been appreciated at the time of designing the initial study. While a rigorous comparison cannot be made between these two figures, the frequency of change in the drugs leading up to the follow-up appears to be similar to that seen prior to the initial study except that it was over a relatively short time. This compared well with data from the "TOMES" study[215] in which 28% of patients treated for mild hypertension stopped their initial treatment within four years compared with 41% of those who received a placebo.

Dose changes were not included in the review of regimen change, as they were considered least likely to have a significant impact upon the medium to long-term adherence. A dose-increase could lead to, dose-dependent side effects and this may lead to stopping that drug or reverting to the lower dose. In this study, dose increases were not common and most frequently involved ACE inhibitors. The most common side effects that could lead to discontinuation of an ACE inhibitor are cough and hypotension. The former is not specifically dose-dependent and the latter is mainly a problem in patients with heart failure. Heart failure was rare in this population and dose increases to an established ACE inhibitor regime are not associated with significant hypotension. It was also recognised that another possible cause of reduced adherence in the short-term could be if the dose increase required the patient to take more tablets. While the health centres do not have a wide range of dose forms in the pharmacy, evidence suggests that it the number of dose intervals that is related to non-adherence rather than the number of tablets taken[83].

It was clear that changes to the prescribed regimen were strongly associated with reports of medium or low adherence at follow-up and with subjects who were not reaching target blood pressure. In most cases the reason for discontinuation were not noted in the medical record. The association could be both causal and incidental. Side effects to medicines early in their use are an important cause of early discontinuation. Adherence may also be reduced while a patient adapts to a new regimen. However, neither of these factors are very likely in this study as most patients had been taking blood pressure medication for more than a year and in cases of addition or substitution of a drug the dose frequency of the new drug was invariably the same as the regime it replaced, so there is little practical disruption. A more likely explanation for the association of regime change and blood pressure control is that the doctor is identifying lack of response to the drug or side effects from the drug, i.e. they are changing the regimen without addressing the issue of adherence. Among the eighteen subjects whose blood pressure was not initially controlled and whose prescription had changed, twelve had reported medium to low adherence.

Also of interest is the small group of twelve patients (14%) who were achieving their target blood pressure despite reporting medium or low adherence. This was also seen in 10% of the original sample. It highlights the potential for medication to be reduced or discontinued in a small number of patients due to the hypertension responding to non-drug interventions or alleviation of the causes of the hypertension or the initial diagnosis being incorrect. Other possible factors affecting the prescription changes include changes forced upon the doctor due to stock shortages at the pharmacy and changes in response to intensive marketing of newer medicines. While occasional shortages do occur, they are relatively uncommon at the follow-up health centre and would be expected to affect all types of patients equally.

Changes of medication in response to intensive pharmaceutical marketing are less likely due to the operation of a restrictive formulary. As expected, prescription changes were more likely in the non-responders than in those who had reached the target blood pressure. One would hope that prescription changes would be targeted at those who were not responding to medication despite their adherence to the regimen. This was not the case as there was no significant difference between the two groups and a trend towards a higher incidence of change among the non-adherers.

5.8 Conclusions

At the follow-up study, changes in the self-reported adherence were common and seen in 40% of patients. Consequently, the self-reported adherence in the initial study was an inefficient predictor of blood pressure control during the follow-up study period (low predictive validity)

Concurrent validity remained high with those subjects reporting high adherence at follow up being twice as likely to have reached their target blood pressure. Furthermore, a decrease in self-reported adherence always resulted in decreased or unchanged blood pressure control and an increase in self-reported adherence always resulted in increased or unchanged blood pressure control.

Regime changes since the initial study were associated with failure to reach the target blood pressure at the initial study

While regime changes were common in those not reaching target blood pressure, within this group, changes were made equally often in adherent and non-adherent subjects

6. Doctor's perspective of medication adherence

Chapter contents

6.1 Background

Over twenty-five years ago it was shown that without assistance from other indicators of adherence, doctors will correctly identify low adherence in around half of their patients and that around three quarters of their predictions about adherence are wrong[216]. While many assume that this is because patients are not completely honest discussing adherence with their doctors, it is not clear if this is true or if the doctor is influenced by factors unrelated to adherence or because the degree and causes of adherence change with time. An instrument that was able to improve upon the doctor's intuition about adherence would be a valuable addition to the management of hypertension.

6.2 Aims

To identify factors influencing the doctors clinical judgement of medication adherence and to compare the doctors impressions with the patient's self reported adherence using the seven-item Arabic self-reporting measure.

6.3 Method

This study was performed simultaneously with the earlier study of the concurrent validity of the self-reporting measure. As patients were recruited in to the study at two health centres the doctor was asked to record their perceptions of the patients medication adherence and other characteristics using a questionnaire described in chapter 4. The doctor completed their questionnaire after the patient had left the consulting room and without knowing the result of the self-reported adherence. The doctor's evaluation was compared with the patient's self reported adherence and the attainment of target blood pressure at the initial study. These comparisons are performed using Crosstab analysis and the Gamma statistic in SPSS 10 is used to determine if the two-way tables are showing a significant difference.

6.4 Results

There were eight doctors involved at the two health centres. Complete responses were available for 198 consultations[L]. The doctor's estimate of adherence was related to the achievement of the target blood pressure (according to JNCVI). The doctor's evaluation of different aspects of the medical situation of each patient was compared with the doctor's adherence estimate and patient self-reported adherence.

As can be seen in Table 29 and Table 33, the doctors estimated adherence to be high (taking more than 80% of doses) in 141 (71%) of patients while 103 (52%) patients were self-reporting high adherence. Although around half of the doctors' estimates were accurate, the large number of patients who were estimated to have high adherence and the large number that self-reported medium or low adherence skews the accuracy in real terms. While the doctor could identify 75% ($^{77}/_{103}$) of high adherence, they identified only 34% of those patients who self-reported medium or low adherence.

Table 29 Relation of Doctor's estimate of adherence and the self-reported adherence

(n=200)		Doctor's estimate of adherence (n, % column total)		
		High	Medium - Low	Sub total
Patients self-reported adherence	High (n=103)	77 (55%)	26 (44%)	103
	Medium-Low (n=97)	64 (45%)	33 (56%)	97
	Sub total (% total)	141 (71%)	59 (30%)	

The target blood pressure had been achieved according to JNCVI in 63 (45%) of those cases, while only 77 (55%) of these patients had reported high adherence. Of those patients assessed as having medium to low adherence, 71% had not reached target blood pressure.

Of the patients who the doctor estimated to have medium to low adherence, 33 (56%) had reported high adherence. There was no significant relationship between the doctor's evaluation of adherence and the patient's self-reported adherence.

[L] Five were excluded. Two patients at first health centre had adherence estimates only, form completely omitted for two patients, and one patient was excluded as they had been treated for less than 3 months

Table 30 Relation of the Doctor's estimate of adherence and the achievement of the target blood pressure

(n=200)		Doctor's estimate of adherence (n, % of column) High	Medium - Low
Achieved target blood pressure?	Yes	63 (45%)	17 (29%)
	No	78 (55%)	42 (71%)
	Sub total (% total)	141 (71%)	59 (30%)

The doctor was asked to evaluate the effectiveness of the anti-hypertensive treatment, quality of doctor-patient communication, the patient's knowledge of their hypertension and medication, and the seriousness of the medical situation. These evaluations are shown in Table 31.

Table 31 Doctor's evaluation of four patient-related characteristics

Doctor's evaluation (198 patients)			
Effectiveness of anti-hypertensive treatment	Good 114 (57%)	Partial 75 (38%)	Poor 9 (5%)
Quality of communication	Excellent 114 (57%)	OK 72 (36%)	Poor 12 (6%)
Patient knowledge	Excellent 75 (37.5%)	OK 107 (54%)	Poor 16 (8%)
Seriousness of condition (5 year risk of major CV event)	High risk 11 (6%)	Increased risk 71 (36%)	Low risk 116 (58%)

The doctors estimated that 57% of the patients had effective antihypertensive drug treatment and 57% had an excellent understanding of their hypertension and it's treatment. They estimated that 58% of their patients had a low five-year risk of a major cardiovascular event. No more than 8% of patients were evaluated as having a "poor" or "high risk" rating on any of the criteria.

The doctor's assessment of treatment effectiveness was compared with the achieving of the target blood pressure. As shown in Table 36, of the 114 patients whose treatment was assessed as being good, 51 (45%) had not reached the target blood pressure recommended by JNCVI. The doctor's assessment of medium and poor effectiveness correlated far better with the JNCVI criteria, although 19% of these ($^{16}/_{(75+9)}$) had reached the JNCVI target.

Table 32 Relation of Doctor's assessment of treatment effectiveness with the achieving of target blood pressure

(n=198)		Doctor's estimate of treatment effectiveness			
		Good[1]	Partial[2]	Poor[3]	
Achieved target blood pressure?	Yes	63	16	0	79
	No	51	59	9	119
		114	75	9	198

[1] Patient has reached their target blood pressure

[2] Some reduction in the blood pressure since starting but not enough

[3] No improvement in the blood pressure since starting this regime

All four estimates of patient related characteristics were significantly correlated with the doctor's estimates of the adherence, Gamma statistic ranging from 0.40-0.42, $p < 0.05$, see Table 33. Higher adherence was more likely to be perceived by the doctor if the doctor also considered that: the patient's treatment was effective; the doctor-patient communication was excellent; the patients knowledge of their hypertension was excellent and if the patient was perceived as having a low five-year cardiovascular risk.

However, for all but one characteristic, the doctor's evaluation had no significant correlation with the patient's self-reported adherence. The doctor's assessment of good treatment effectiveness, excellent quality of communication and excellent patient knowledge, was associated with around half of the patients who reported high adherence.

Table 33 Relation of the doctor's evaluation of the medical situation to the doctor's evaluation of adherence and the self-reported adherence

Doctor's evaluation (n=198)	Doctor's Evaluation % High adherence	Gamma	Patient Self report % High adherence	Gamma
Adherence				
High	71		55	
Medium-Low			43	0.21
Effectiveness of treatment				
Good (114)	79		54	
Partial-Poor (84)	60	0.42*	48	0.14
Quality of communication				
Excellent (114)	78		51	
OK-Poor (84)	61	0.40*	52	-0.03
Patient knowledge				
Excellent (75)	81		51	
OK-Poor (123)	64	0.42*	52	-0.03
Seriousness of medical situation				
Low CV risk (116)	77		45	
High-Increased CV risk (82)	58	0.42*	61	-0.32*

* = p <0.05

Only the doctor's evaluation of the seriousness of the medical situation showed a significant correlation with the self-reported adherence and this was in the opposite direction (Gamma statistic –0.32, $p<0.05$). The doctor's perceived that those patients with the lower five-year cardiovascular risk would have the higher adherence, while in fact, patients who the doctors perceived as having a high to medium five year cardiovascular risk reported higher adherence.

The doctor was also asked to select one of three reasons for the patient not reaching their target blood pressure (Item 9); non-adherence, non-ideal regime or other reason (see Table 34). This question was answered for 71 (85%) of the 84 patients who the doctor considered to have partial or poorly effective medication. Non-adherence was the most commonly cited reason (41%).

Table 34 Doctor's explanation for partial or poor effectiveness of blood pressure medication

For 84 patients described by the doctor as having partial or poor control	Non adherence	Non-ideal drug regime	Other reason	Not stated
Reason for BP control being partial or poor	34 (41%)	22 (26%)	15 (18%)	13 (16%)

The doctor was asked to record if they had changed the antihypertensive medication at that consultation (item 10a), and if so, why (item 10b)? This question was answered for 177 consultations and showed that the regime was changed at 24 (14%) of those consultations, the majority of which were in patients with sub-optimal blood pressure control. Out of the 53 patients with partial or poor control, 18 (34%) had their regime changed. There were 159 responses to item 10b and these included 23 of the 24 instances where the regime was changed. In 20 (87%) of these cases, the reason for changing the medication was "to improve control" with only 2 (9%) of changes being due to side effects or other reasons (1 case).

6.5 Discussion

The doctor's ability to distinguish between non-adherence and the need to change the regime is at the heart of successful hypertension management and the identification of non-adherence is the first step towards improving adherence.

The doctor's estimated 71% of the patients to have high adherence, which was far greater than the 52% of patients who reported high adherence. Failure to reach the JNCVI target for blood pressure control did not appear to be a significant factor influencing their estimate of the adherence. This would appear to be due to the doctor's threshold for "control" tending to be being less rigorous than the JNCVI criteria. Only 45% of those patients considered by the doctor to have "Good" blood pressure control were achieving the JNCVI levels of control, while 81% of those considered to have "Partial to Poor" blood pressure control had not reached JNCVI targets. Therefore, this study highlights that there are clear continuing education needs relating to the blood pressure targets for drug treatment.

The doctors' assessments of treatment effectiveness, quality of communication, patient knowledge and seriousness of the condition were all statistically related to their estimate of adherence. However, in most cases, when a doctor estimated there to be a high to increased risk of suffering a serious cardiovascular event, the doctor also reported that these patients had medium to low adherence, which was the complete opposite to what the patient was reporting.

No causal association can be proved from this data, but the overall impression is that the doctor's estimate of adherence is more closely related to their overall sense of well being

about a case than objective data, e.g. blood pressure control. There was a reluctance to assess a patient characteristic as having a particularly adverse rating. This "rosy" view of a case may arise from a lack of rigorous clinical audit and may be compounded by an instinctive reluctance for the Arab expatriate doctors to avoid reporting anything that would make them look less than a successful family physician for risk of there being action taken against them by the employer.

The doctor's estimate of medium to low adherence coincided with 40% of the 84 assessments of "Partial to Poor" treatment effectiveness), and when asked directly about those patients (item 9), there were 74 responses in which the doctor estimated that 34% of the failures to control blood pressure were due to non-adherence. While 52% of patients in this group self-reported medium to low adherence, this similarity to the doctor's figure was a coincidence as the doctor's evaluation of non-adherence (medium to low) agreed with the self-reported adherence only 34% of the time.

These results are remarkably similar to those reported by Goldberg et al in the paper from which the doctor's questionnaire was reported[45]. In that study, 138 asthma patients were studied at an outpatient health centre and the doctors over estimated adherence and associated a less serious condition, effective treatment, excellent quality of communication and excellent knowledge to high adherence. The doctors were also wrong about the effect of a serious condition upon adherence. In the Goldberg study, those asthmatics with the worst prognosis reported higher adherence.

The UAE study design did not provide a way of validating the doctor's perceptions of factors other than adherence and blood pressure control. It would have been interesting to compare the doctor's estimates of the patient related characteristics with the patient's perceptions of quality of communication and their own knowledge. It may well be that, like adherence, the doctor's perception of these factors were at variance with the patient's perceptions. A qualitative study of patient-doctor communication at hypertension consultations in Sweden reported that doctors and patients often have very different discussion priorities with the doctor focussing on the medication and the patient wishing to talk about their experience of taking the drug[217]. Miscommunication may be the main factor behind the lack of association between doctor perceptions and other patient outcomes. A Swedish study of audio-recordings from 51 consultations found that although doctors asked about adherence to antihypertensive medication, the question often lacked depth and follow-up[217].

As discussed in chapter two, the patient's risk of suffering a major cardiovascular event depends upon a range of cardiovascular risks, of which blood pressure is only one. If more clinical data had been recorded, especially blood lipid data, then the cardiovascular risk could have been estimated post hoc using one of the available tools such as the

Framingham risk equations[218], Dundee Coronary Risk equation[219] or the PROCAM risk equation[220]. This could then have been used to validate the doctor's estimates of disease risk. However, lipid-screening data was not routinely available and the validity of these equations in a Gulf Arab or sub-continental population has not been demonstrated. Furthermore, the doctors were asked to estimate the absolute risk over the next five years (five years was chosen after discussion with the doctors at the first health centre as a more practical, medium term time frame). Validation would have required careful re-wording of the item as some tools provide an estimate of risk over a 10-year period (e.g. Framingham) or their relative risk (e.g. Dundee Coronary Risk equation) or have not been validated for use in women (e.g. PROCAM risk equation or the British regional Heart Study Risk equation).

The failure to identify non-adherence will make it very difficult for the doctor to distinguish between the need for a regimen / dose change and the need for a review of the patient's motivations and beliefs relating to the drug therapy. Only after such a review can a strategy be identified to help improve adherence. Consequently, many regime changes will be made in patients who already have poor adherence and the change is unlikely to improve blood pressure control.

6.6 Conclusion

The doctors consistently exaggerated the level of adherence and over estimated the quality of blood pressure control compared with JNCVI criteria.

The doctors' estimates of adherence were related to their perceptions of treatment effectiveness, quality of communication, patient knowledge and the seriousness of the condition. These did not relate with the patients self reported adherence.

The doctors estimated adherence to be low in most patients who they perceived as having a more serious condition, whereas those patients reported relatively high levels of adherence.

The practical assessment of adherence (and hence drug management) would have been greatly enhanced if the Arabic / English self-reporting measure had been used in clinical practice.

7. Summary of conclusions

The key conclusions from the preceding research are presented below in bullet format as a convenient summary.

- A seven-item Arabic / English scale for self-reported adherence was developed.
- The reliability and internal reliability of this scale was well within acceptable limits for an instrument of this kind.
- The patient's score on the self-reporting scale correlated with the change in systolic blood pressure, diastolic blood pressure and the change in systolic blood pressure since the start of drug treatment.
- Concurrent validity was strong and at the initial study and during follow-up, those reporting high adherence were twice as likely to have reached their target blood pressure than patients who had reported medium or low adherence.
- The self-reported adherence in the initial study was an inefficient predictor of blood pressure control during the follow-up study period (low predictive validity)
- After seven to nine months, changes in the self-reported adherence were common and seen in 40% of patients.
- An increase in self-reported adherence always resulted in increased or unchanged blood pressure control
- A decrease in self-reported adherence always resulted in decreased or unchanged blood pressure control
- Regime changes were more likely to be associated with failure to reach the target blood pressure
- Regime changes were common in those not reaching target blood pressure and were made equally often in adherent and non-adherent subjects
- The Doctors consistently exaggerated the level of adherence and also over estimated the quality of blood pressure control compared with JNCVI criteria.
- The doctors' estimates of adherence were related to their perceptions of treatment effectiveness, quality of communication, patient knowledge and the seriousness of the condition. These did not relate with the patients self reported adherence.
- The doctors estimated adherence to be low in most patients who they perceived as having a more serious condition, whereas those patients reported relatively high levels of adherence.

- The practical assessment of adherence (and hence drug management) would have been greatly enhanced if the Arabic self-reporting measure had been used in clinical practice.

8. Consequences for clinical practice

Chapter contents

8.1 Recommendations for future research work

8.1.1. Reproduce the results from the self-reporting measure

The success of this self-reporting measure in highly encouraging but should be reproduced in other UAE health centres to confirm that this instrument is robust and reliable in a routine clinical environment. It will be important in future studies to emphasise the need to carefully record the details of patients who decline to provide a self-report of adherence. Although the follow-up sample reported above was highly representative of the initial group, the possibility remains that initial sample may not have been truly representative cross-sectional due to patients declining to participate.

8.1.2. Follow-up the original cohort

The change in self-reported adherence in the above study has important consequences for the development of strategies to improve adherence. It is an aspect of adherence that has not been widely studied and a further follow-up study of the patients e.g. after 2 years would provide unique and valuable information regarding the variation in adherence over time. A health information system is currently being installed and piloted at the second health centre and this could make it possible to track down all of the original 157 patients at the second health centre

8.1.3. Relationship of self-reported adherence to health beliefs

Eliciting the views and health-beliefs could help to understand how patients balance their personal reservations about therapy against their decision to adhere to treatment[37]. Arrays of instruments have been developed to assess the health beliefs of patients regarding their disease and its management. Of particular importance to adherence is the study of how health beliefs influence the self-regulatory model of illness. The pioneering work of Weinman and Horne at the United Medical and Dental School in London has lead to a "Beliefs about Medicines Questionnaire"[21] . The Horne and Weinman instrument has 34 items and would be more difficult to translate and more intrusive to administer. However, the translation of this instrument in to Arabic would provide a valuable tool and would enable a future study in which one could determine the influence of health beliefs upon the self-reported adherence of the UAE nationals.

8.1.4. Patient perceptions of the doctor consultation(s)

The dissonance between the doctor's perceptions of adherence and the patient's self-reported adherence raises important questions about the quality of communication during the consultation. Patient satisfaction with the consultation is a difficult concept to quantify but research has shown that a satisfied patient is more likely to adhere to their medication[76] [221] [222], and to have better outcomes[96] [223]. The accuracy of doctor's perceptions of adherence and its relation to patient satisfaction in this population would be a unique and fascinating future study.

8.1.5. Introduce the self reporting measure to clinical practice

This would be an excellent outcome to this research project. Not only would it provide an effective tool for monitoring adherence in the health centres but also the discussion with clinic staff and training of staff to use the measure will be a catalyst for change. The introduction would stimulate the health workers to focus on adherence and on their management of chronic therapies in general.

8.2 The burden of non-adherence

Before proposing a strategy to address the adherence problems identified above it is important to appreciate the magnitude of the adherence problem in terms of morbidity and money.

Medical non-adherence has been identified as a major public health problem. Attempts to estimate the cost of this burden vary and many use different methodologies. In the USA, one estimate put it at $100 billion per year. This includes an estimated 10% of all hospital admissions and 23% of nursing home admissions[224]. Using prescription refills as a marker of adherence showed an increase rate of hospitalisation in patients who failed to refill their prescriptions for anti-hypertensive drugs[225].

Stroke is the most serious consequence of high blood pressure (2.7.1 above) and an increased risk of stroke has been reported for non-adherent patients. In a study of intracerebral haemorrhage, Australian researchers studied the prescription records of 331 patients admitted to hospital with intracerebral haemorrhage. As expected, the risk of stroke was doubled in the hypertensive population (odds ratio of 2.45). However, when they looked at the hypertensives who had stopped taking their medication the risk was twice that of the hypertensives who had not stopped taking their medication (odds ratio 4.98 compared with 1.95[226]. In the UK, a study commissioned by the Stroke Association compared the prescription records of 1,550 stroke victims with those of a control group. Over the six months preceding the stroke, missing seven days of hypertension treatment increased the risk of stroke compared with the control group[227].

One study estimated that in America, the total health care costs of a patients who was more than 80% adherent on monotherapy were half those of patients who were less than 30% adherent; $341 per year compared with $735 per year[228]. Increased hospitalisation and failure to persist with medication adds greatly to the economic burden of hypertension.

Unless a study looks beyond drug costs, discontinuation of therapy will reduce the direct costs compared with persistence. In the UK, a retrospective review of the direct costs of treating hypertension included doctor consultations and admissions to hospital. It estimated the total cost to be GBP 76.5 million, of which GBP 26.9 million (35%) was attributed to patients who switch or discontinue therapy[229]. Similar research in Italy found persistence with drug treatment accounted for under half the total cost of the hypertension management, while switching agents accounted for 20.8% and discontinuation represented 31.1% of total costs[230]. As in the UK, Italian data shows direct drug costs are less than half the direct cost of treating hypertension[231]. Conventional cost-effectiveness studies of antihypertensives have focussed on blood pressure reduction when estimating direct costs. The higher direct costs of newer agents such as angiotensin receptor antagonists are far higher than the direct costs of generic (multi-source) thiazide diuretics; however, greater persistence and reductions in target-organ damage are bound to reduce these differences when total costs are studied[232 233].

8.3 Improving the cardiovascular outcomes of individuals through Pharmaceutical Care

8.3.1. Taking responsibility for adherence through Pharmaceutical Care

There have been several national and international calls to address the problem of medication adherence[1 234 235],. However, there is little evidence that this has become a mainstream health agenda. Perhaps one reason for this is that while these reports rightly identify the need for a multi-disciplinary solution, in routine clinical practice no one professional group has stepped forward to accept the role of clinical leadership. The pharmacist is very well placed to take on such a role and thereby champion a very cost effective and tangible facet of pharmaceutical care. Pharmaceutical care is a term first defined by Hepler and Strand in 1990 when they urged pharmacists to "*accept their social mandate to ensure the safe and effective drug therapy of the individual patient*"[236]. While the exact definition has been debated since that time the central message remains clear and that is a pharmacist has a responsibility to ensure that the patient gets the greatest benefit from available medicines. A key aspect of that responsibility is the need to provide leadership. Numerous studies have shown that patient focussed pharmaceutical care delivers benefits while containing and sometimes, reducing costs[237 238 239 240].

8.3.2. Lack of robust data to show the benefit of pharmaceutical care upon adherence

Despite the pharmacist having such good access to patients, there is no clearly defined operational model through which pharmacists deliver pharmaceutical care. Consequently, the research into this area is quite fragmented. Some controlled studies have demonstrated the benefits of "counselling" upon adherence, however they have been in high risk patient groups e.g. elderly heart failure patients[241] and were often complex interventions designed to address the health beliefs of the individual patient

8.3.3. Individualised approach

Several reviews of the literature on improving adherence have concluded that the only effective interventions employ a variety of tools according to the needs of individual patients and must be sustained[111 224 242]. There is also growing evidence that behaviour change strategies should be individualised and that the type of intervention should be tailored to the patients willingness to change, in this case to a greater adherence to chronic therapy[243]. Instruments are being developed to determine the patient's readiness for behaviour change.

The lack of a standard service model with which to deliver pharmaceutical care to hypertensive and other high risk cardiovascular is seen in all countries. A study of twelve different service models for pharmaceutical care of patients with hypertension in the USA found a lot of variation[244]. None of the models would be easily transferred to the UAE. An important feature of these services was the use of software to record the care, track the patient and communicate with other health professionals.

Information Technology provides many opportunities to enhance adherence. However, not all will help all patients. Easier access to printed educational material may improve patient satisfaction and knowledge but may not improve adherence[60]. Technology can also be used to keep in contact with the patient and to provide reminders and motivation to return for refills and continue with treatment. Telephone and postal reminders have been reported to improve adherence and outcomes[245, 246] but this is not a consistent finding[247]. The UAE has one of the highest rates of mobile phone and Internet use in the world. It would be valuable to study the ways in which the text messaging facility of mobile telephone and the Internet could be used to keep contact with patients taking medication for chronic conditions. This could be especially important in the UAE where appointment systems for government sector outpatients are relatively unusual. This should involve both the patient and family members. Most UAE nationals have a strong extended family system and reminders could be sent to family members, encouraging them to support adherence in their mother, spouse etc.

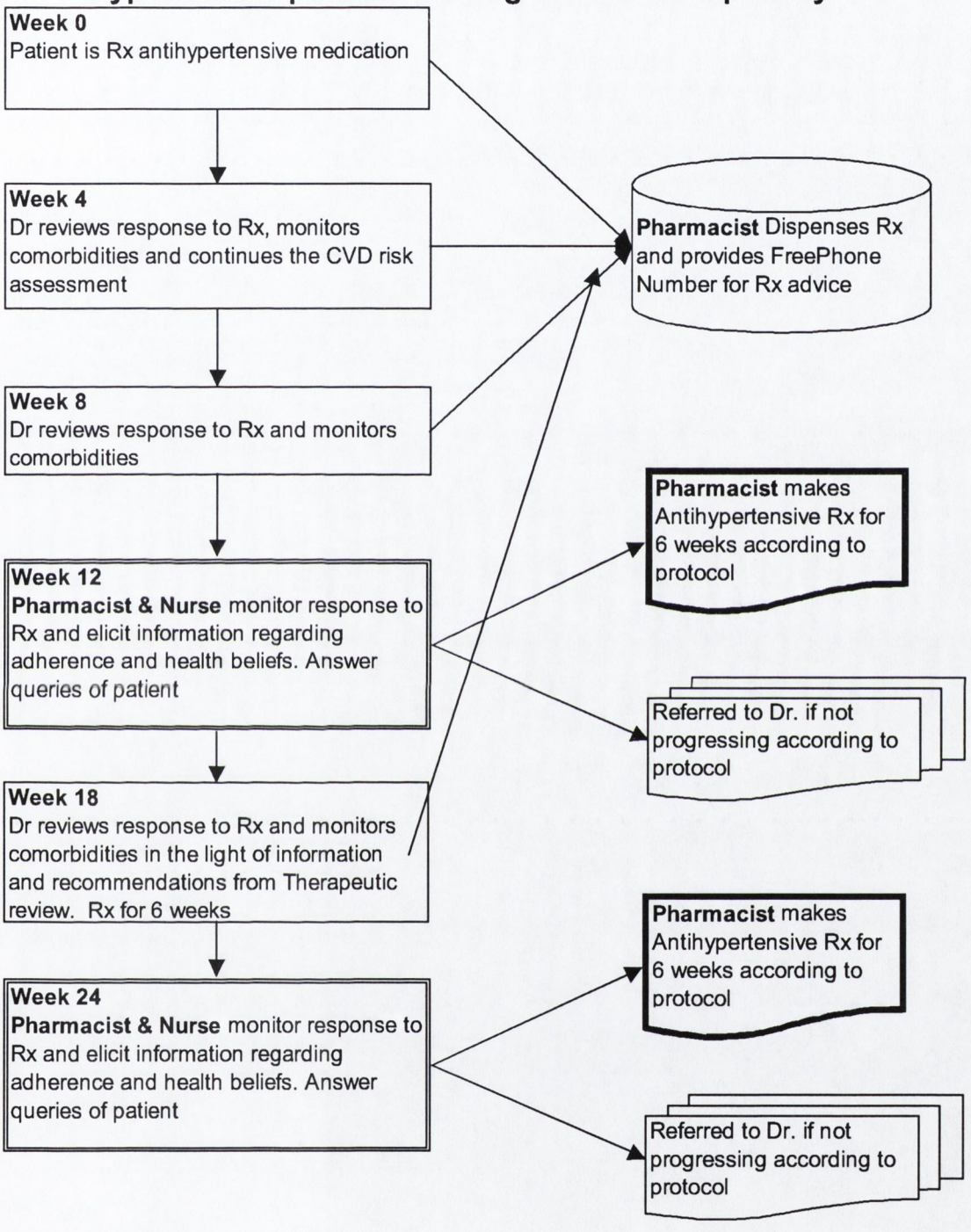
However, these types of initiatives can distract one from the key issue when identifying and resolving adherence problems: the need to elicit the patient's beliefs and behaviour

regarding their diagnosis and treatment. The Arabic self-reporting measure described in this thesis provides a simple tool around which one can encourage the patient to express their concerns and beliefs along with any practical difficulties they experience with their treatment.

8.3.4. How can pharmacists help to increase patient contact time within an over-stretched health system?

The quality of the patient-doctor relationship has been emphasised in many studies as being an area where improvements are likely to improve adherence. Doctor-patient contact times are getting shorter and the call to increase the time spent eliciting beliefs appear to add to the time pressures on doctors. Unless that is, one takes a fresh look at the care process. In the UAE, most hypertensive government outpatients are expected to see the doctor every month. This is an outmoded concept. Beyond the first three to six months, for most patients, there is no reason to review the patient for target organ damage more than every three months. This opens up the opportunity for the patient to attend in between major appointments e.g. also every three months at which time they could have a "therapeutic review" with the pharmacist and nurse at which progress with their lifestyle changes, medication adherence and blood pressure targets could be discussed. There would be no need to see the doctor unless they asked to or unless they had deviated significantly from the treatment plan. If there was concern over the possible waste of prescribing therapy every 3 months then six-weekly prescriptions could be issued by the pharmacist in accordance with an agreed protocol. The actual frequency of review would depend on the time since diagnosis, success of treatment and co-morbid conditions. The concept is shown in Figure 45.

Figure 45 Integrated pharmaceutical care of a newly diagnosed with hypertensive patient: Making adherence a priority



8.4 Making a difference to clinical practice in the UAE

Cardiovascular disease is the main cause of death among UAE nationals and this burden will increase as this unusually young population ages. Doctors are using the latest antihypertensive medication but this research has shown that more than half the patients are not adhering to their treatment.

There is a need for more research in to adherence and the health beliefs among UAE nationals and the health professionals who care for them. Continuing education of health care workers must promote the development of a better understanding of adherence and of the skills required to improve it. The financing of health in the UAE needs to focus on reducing the total cost of health rather than focussing on direct costs. More pharmacists with pharmaceutical care skills need to be made available in primary health care as part of an integrated commitment to improving adherence.

Meanwhile, an Arabic self-reporting measure has been developed that could be used as part of an integrated solution to this waste of valuable resources and the missed opportunity to reduce morbidity and mortality.

Annex 1 Patient data collection form

This annex shows the form used for collecting the patient data. The first part of the form was completed by the nurse while the patient had their blood pressure measured, before they had the consultation with the doctor.

In the first phase of the study, this form was printed on both sides of blue A4 paper. During the follow-up study, this form was printed on pink A4 paper to help distinguish between data sheets from the two studies.

A further explanation of how the data was recorded in an Excel spreadsheet is provided in annex 2.

Blue

Study Number_____ File Number_____

THIS SECTION TO BE COMPLETED BY NURSE / PHYSICIAN

Date of Recruitment (dd/mm/yy) _____ / _____ /_____

Patient Name _____

File No. _____ Height_____ Weight_____

DOB. (dd/mm/yy) ____ / ____ / ____ Sex M ☐ F ☐

Health Card No. _____

Nationality _____ Family in the UAE? Y ☐ or N ☐

PO Box _____ Tel. Home _____ Tel. Mobile _____

Years of education (tick): Primary ☐ Secondary ☐ Graduate ☐ Postgraduate ☐

Smoker? Y ☐ or N ☐

Household Income: (tick)

Less than Dh4,000 ☐ Dh4,001-8,000 ☐ Dh8,001-12,000 ☐ Dh12,001- 16,000 ☐

Dh16,001-20,000 ☐ Dh 20,000 – 24,000 ☐ *More than* 24,000 ☐

Prefers not to say ☐

Mother tongue _____ Second language _____

Date of last appointment (dd/mm/yy) _____ / _____ /_____

THIS SECTION TO BE COMPLETED BY RESEARCHER

First treated for HTN (dd/mm/yy) _____ / _____ / _____

Systolic BP at start of treatment _____ mm Hg.

Diastolic BP at start of treatment _____ mm Hg

Systolic BP today _____ mmHg

Diastolic BP today _____ mmHg

Pulse **(beats per minute)** today _____

Study Number_____ File Number_____

Medication

Current Anti-HT drug & dose	**Since** (dd/mm/yy)	

Previous Anti-HT drugs – comment / description

No. of antihypertensive drugs 1 ☐ 2 ☐ 3 ☐

No. of antihypertensive doses per day 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐

Other medicines including Non-Prescription (current)

Drug	**Dose**	**Indication**

No. of other chronic drugs 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐

No. of doses of other chronic drugs per day 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐

No. of other chronic diseases requiring regular medication 1 ☐ 2 ☐ 3 ☐ 4 ☐

List of other chronic diseases <u>requiring medication</u>

Diabetes ☐
Dyslipidaemia ☐
Ischaemic heart disease ☐
Peripheral Vascular Disease ☐
Asthma ☐
Musculo-skeletal ☐
Thyroid ☐
CNS ☐
Other ☐
_____ *comment*

Annex 2 Description of the Patient data

The following parameters were recorded for all patients if the data was available in the medical record or elicited from the patient. There is a description of the parameter and a short description of how it was recorded in the database

Parameter	Description / comment
Today's date	The date of the consultation (dd/mm/yy)
Is today's attendance a "Walk in" / Appointment	Tick box. At the start of the pilot the health centre was introducing an appointment system for chronic conditions such as hypertension
File number	The unique health centre number. Numeric (family no. – member no.)
Height	Metres (from the notes or measured by nurse if N/A)
Weight	Kilograms (measured on the day by the nurse)
Date of Birth	dd/mm/yy
Sex	Tick box: Male or Female
Health card number	Numeric. From the medical record
Nationality	Free text
Family in the UAE for >6 month of year?	Tick box: Yes or No
PO Box number	Numeric
Home tel no.	Numeric
Mobile phone no.	Numeric
Years of education	Tick box: None, Primary, Secondary, Graduate, Postgraduate
Smoker?	Tick box: Yes or No
Household income	Tick box: Less than Dh 4000, Dh4,001-8,000, Dh 8,001-12,000, Dh 12,001-16,000, Dh 16,001-20,000, Dh 20,000-24,000, More than Dh 24,000, Prefers not to say
Mother tongue	Free text
Second language	Free text
Date of last attendance	dd/mm/yy
	continued

continued Parameter	Description / comment
Was previous attendance a "Walk in" or by appointment	Tick box. At the start of the pilot the health centre was introducing an appointment system for chronic conditions such as hypertension
First treated for HTN	Dd/mm/yy
BP at start of treatment	mmHg, Systolic / Diastolic
BP at today's attendance	mmHg, Systolic / Diastolic
Two previous BP measurements	mmHg, Systolic / Diastolic At least one month apart
Pulse at today's attendance	Beats per minute
Current BP medication & start date	Free text & dd/mm/yy
Previous BP medication	Free text and any comments
Number of BP drugs	Numeric
Number of BP drug dose per day	Numeric
Other medicines including OTC drugs	Free text to include the indication
Number of non BP drugs per day	Tick box 0-6 Numeric – for chronic diseases only
Number of doses of non-BP drugs per day	Tick box 0-6 Numeric – for chronic diseases only
Number of chronic diseases requiring regular medication	Tick box 0-4 Numeric
List of other chronic diseases requiring medication	Tick box: Diabetes, Dyslipidaemia, Ischaemic heart disease, Peripheral vascular disease, Asthma, Musculo-skeletal, Thyroid, Nutrition, CNS, Other

Annex 3 Self reported adherence form – English

This annex presents the self-reported adherence measure as it was used in the follow up study.

The two-page form was printed, single side, on two A4 yellow sheets. The Arabic version of this form was copied on the reverse so that page one of the English had page two of the Arabic on the back and page two of the English had page one of the Arabic on the back (see Annex 4). The two sheets were then stapled together and copies of the form were kept with the nurses. The completed form was retained by the nurse for collection by the researcher within 24 hours.

Item nine is presented as a Likert scale; however it was treated as a dichotomous response. During Principal component analysis and when calculating the score, "Never" was taken as zero and other response to this item was considered as a one.

The patient identification information was chosen so to maximise the chances of matching the right form to the right patient data and doctor questionnaire data (initial study).

Patient Initials _____ **File No.** _____ **DOB. (dd/mm/yy)** ____ / ____ / ____ ***tick*** **Male** ☐ **Female** ☐

1. Some people have difficulty remembering to take their medicines. Do you ever forget to take a dose of your blood pressure medicine?	☐ **Yes** ☐ **No**
2. People sometimes miss taking their medicines for reasons other than forgetting. Over the past two weeks, were there any days when you did not take your blood pressure medicines?	☐ **Yes** ☐ **No**
3. Have you ever cut back or stopped taking your blood pressure medicines (without telling your doctor) because you felt worse when you took it?	☐ **Yes** ☐ **No**
4. When you travel or leave home, do you sometimes forget to bring along your blood pressure medication?	☐ **Yes** ☐ **No**
5. Did you take your blood pressure medicine today?	☐ **Yes** ☐ **No**

6. Some people have a special routine or reminder system to help them take their blood pressure medicine. What do you do? (*tick one*)

Comments

☐ I **do not** have a special reminder

☐ I take it with the same meal each day

☐ I take it as I wake up / go to bed

☐ My wife / husband reminds me

☐ I take it at work

☐ Other reminder system

Question 7 on next page.....

Patient Initials _____ **File No.** _____ **DOB. (dd/mm/yy)** ____ / ____ / ____ *tick* **Male** ☐ **Female** ☐

7. When you feel like your blood pressure is under control, do you sometimes stop taking, or reduce the dose of your medicine? ☐ **Yes** ☐ **No**

8. Some people find it very inconvenient to take their blood pressure medicine every day. Do you ever feel stressed about having to follow your blood pressure treatment? ☐ **Yes** ☐ **No**

9. How often do you have difficulty remembering to take all your blood pressure medicine?

tick ☐ All the time ☐ Usually ☐ Sometimes ☐ Once in a while ☐ Never

10. Some people feel unhappy that they have to take medication every day for their blood pressure e.g. some people are embarrassed or feel that it is a sign of weakness. Do you ever feel unhappy that you have to take your blood pressure tablets? ☐ **Yes** ☐ **No**

Questionnaire completed by: _____ **(Initials)** _____ **(Signature)** _____ **Date**

Patient No.

Annex 4 Self reported adherence form – Arabic (pilot and final version)

The Arabic versions of the Self-reporting measure are presented below. There is the Pilot study version and the final, validated version.

استبيان للأطباء عن انتظام مرضى ارتفاع ضغط الدم فى العلاج

(هذا الأستبيان يسجل وجهة نظر الطبيب- من فضلك لا تسأل هذه الأسئلة بشكل مباشر)

الجنس: ذكر انثى رقم الملف---------- التاريخ: / / اسم المريض----------

1- هل تعتقد أن هذا المريض ينسى أخذ الجرعة المحددة من الدواء ؟ نعم لا

فى حالة نعم:

كم معدل النسيان ؟ * 1-2 يوم كل شهر 3-4 يوم كل شهر 5-6 يوم كل شهر 7-8 يوم كل شهر * 2-3 يوم كل أسبوع 3-4 يوم كل أسبوع أكثر من 4 أيام كل أسبوع

2- هل تعتقد أن هذا المريض أحيانا يأخذ الجرعة متأخرة أكثر من 6 ساعات؟نعم لا

فى حالة نعم:

ما هو المعدل؟ * 1-2 يوم كل شهر 3-4 يوم كل شهر 5-6 يوم كل شهر 7-8 يوم كل شهر * 2-3 يوم كل أسبوع 3-4 يوم كل أسبوع أكثر من 4 أيام كل أسبوع

3- هل تعتقد أن هذا المريض يتوقف أحيانا عن أخذ الدواء عندما يشعر بتحسن؟ نعم لا

فى حالة نعم:

ما هو المعدل؟ * 1-2 يوم كل شهر 3-4 يوم كل شهر 5-6 يوم كل شهر 7-8 يوم كل شهر * 2-3 يوم كل أسبوع 3-4 يوم كل أسبوع أكثر من 4 أيام كل أسبوع

4- هل تعتقد أن هذا المريض أحيانا يوقف العلاج عندما لا يشعر بتحسن؟ نعم لا

فى حالة نعم:

5- ما هو المعدل؟ * 1-2 يوم كل شهر 3-4 يوم كل شهر 5-6 يوم كل شهر 7-8 يوم كل شهر * 2-3 يوم كل أسبوع 3-4 يوم كل أسبوع أكثر من 4 أيام كل أسبوع

6- قيم درجة لتأثير دواء ارتفاع ضغط الدم الموصوف لهذا المريض؟ 1- ممتاز 2-جيد 3- ضعيف

7- قيم العلاقة بينك و بين هذا المريض؟ 1- ممتاز 2-جيد 3- ضعيف

8- قيم معلومات هذا المريض عن مرض ارتفاع ضغط الدم و الأدوية المستخدمة لعلاجه؟ 1- ممتاز 2-جيد 3- ضعيف

قيمم مستقبل حالة القلب و الأوعية الدموية لهذا المريض؟ 1- ممتاز 2-جيد 3- ضعيف

الأحرف الأولى من أسم المريض _____ رقم الملف_____ تاريخ الميلاد(اليوم/الشهر/السنة) _____ ذكر انثى

الاستطلاع الخاص بالتزام المريض بعلاج ارتفاع ضغط الدم

(1 بعض الناس يجدون صعوبة في أن يتذكروا تناول أدويتهم ، هل صادف و أن نسيت تناول جرعة من دوائك الخاص بارتفاع ضغط الدم؟
نعم كلا

(2 تفوت على بعض الناس فرصة تناول أدويتهم لأسباب غير تلك التي تتعلق بالنسيان ، هل حدث لك ذلك في بعض الأيام خلال الأسبوعين الأخيرين فيما يخص أدوية ارتفاع ضغط الدم؟
نعم كلا

(3 هل صادف و قللت أو امتنعت عن تناول الدواء الخاص بارتفاع ضغط الدم(بدون أن تأخذ إذنا من طبيبك) لأنك شعرت بأنك أسوء حالا عندما كنت تتناوله؟
نعم كلا

4)هل تنسى في بعض الأحيان أن تأخذ الدواء الذي تتناوله لعلاج ارتفاع ضغط الدم عند سفرك أو عندما تكون بعيدا عن المنزل؟

نعم كلا

5) هل تناولت دوائك الخاص بارتفاع ضغط الدم هذا اليوم؟
نعم كلا

تابع السؤال السادس في الصفحة الثانية

تم إكمال الاستطلاع من قبل:_____ الأحرف الأولى من الاسم _____ التوقيع _____ التاريخ_____

الأحرف الأولى من أسم المريض _____ رقم الملف _____ تاريخ الميلاد(اليوم/الشهر/السنة) _____ ذكر انثى

6) بعض الناس يعتمدون أسلوبا أو نظاما معينا لتذكيرهم بتناول علاج ارتفاع ضغط الدم. ماذا تفعل أنت لتتذكر؟

لا أعتمد أي أسلوب للتذكير. زوجتي أو زوجي يذكرني أو تذكرني به. أتناوله مع نفس وجبة الطعام كل يوم.

أتناوله أثناء تواجدي في العمل. أتناوله بمجرد استيقاظي من النوم أو قبل رقادي.

أي أسلوب تذكير آخر.

---

7) هل تتوقف عن أو تقلل بعض الأحيان جرعة دوائك عندما تشعر بأن ارتفاع ضغط الدم لديك قد انتظم؟

نعم كلا

---

8) بعض الناس يشعرون بأنه من غير المناسب أن يتناولوا علاج ارتفاع ضغط الدم الذي يعانون منه بصورة يومية ، هل سبق و أن خالجك شعور بأنك واقع تحت ضغط متابعة تناول علاج ارتفاع ضغط الدم؟

نعم كلا

---

9) ما هو معدل أن تجد صعوبة في تذكر تناول علاجك الخاص بارتفاع ضغط الدم؟

أشر على الدوام عادة بعض الأحيان مرة واحدة كل فترة أبدا

---

10) يشعر بعض الناس بعدم الرضا لكونهم مجبرين على تناول الدواء الخاص بارتفاع ضغط الدم الذي يعانون منه بصورة يومية ، بمعنى آخر يشعر بعضهم بالحرج أو ربما يخالجهم شعور بأنها من علامات الضعف. هل سبق و أن شعرت بالحزن عند تناول أقراص الدواء الخاص بارتفاع ضغط الدم؟

نعم كلا

---

11) و أخيرا ، هل تدخن التبغ؟

نعم كلا

Annex 4 Doctor's perception form

This annex presents the Doctor's questionnaire that was used during the initial study to elicit and record their perceptions of the patient and their medication adherence.

It was printed, double sided, on pink A4 paper. The doctors were shown how to complete the form before hand but were not given any support during or after a consultation.

They were asked not to deviate from their usual routine, and in particular, not to ask the patient about the form they had completed before the consultation. However, if they would normally ask the patient about their medication adherence then they should do so as usual.

Patient Initials _____ **File No.** _____ **DOB. (dd/mm/yy)** ____ / ____ / ____ *tick* **Male** ☐ **Female** ☐

Physician's questionnaire
After the consultation and after reviewing the file, please use this form to record your PERCEPTIONS

---

1. Do you think that this patient ever **forgets** to take a dose of their blood pressure drugs? ☐ **Yes** ☐ **No**

---

2. Do you think that this patient sometimes stops taking or reduces the dose of their blood pressure drugs because they feel better or because they feel that their blood pressure is under control? ☐ **Yes** ☐ **No**

---

3. Do you think that this patient sometimes stops taking or reduces the dose of their blood pressure drugs because they feel worse, e.g. due to side effects? ☐ **Yes** ☐ **No**

Questionnaire completed by: _____ **(Initials)** _____ **(Signature)** _____ **Date**

Patient Study No.

Patient Initials _____ **File No.** _____ **DOB. (dd/mm/yy)** ____ / ____ / ____ *tick* **Male**☐ **Female**☐

8. How would you describe the effectiveness of this patient's current antihypertensive medication? (tick box)

☐ Patient has reached their target BP ☐ Some reduction in the BP since starting the regime, bit not enough ☐ No improvement in the BP since starting this regime

9. How do you rate the communication and openness between you and this patient? (tick box)

☐ Excellent ☐ OK ☐ Poor

10. How do you rate this patient's knowledge of their hypertension and of their antihypertensive medication? (tick box)

☐ Excellent ☐ OK ☐ Poor

11. After considering the patient's age and sex, how do you rate this patient's risk of suffering a major cardiovascular event in the next 5 years? (tick box)

☐ Unlikely ☐ Increased risk ☐ Greatly increased risk

Annex 5 A description of Internal Reliability and Factor analysis

Internal reliability (consistency): Cronbach's alpha is the most common estimate of internal reliability. In this context internal reliability is the extent to which response to individual items correlate highly with each other. This measure ranges from 0 (*no internal reliability*) to 1 (*perfect internal reliability*). The widely accepted cut-off is that alpha should be 0.7 or higher for a set of items to be considered a scale (or measure). However, this varies and in social sciences the lower level is often set at 0.6. The cut-off of 0.7 is reflected in the fact that when alpha is 0.7, the standard error of measurement will be over half (0.55) of one standard deviation. The Cronbach alpha is easily calculated using SPSS. The Cronbach alpha is related to the *dimensionality* (clustering) of the measure, but is not an accepted estimate of dimensionality and Factor analysis is recommended for this estimate.

SPSS (Version 10) procedure for Internal reliability

After importing the data from Excel, the following menu steps are taken: Analyse; scale; reliability analysis; scale; alpha

Factor analysis:

In statistical terms, a simple scale such as a self-reporting measure of medication adherence is only considered useful if it can be shown to be one dimensional. That is, that the combined response to a variety of questions (items) can be combined to describe a single construct (characteristic), in this case the tendency towards adherent, or non-adherent behaviour. Factor analysis is the statistical tool used to describe the latent structure (dimensions) of a scale such as the self-reported medication measure. Furthermore, it allows one to refine a scale by excluding those items that are not contributing to this single aim.

The most common type of factor analysis used to study scales such as the self-reported adherence measure is *Principal Component Analysis* (PCA). This analysis describes the maximum variance in the response to each item.

SPSS (Version 9) procedure for PCA

After importing the data from Excel, the following menu steps are taken: Select analyse; data reduction; factor; variables (input variables); descriptives; under correlation matrix; check KMO and Anti-image to get overall and individual KMO statistics; extraction; method (principal components) and analyse (correlation matrix) and display (scree plot) and extract (eigenvalues over 1.0); continue; rotation; under method; choose varimax; continue; scores; save as variables; continue; OK.

Estimating the sample size required when using Factor Analysis to develop a scale

There are several rules; most of them dependent upon the number of items under analysis, and different statisticians recommend different ones. They are summarised in Figure 46 below.

Figure 46 Sample size required for effective factor analysis of a 10-item instrument

Adapted from Garson 2002 [248]

Rule	Description	Sample size required
Literature review	See what people did in similar, published studies	80-400[M]
Rule of 10	There should be at least 10 cases for each item in the instrument being used	100
STV Ratio	The subject to variables ratio should be not less than 5	At least 50
Rule of 200	There should be at least 200 cases regardless of the STV ratio	At least 200
Rule of 150	At least 150 – 300. Closer to 150 if there are few highly correlated variables	150-300
Rule of 100	The number of subjects should be the larger of 5 times the number of variables or 100	At least 100
Significance rule	There should be at least 51 more cases than the number of variables	At least 61 in this case

[M] Based upon a survey of various published studies looking at the use of sef-reporting scales

Annex 6 Quality assessments of blood pressure data

Introduction

The blood pressure data used in this study was extracted form the routine medical record. As discussed in chapter 2, the measurement of hypertension is susceptible to a variety of observer errors and bias: Systematic errors; Terminal digit preference and Observer bias.

Systematic errors

Systematic error was assessed according to the most common examples highlighted by the British Hypertension Society consensus report[162]. Qualified nurses made the measurements using mercury sphygmomanometers. The measurements were made in a side room away from the main waiting area and used only for the nurse examinations. The patient was always seated and a desk was next to the chair for resting the arm. All these would be considered good practice. The nurse was seated on a non-adjustable chair and therefore, for some nurses, the manometer scale would have been slightly below the eye level (ideally should be at eye level). . The nurse's ability to identify the correct auscultatory sounds was not tested although they reported that they used the "phase V", disappearance of auscultatory sounds to demark the diastolic blood pressure. This would be fine for the majority of patients, although the "phase IV" softening of sounds may be more appropriate for some patients such as those who are elderly. The right arm was always used due to the configuration of the desk and chairs. There was no evidence in the notes that the pressure was ever measured in both arms. On some occasions the notes recorded that if the pressure seemed higher than expected, the patient was asked to come back later that day or the next day, in these cases the lower pressure was used for the study. Although larger inflatable cuffs were available, there were no written criteria for when the larger cuff should be used.

Overall, the risks of systematic error were minimised through having a dedicated environment for blood pressure measurement. The potential errors were relatively minor and not expected to significantly affect the data collection. A number of the recommendations of the British Hypertension Society could be implemented to further minimise the risk of systematic error.

Terminal digit preference

The quality of the blood pressure data was studied to identify the extent of the most common source of measurement error, terminal digit preference. In addition to the pressure recorded at the time of starting treatment, three blood pressure measurements were available for most patients and for 86 patients at the second health centre, three later measurements were available from the follow-up period. The data was also studied to identify any differences between the two health centres. This data is summarised below.

	Health centre	Terminal digit preference for;
Table 35	1 & 2	SBP
Table 36	1 & 2	DBP
Table 37	1	SBP
Table 38	1	DBP
Table 39	2	SBP
Table 40	2	DBP
Table 41	2 at follow up	SBP
Table 42	2 at follow up	DBP

Table 35. Both Health centres: Terminal digit preference among measurement of Systolic Blood Pressure

(n=202 for SBP1, 194 for SBP2&3) Terminal Digit	% Readings SBP1	SBP2	SBP3
0	91%	91.7%	91.6%
5	6.5%	6.0%	5.6%
Other	3.0%	2.0%	2.5%

Table 36. Both health centres: Terminal digit preference among measurement of Diastolic Blood Pressure

(n=202 for DBP1, 194 for DBP2&3) Terminal Digit	% Readings DBP1	DBP2	
0	79.8%	82.4%	83.0%
5	13.3%	11.3%	10.2%
Other	7.0%	6.0%	6.5%

Table 37. Health Centre 1: Terminal digit preference among measurement of Systolic Blood Pressure

(n=38) Terminal Digit	% Readings SBP1	SBP2	SBP3
0	89.4%	97.4%	92.2%
5	7.9%	2.6%	7.9%
Other	2.6%	0.0%	0.0%

Table 38. Health Centre 1: Terminal digit preference among measurement of Diastolic Blood Pressure

(n=38) Terminal Digit	% Readings DBP1	DBP2	DBP3
0	71.2%	76.3%	78.8%
5	26.3%	21.0%	18.4%
Other	2.6%	2.6%	2.6%

Table 39. Health Centre 2: Terminal digit preference among measurement of Systolic Blood Pressure

(n=156) Terminal Digit	% Readings SBP1		SBP3
0	90.2%	90.4%	91.5%
5	5.6%	6.9%	5.6%
Other	3.7%	3.6%	3.0%

Table 40. Health Centre 2:Terminal digit preference among measurement of Diastolic Blood Pressure

(n=156) Terminal Digit	% Readings DBP1	DBP2	DBP3
0	81.4%	83.9%	84.0%
5	10.2%	9.0%	8.2%
Other	8.1%	6.9%	7.7%

Table 41. Health Centre 2 Follow-up: Terminal digit preference among measurement of Systolic Blood Pressure

(n=86) Terminal Digit	% Readings SBP1	SBP2	SBP3
0	89.6%	95.3%	93.1%
5	7.0%	2.3%	5.9%
Other	3.6%	2.3%	1.2%

Table 42. Health Centre 2 Follow-up: Terminal digit preference among measurement of Diastolic Blood Pressure

(n=86) Terminal Digit	% Readings DBP1	DBP2	DBP3
0	88.4%	87.3%	90.7%
5	10.6%	8.2%	7.0%
Other	1.2%	4.7%	2.4%

Among the blood pressure data used in this study, the preference for zero, as the terminal digit was high and between 71 and 94% of measurements were recorded as ending in a zero. It was generally lower for the diastolic pressure records, ranging from 71 to 88% and for systolic pressure records the preference for zero affected 91 to 97%. The majority of the other recorded values showed a preference for a five as the terminal digit.

Discussion of terminal digit preference

If the nurses had been following the European Society of Hypertension's international protocol for blood pressure measurement using a mercury sphygmomanometer, then blood pressures should have been measured to the nearest two millimetres of mercury. If one assumes that a reading ending in a one or a nine might be rounded up or down to a number ending in a zero, then the recorded terminal digit would be zero in approximately 10-30% of cases. In this study the preference for zero as the terminal digit was higher at 71 to 88% for diastolic and 91 to 97% for systolic values. The majority of the recorded values showed a preference for a five as the terminal digit.

Terminal digit preference is a very strong behavioural bias and affects a variety of clinical measurements ranging from neonatal birth-weight249 through to hypertension134 ,250. Terminal digit preference involving the measurement of the blood pressure by nurses and doctors is a common finding reported in a variety of clinical settings. The levels of digit preference are clearly high in these two health centres but comparable with observations from around the world (table 43)). Interestingly, the level of error or bias in the blood pressure data is rarely reported in adherence studies that look at blood pressure, including the original Morisky study of self-reported adherence.

Some of the data reported in (table 43) are from formal, prospective studies. Therefore, the nurse or doctor knew that the reading would be used in a clinical study, but still recorded a zero preference, underlining the strong subconscious

tendency to round the recorded pressure up or down. This may be even greater when a practitioner is measuring the blood pressure to monitor rather than diagnose the hypertension. The implications for the management of hypertension are varied. Terminal digit preference in this population was greatest for the systolic blood pressure. In addition to possibly being related to the greater range of measurements for the systolic blood pressure, this may also reflect a greater perceived importance of the diastolic reading compared with the systolic reading. This is contrary to current thinking and the many observational studies showing the systolic blood pressure to be more closely related to end organ damage and major cardiovascular events than is the diastolic blood pressure.

Whatever, the reasons behind the terminal digit preference in this study it reflects the way that blood pressure is measured in these two health centres, and it is on the basis of these results that management decisions are taken. As this study looks at adherence and its relationship to blood pressure control, the data, although flawed, is comparable to international norms and is therefore a valid basis for evaluating the influence of self-reported adherence.

Table 43 Preference for zero as the terminal digit when measuring blood pressure using a manual sphygmomanometer

Level of zero preference	Number of patients	Result recorded by	Setting	Reference and other observation
65-85%	1,072 and >5,500 readings	Doctors	UK Family medicine	[251] Zero preference was greater close to thresholds
62%	146	Doctor & Nursing Home Nurses	UK Elderly nursing home	[252] Systolic often underestimated; Diastolic overestimated; Up to 21% readings incorrect
78%	28,841	Doctors & nurses	Prenatal clinic Quebec, Canada	[253] Zero preference consistent across the range of pressures; Same for Systolic and diastolic Changing the definition of hypertension to be >140mmHg reduce the "incidence" of hypertension by 50%
42-83%	20, 992 diastolic readings	Doctors & nurses	UK 8 family medicine practices, 27 doctors and 16 nurses	[254] Constructed distribution charts to provide feed back to doctors and nurses as an educational tool.
10-82%	1,000 – 7,000	Doctors & Nurses	Global study on hypertension	[255] QA data from the WHO global study of hypertension "MONICA" Number of subjects varied from country to country Large inter-region variation despite staff training
32%	78 nurses in Survey	Teaching hospital nurses	Australia	[256] Identified inadequate level of knowledge among nurses

The main problem of zero preference for research studies is that it distorts the frequency distribution curve of blood pressure and reduces the power of any analysis that uses the data. In this study, the blood pressure used when studying the relationship between self reported adherence and blood pressure, was an average of the last three measurements, usually over a six to twelve week period. This will have helped to ameliorate some of the effects of the zero preference. However, as each of the three results will have a high incidence of zero as the terminal digit, this introduces a similar preference for zero, three and seven after calculating the average of the three results and rounding to the nearest whole number, e.g.

Average of 140, 140 and 150 = 143

Average of 140, 150 and 150 = 147

Therefore, while only 66 (33%) of the 202 patients had an average systolic blood pressure ending in a zero, there were a further 90 (45%) of readings ending in a three or a seven, i.e. the equivalent of a zero preference in 77% of the average systolic blood pressure readings.

As the important breakpoints usually have a zero as the terminal digit, e.g. 140/90 mmHg, one might expect zero preference to be more common closer to these readings. This has been reported in a family medicine setting by [251] but in the prenatal clinic setting the level of zero preference was similar across the range of readings [253]. An increased frequency of zero preference close to breakpoints highlights that there is also another source of error, that of observer bias.

Observer bias

The observer adjusts the measurement to suit their perceptions of control, especially when the result is close to a target pressure. For example, an observed result of 144/ 82mmHg might be recorded as 140/80mmHg if they wish to encourage an otherwise young and fit patient by recording a "target" result even if they are slightly over target. Alternatively, in an older, obese patient the same result might be rounded to 145/80mmHg. Furthermore, the awareness that blood pressure is under study may lead to the observer reporting the pressure to be "on target" where possible.

In this study the nurse who measured the blood pressure was the nurse who recruited the patient and this could have increased their bias. In the above tables showing three pressure recordings at the two health centres, the readings denoted as SBP3 and DBP3 were those measured on the day of recruitment. The level of

zero preference at the day of recruitment tended to be marginally higher on these occasions than on the preceding two occasions although this was not significant.

The level of observer bias is difficult to quantity but one indicator is to look at the effect of slightly changing the breakpoint for blood pressure control. For most patients, the JNCVI breakpoint for hypertension is a pressure greater than 140 / 90 mmHg for none diabetics and 135/85 mmHg for diabetics. By reducing this breakpoint by 1mmHg (i.e. 139/89 or 134/84 mmHg) one can highlight the effect of rounding up or down to breakpoint values. It has been reported that retrospectively changing the threshold for hypertension by 1mmHg would have changed the number of prenatal women diagnosed with hypertension by as much as 50%[253]. In this study, for the 202 patients treated for three or more months at the two health centres, reducing the threshold for control by 1mmHg changes the percentage of patients with "controlled" blood pressure from 40% to 32%. This suggests that there is a predominant rounding down of blood pressure readings to meet the criteria of "controlled" blood pressure. While some patients will genuinely have a blood pressure of 140/90 mmHg, and after accepting a zero preference of 80-90%, this suggests an underestimate of hypertension in approximately 7-8% of patients due to the zero terminal digit preference. An analysis of the follow-up data found that reducing the target blood pressure by 1mmHg made no difference to the number of patients who had attained target blood pressure (43% in both cases). This suggests that the level of observer bias is low compared with some reports and probably of no significance.

Quality implications for this study

As in all clinical and epidemiological studies of blood pressure that use "real-life" measurements, the high level of zero terminal digit preference in the blood pressure recordings will weaken any association between the actual blood pressure and other factors, such as adherence. However, the consequences for this study will be reduced by the fact that it was the number of patients reaching target blood pressure, i.e. below the JNCVI thresholds that was compared for different levels of self-reported adherence. As seen above, the predominant error affecting whether a patient is above or below the target pressure is observer bias, and this appears to have been low, in the region of 7-8%.

The relationship between adherence and the change in blood pressure will have been affected more by the zero end-digit preference; however, the same level of bias is likely to have affected the blood pressure recorded at the start of treatment and the

averaging of three results to get the "current" blood pressure will have ameliorated the effect of the zero digit preference.

The results most affected by the zero terminal digit preference will have been the correlation between the average blood pressure and the level of adherence. Indeed, as seen in section 5.2, although some of these relationships were statistically significant, the correlations were weak. A more accurate clinical measurement of the blood pressure could have helped to demonstrate a stronger relationship between the current blood pressure and the score on the self-reported adherence scale.

Conclusion

Blood pressure measurements taken from the routine clinical record are affected by a variety of errors and bias. In this study, there was evidence of error and bias but it was not a lot higher than in clinical reports in a variety of international settings. Terminal digit preference for zero was the most prevalent error; however, for most of the correlations involving blood pressure and adherence, the impact of this was low. Observer bias did not greatly affect the number of patients achieving "target" blood pressure, mainly due to the JNCVI breakpoint for most patients ending in a zero.

The most important aim of this study is to demonstrate the validity of a simple self-reporting scale for use in a routine clinical environment. The fact that this could be demonstrated with the partly flawed, routine data used to guide clinical decision making reinforces the usefulness of this scale.

Annex 7 Selecting the statistical tests used in the research

In addition to the statistical analysis of the internal reliability and principal component analysis, inferential tests were performed on selected data. The tests were performed according to the recommendations of standard statistics texts and the advice of Dr. Abdul Bari Bener of the Faculty of Medicine at the UAE University, Al Ain, United Arab Emirates. These are summarised below.

Chi-square

This test for association was used for comparing categorical data, mainly adherence levels (ordinal; High / Medium or Low) between initial and follow-up studies and adherence levels with attainment of target blood pressure (dichotomous; Yes or No). The Chi-square statistic was always calculated using the raw score, never percentages. Although this can be easily calculated using SPSS, many of the calculations were performed using a simple Excel template (2 x 2 or 2 x 3) designed by the author and based upon the operation schedule described by Clegg in Simple Statistics; A course book for the social sciences[N] 1990; Cambridge University Press. As recommended, a Yates correction for continuity was always used.

Spearman's Rho

This test was used to calculate the correlation between the self-reported adherence scale scores (0-7) with the average SBP and DBP and the change in the SBP and DBP since the start of treatment. It was calculated using SPSS. Scatter diagrams were generated to identify any lack of linearity in the data.

Gamma statistic

This test was used to compare the doctors' evaluations of patient characteristics with the doctors' estimate of adherence and the patients' self-reported adherence. The test is also known as Goodman and Kruskal's gamma. It is a test of association between pairs of ordinal or categorical data. It includes a calculation of the significance of the association. It is calculated by SPSS in the CROSSTABS module.

[N] Clegg, F in Simple Statistics; A course book for the social sciences 1990; Cambridge University Press ISBN 0 521 28802 9

Annex 8 Papers submitted for publication

The following two manuscripts have been submitted for publication to the Annals of Pharmacotherapy[♠]. They have been accepted pending satisfactory responses to the comments received from five reviewers. These were in process at the time of submission.

The format of these articles is in accordance with the requirements of the journal's editorial style (http://www.theannals.com/guidelines.html)

The papers are titled:

An Arabic / English self-reported measure for medication adherence

and

Doctor and patient perceptions of adherence to antihypertensive medication

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An Arabic / English self-reported measure for medication adherence

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Abstract

Objective: To develop an Arabic self-reporting measure of medication adherence

Method: An English, self-reporting measure was adapted and translated in to Arabic. Validity of the scale was assessed in patients attending two government primary health care centres for management of their hypertension. Each item had a Yes or No response and a response indicating non-adherent behaviour (usually Yes) scored 1. A score of greater than zero was indicated non-adherence (<80% doses). Follow-up was done after 6-9 months.

Results: 203 patients completed the self-reporting measure in two health centres and 86 of these were followed up after 6-9 months. After Principal component analysis, two of the items were eliminated leaving a 7-item one-dimensional model with high internal reliability (Cronbach alpha = 0.76). 52% (106) reported high adherence. Those reporting high adherence were almost twice as likely to have reached target blood pressure as those who reported medium or low adherence; 52% control vs. 28% control. The adherence scale score was correlated with systolic and diastolic blood pressure and with the change in Systolic blood pressure since the start of treatment ($p<0.05$). Prospective validity at follow up (average 7.6 months) was weak and 30 (35%) of the 86 follow-up subjects changed their reported adherence. Concurrent validity remained high.

Conclusion: A 7 item Arabic scale was developed for assessing adherence in a routine Arab healthcare setting. The scale has good concurrent validity with respect to blood pressure control and identified significant changes to self-reported adherence over a 6-9 month period.

Introduction

Self reported adherence is the simplest method of assessing medication adherence in a routine clinical setting. Several self-reporting scales have been described and consist of between 3 and 9 items and the responses are recorded as "Yes" / "No" or via a Likert scale[1-3]. One of the most widely cited scales is a four item, dichotomous instrument first described by Morisky et al[39] who used it to study adherence in hypertension. The instrument has been used in a variety of diseases and clinical settings and has been translated into Spanish[2-11]. The Morisky scale has been compared with several other methods including tablet counts, electronic monitoring and other self-reporting scales[2,3,6-8,10]. There are no published, validated Arabic self-reporting scales and this has impeded research into medication adherence among Arabic speaking populations. The United Arab Emirates is an oil-rich federation of seven states on the Arabian Gulf. Over 80% of the population are expatriate workers from over 100 countries. Arabic is the official language but because of the diversity of nationalities, English is widely spoken. This profile is similar to many countries in the region and therefore an Arabic measure would be very useful in the region or any Arab expatriate community.

Method

An Arabic self reported medication adherence measure was developed through the adaptation and translation of an English instrument first described by Morisky et al[39] and since updated to nine items[12]. The measure's concurrent validity was assessed in two outpatient government health centres in Abu Dhabi, UAE. The Ministry of Health granted ethics approval. Patients were recruited prospectively and included any hypertensive adult who attended the health centre for the management of their hypertension, who had been on their current antihypertensive medication for at least 3 months and who verbally consented to participate. A follow-up was performed at one of the two health centres between six and nine months later.

The self-reported adherence measure (final form shown in table 1) was designed to encourage reporting of non-adherence to the antihypertensive medication arising from any of four different ways: forgetting, carelessness, omitting the drug when feeling better or omitting the drug when feeling worse. Each item has a "Yes" or "No" answer and a score of one or zero is assigned to each response (usually score one for a "Yes" response). A zero score indicates adherence and higher scores are taken to indicate medium or low adherence. A zero score in the original four-item measure was shown to correlate with taking more than 80% of

doses when compared with electronic adherence monitoring[10]. In this study, adherence was considered to indicate that 80% or more of doses of the blood pressure medication were taken correctly as this is the widely recognised minimum adherence required for blood pressure control.

An Arab pharmacist, fluent in Arabic and English performed the Arabic translation. This was reviewed by other Arab physicians and pharmacists to determine a broad agreement on the translation and then validated by a process of back translation by Arabic / English speaking pharmacists and nurses.

Upon arrival at the health centre the patient was screened by a nurse and invited to participate. The nurse or the pharmacist, depending upon the health centre, read the items to the patient in the patient's preferred language (usually Arabic). Current blood pressure was the average of the last three measurements in the medical record. The blood pressure at the start of drug treatment was the average of the three blood pressure recordings prior to the start of drug treatment (if available). The procedures of the health centres concur with British Hypertension Society (BHS) guidelines for the measurement of blood pressure[13,14]. The target blood pressure was taken from the JNC VI recommendations of not more than 140/90mmHg or not more than 135/85mmHg for diabetics[15]. If both the systolic and diastolic pressure were at or below these limits the patient was considered to have reached their target blood pressure. The responses to each item plus an array of blood pressure measurements and demographic data were entered into a Microsoft Excel 2000 workbook and analysed using Excel or SPSS version 10.

The internal reliability of the scale, calculated using Cronbach's alpha, was used to determine internal reliability of the scale. This measure ranges from 0 (no internal reliability) to 1 (perfect internal reliability). The association of the scale to blood pressure control was determined using the Chi square test and correlation with average blood pressure readings was determined using the Spearman's correlation coefficient (Spearman's Rho).

Dimensionality of the scale was determined using principal component analysis (PCA). This determines the extent to which the set of items measured the same construct or measured two or more clusters of variables that represent different dimensions of adherence. The aim was to have a one-dimensional scale. The minimum number of subjects required to perform PCA on a 9-item scale can be determined according to several guidelines, but it would be between 50 and 300.

The quality of the blood pressure measurement was assessed by direct observation and by analysis of the recorded results for terminal digit and observer bias.

Results

Two hundred and three patients completed the self-reported adherence measure. The average age (±SD) was 52 years (± 8.9) years but a reliable date of birth was available for only 197 subjects. There were slightly more men (58%) and the median time since the start of hypertension treatment was 5.2 years (range 0.2-27.3 years) and was known for 193 of the subjects. Most patients, 125 (62%) were taking only one antihypertensive with 67 (33%) taking two drugs, 10 (5%) taking three drugs and one patient prescribed four drugs. The target blood pressure had been reached in 82 (40%) subjects and the median (±SD) systolic blood pressure (average of three readings) was 140.0 mmHg (± 17) and diastolic blood pressure was 88mmHg (± 10). The Body Mass Index (mean ±SD) was 31 ± 6.5 and non-insulin dependent diabetes had been diagnosed in 61 (30%) of the subjects. The majority of patients visited the health centre approximately every 2-4 weeks for a repeat prescription.

Principal component analysis (PCA) and internal reliability of the self reported adherence measure

A PCA of responses to the nine items showed them to represent a three-dimensional model. Step-wise elimination of two items improved the internal reliability and produced a one-dimensional model. The internal reliability, Cronbach alpha, of the remaining 7-item scale was 0.76. Therefore, the 7-item scale was used for further validation. The item to total correlation of the seven remaining items is shown in table 1 (Arabic version available on request).

Relating the scale score to adherence

The distribution of scale scores is shown in table 2. Scores ranged from zero to seven. As in the original Morisky scale, a zero score was assigned as high adherence.

High adherence (zero score) was reported by 106 (52%) of subjects. The remaining scores were divided into two between medium and low adherence. Medium adherence was taken as a score of one to four and showed that 87 (43%) of subjects reported medium adherence. Low adherence was taken as a score of five or greater and showed eleven subjects (5%) reporting low adherence. Out of the 106 subjects reporting high adherence, fifty-five (52%) of these reached target blood pressure. Out of the 87 subjects who scored 1-4, 26 (30%) reached the target blood pressure and of the eleven scoring more than

four, only 1 (10%) reached the target blood pressure. This association was significant ($p>0.01$, Chi square = 12.584, 2 degrees of freedom).

Quality of blood pressure data

Direct observation of blood pressure measurement found no major deviations from the BHS protocol. Terminal digit preference was found and showed a high zero bias (range 70-93%) with only 1-3% not ending in a 5 or a 0. This was seen in both recent readings and those at the start of therapy.

Correlation with blood pressure

The blood pressure at the start of treatment was available for 184 subjects and for these the raw score correlated with the change in systolic blood pressure ($p>0.006$, Spearman's Rho = 0.185) but the correlation with the change in diastolic blood pressure did not reach significance ($P=0.153$, Spearman's Rho = 0.076). The raw score correlated with both the systolic blood pressure ($p=0.018$, Spearman's Rho=0.111) and the diastolic blood pressure ($p=0.0004$, Spearman's Rho = 0.232). One patient was excluded from this calculation ($n=202$) because they had recently transferred to the health centre only six weeks blood pressure data was available.

Follow up

Eighty-six patients were followed up after an average of 7.6 months (range 5.8-9.1 months). Demographically the follow-up sample was very similar to the initial sample. When the self reported adherence assessment was repeated, the overall levels of adherence for the sample were not significantly different from the initial study, with 48 (56%) reporting high adherence, 34 (40%) reporting medium adherence and 4 (5%) reporting low adherence. The number of patients reaching the target blood pressure had increased overall from 40% to 52%. In the high adherence group 32 (67%) had reached the target blood pressure compared with 22 (50%) at the initial study. However, the overall differences between the blood pressure control at the initial and follow-up studies did not reach significance. The original adherence reports were only weakly related to the blood pressure control at follow-up (low predictive validity). However, there was a significant change of reported adherence for individual patients with 30 (35%) reporting a different level of adherence compared with their report 6 to 9 months earlier ($p>0.01$, Chi Square = 7.381, 2 tailed).

The concurrent validity with respect to blood pressure remained high. At follow-up, target blood pressure was reached in 32 (67%) of those reporting high adherence compared with 12 (32%) of those reporting medium or low adherence, a highly significant association ($p>0.001$, Chi square = 11.9018, one tailed).

The relationship between adherence change and reaching target blood pressure is shown in detail in table 3.

Discussion

The translation of the items underwent extensive discussion and revision. The Arabic was chosen carefully so to be easily understood by patients. Some words proved difficult to translate. The word "hassled" was used in one of the original English items and no single Arabic equivalent word could be agreed upon.

The Cronbach alpha was 0.76 and this is quite acceptable for a social sciences scale where the generally accepted lower value is 0.6. Principal component analysis of the nine items produced a three dimensional model and this became a one-dimensional model after rejecting the two items with the weakest item-total correlation. The rejected items were; "Did you take your blood pressure today?" and "Do you have a special routine or reminder system to help you to take your blood pressure medicines?" The original questionnaire had asked did you take your medication "yesterday" instead of "today". This had been changed after discussions with doctors locally during which it was felt that most patients took their medication in the morning and most hypertension patients attended in the evening; however, reports of missed doses on the day of the study were made less than half as frequently as expected (9%). It is possible that by changing the item to "today" from "yesterday" made the question too direct for many patients to answer truthfully or there may be an improvement in adherence on the day of clinic attendance. This increase in reported adherence prior to an out-patient appointment has been reported among epilepsy patients[16]. The item about reminder systems produced a "No" response (scored 1) among 41% of respondents, which was two to three times more frequent than compared with the other items. The Arabic translation has been double-checked and was not the cause of this discrepancy. Although the item could not be used as part this scale, this would be an interesting area for further study.

Surprisingly, around 35% of patients changed their self-reported adherence to indicate a move towards or from adherence. The continued strong association between blood pressure control and self-reported adherence implies that this was not a quirk of the scale. Out of the 20 subjects who reported increased adherence, 6 (30%) had regained control of their blood pressure and none had lost control. Out of the 14 who reported lower adherence, none regained blood pressure control and 4 (29%) lost blood pressure control. The dynamics of adherence to chronic medication over the medium and long-term has not been studied. Morisky's original studies describe a 5-year follow-up of blood pressure

outcomes following educational interventions aimed at improving adherence, but did not reassess adherence[1, 17]. While this observation needs to be confirmed in a larger population, it raises important questions about why adherence would change in so many patients. Many of the factors that have been associated with adherence and non-adherence are non-modifiable e.g. age, sex, socio-economic status. The number of medications[18] and frequency of dosing[19] can change but did not appear to be factors in this case. The health beliefs of patients (and their carers) and their association with medication adherence have become the focus of intense research in recent years and they are considered to have a central role in determining a patient's adherence to medication[20-23]. Therefore, future work must address the relationship between the self-reported adherence and the perceptions and health beliefs of both patients and their carers. Meanwhile, care providers must be aware that adherence to chronic medication is not fixed and that self-reported adherence is a simple tool for routine monitoring.

Conclusions

A seven-item Arabic / English scale for self-reported adherence was developed. The reliability and internal reliability of this scale was well within acceptable limits for an instrument of this kind.

The patient's score on the self-reporting scale correlated with the change in systolic blood pressure, diastolic blood pressure and the change in systolic blood pressure since the start of drug treatment. Those categorized as having high adherence were twice as likely to have reached their target blood pressure than patients who had reported medium or low adherence. At follow-up, changes in self-reported adherence were common and related to changes in blood pressure control.

This self-reporting scale provides a tool for studying medication adherence in Arabic speaking patients within a typical clinical setting. The clinical usefulness of the scale will be determined by comparing the self-reported adherence with that perceived by the prescriber during routine follow-up of hypertensive patients. This together with studies of the health beliefs of Arab hypertensives will help to improve the management of hypertension among this patient group.

Acknowledgements

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Table 44 The final seven items of the Arabic / English Self-reported Medication taking scale (English version) and the Item to Total Correlations

Item 1	Some people have difficulty remembering to take their medicines. Do you ever forget to take a dose of your blood pressure medicine?	0.642
Item 2	People sometimes miss taking their medicines for reasons other than forgetting. Over the past two weeks, were there any days when you did not take your blood pressure medicines?	0.700
Item 3	Have you ever cut back or stopped taking your blood pressure medicines (without telling your doctor) because you felt worse when you took it?	0.687
Item 4	When you travel or leave home, do you sometimes forget to bring along your blood pressure medication?	0.557
Item 5	When you feel like your blood pressure is under control, do you sometimes stop taking, or reduce the dose of your medicine?	0.663
Item 6	Some people find it very inconvenient to take their blood pressure medicine every day. Do you ever feel stressed about having to follow your blood pressure treatment?	0.511
Item 7	How often do you have difficulty remembering to take all your blood pressure medicine?	0.627

Cronbach alpha = 0.76

Table 45 Distribution of the Self-reported Adherence Scale scores and response to antihypertensive therapy (n=203)

Patient' Self reported score	Frequency		At target BP		Adherence n (% total), [% at target BP]	
	n	%	*n*	%		
0	106	52%	55	2%	High 106 (52%), [*52%**]	
1	39	19%	11	28 %	Medium 87 (43%) [*30%**]	Medium to Low 98, (48%) [*28%*]
2	21	10%	4	19 %		
3	12	6%	5	42 %		
4		7%	6	40 %		
5	5	3%	1	20 %	Low 11 (5%), [*10%**]	
6	3	2%	0			
7	2	1%	0			
Total	203		82	40 %		

* p > >0.001, Chi Square = 12.584, 2df

Table 46 Comparison of adherence and blood pressure data between the initial and follow-up studies

Self reported Adherence and the reaching of target BP (No, Yes)		Follow-up data									
		High			Medium			Low			Grand Total
Initial data		No	Yes	Sub Total	No	Yes	Sub Total	No	Yes	Sub Total	
High	No	10	8	*18*	3		*3*	1		*1*	22
	Yes		13	*13*	4	4	*8*		1	*1*	22
Sub total		10	21	*31*	7	4	*11*	1	1	*2*	44
Medium	No	6	5	*11*	14	1	*15*	1		*1*	27
	Yes		6	*6*	2	3	*5*				11
Sub total		6	11	*17*	16	4	*20*	1		*1*	38
Low	No				1	1	*2*		1	*1*	3
	Yes					1	*1*				1
Sub total					1	2	*3*		1	*1*	4
Grand Total		16	32	48	24	10	34	2	2	4	86

References (Annex 8, Paper1)

1. Morisky, D.E., L.W. Green, and D.M. Levine, Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care, 1986. 24(1): p. 67-74.
2. Gao, X. and D.P. Nau, Congruence of three self-report measures of medication adherence among HIV patients. Ann. Pharmacother., 2000. 34(10): p. 1117-22.
3. Pratt, R.J., N. Robinson, H.P. Loveday, C.M. Pellowe, P.J. Franks, M. Hankinset al., Adherence to antiretroviral therapy: appropriate use of self-reporting in clinical practice. HIV Clinical Trials, 2001. 2(2): p. 146-59.
4. Morisky, D.E., C.K. Malotte, P. Choi, P. Davidson, S. Rigler, B. Suglandet al., A patient education program to improve adherence rates with antituberculosis drug regimens. Health Educ. Q., 1990. 17(3): p. 253-67.
5. Val Jimenez, A., G. Amoros Ballestero, P. Martinez Visa, M.L. Fernandez Ferre,

and M. Leon Sanroma, [Descriptive study of patient compliance in pharmacologic antihypertensive treatment and validation of the Morisky and Green test (see comments)]. Aten. Primaria, 1992. 10(5): p. 767-70.

6. Pineiro, C.F., G.V.F. Gil, O.M. Donis, B.D. Orozco, L.R. Pastor, and S.J. Merino, [Validity of 6 indirect methods in the evaluation of compliance to drug treatment of non-insulin dependent diabetes mellitus]. Rev. Clin. Esp., 1997. 197(8): p. 555-9.
7. Pineiro, C.F., G.V.F. Gil, O.M. Donis, B.D. Orozco, M.T. Torres, and S.J. Merino, [The validity of 6 indirect methods for assessing compliance with pharmacological treatment in dyslipidemias]. Aten. Primaria, 1997. 19(9): p. 465-8.
8. Pineiro, C.F., G.V.F. Gil, O.M. Donis, B.D. Orozco, L.R. Pastor, and S.J. Merino, [The validity of 6 indirect methods for assessing drug treatment compliance in arterial hypertension]. Aten. Primaria, 1997. 19(7): p. 372-4, 76.
9. Ramalle-Gomara, E., R. Bermejo-Ascorbe, R. Alonso Marin, I. Marino Alejo, M.I. Saenz de Cabezon Bustinduy, and C. Villaro Amilburu, [Compliance with antibiotic treatment in nonhospitalized children]. Aten. Primaria, 1999. 24(6): p. 364-7.
10. George, C.F., R.C. Peveler, S. Heiliger, and C. Thompson, Compliance with tricyclic antidepressants: the value of four different methods of assessment. Br. J. Clin. Pharmacol., 2000. 50(2): p. 166-71.
11. Patel, R. and S. Taylor, Factors affecting medication adherence in hypertensive patients. Ann. Pharmacother., 2002. 36: p. 40-5.
12. Ward, H.J., D.E. Morisky, N.B. Lees, and R. Fong, A clinic and community-based approach to hypertension control for an underserved minority population: design and methods. Am J Hypertens, 2000. 13(2): p. 177-83.
13. Beevers, G., G.Y. Lip, and E. O_Brien, ABC of hypertension: Blood pressure measurement. Part II-conventional sphygmomanometry: technique of auscultatory blood pressure measurement. BMJ (Clinical Research Ed.), 2001. 322(7293): p. 1043-7.
14. British Hypertension Society, Blood Pressure Measurement - Recommendations of the British Hypertension Society. 3rd ed, ed. O.B.E.e. al. 1997.
15. Joint National Committee on Prevention Detection Evaluation and Treatment of High Blood Pressure, The Sixth Report of the Joint National Committee on

Prevention, Detection, Evaluation and Treatment of High Blood Pressure. Archives of Internal Medicine, 1997. 157: p. 2413-46.

16. Cramer, J.A., R.D. Scheyer, and R. Mattson, Compliance declines between clinic visits. Arch Int Med, 1990. 150(7): p. 1509-10.

17. Morisky, D.E., D.M. Levine, L.W. Green, S. Shapiro, R.P. Russell, and C.R. Smith, Five-year blood pressure control and mortality following health education for hypertensive patients. Am J Public Health, 1983. 73(2): p. 153-62.

18. Shalansky, S.J. and A.R. Levy, Effect of Number of Medications on Cardiovascular Therapy Adherence. Ann. Pharmacother., 2002. 36: p. 1532-9.

19. Claxton, A.J., J. Cramer, and C. Pierce, A systematic review of the associations between dose regimens and medication compliance. Clin. Ther., 2001. 23(8): p. 1296-310.

20. Greenfield, S.F., J. Borkan, and Y. Yodfat, Health beliefs and hypertension: a case-control study in a Moroccan Jewish community in Israel. Cult. Med. Psychiatry, 1987. 11(1): p. 79-95.

21. Horne, R. and J. Weinman, Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J. Psychosom. Res., 1999. 47(6): p. 555-67.

22. Horne, R., J. Clatworthy, A. Polmear, and J. Weinman, Do hypertensive patients' beliefs about their illness and treatment influence medication adherence and quality of life? J Hum Hypertens, 2001. 15 Suppl 1: p. S65-8.

23. Benson, J. and N. Britten, Patients' decisions about whether or not to take antihypertensive drugs: qualitative study. BMJ, 2002. 325: p. 873-7.

Doctor and patient perceptions of adherence to antihypertensive medication

Author details as for the first paper

Abstract

Objective

To determine the doctor's perceptions of adherence to antihypertensive mediation and to compare this with their perceptions of the clinical situation and with the patient's self-reported medication adherence.

Method

In an Arab primary health care setting a 10-item questionnaire was developed to elicit the doctor's perception of adherence (taking >80% of doses) and of the treatment and overall condition. A 7-item self-reported adherence measure was used to determine the adherence to hypertensive medication in 2 health centres. The doctors perceived high adherence in 71% of patients compared with 52% who self-reported high adherence. The doctor identified 75% of reported high adherence and 34% of medium or low adherence. Only 71% of patients assessed as having good response to treatment had reached their JNC VI target blood pressure and 19% assessed as having a poor or partial response had reached the JNC VI target. Higher adherence was more likely to be perceived by the doctor if the doctor also considered that: the patient's treatment was effective; the doctor-patient communication was excellent; the patients knowledge of their hypertension was excellent and if the patient was perceived as having a low five-year cardiovascular risk. Only the cardiovascular risk was related to patient self-reported adherence and this was in the opposite direction.

Conclusion

The practical assessment of adherence and drug management would have been greatly enhanced if the results of the Arabic / English self-reporting measure had been available to the doctors in the course of routine practice In chronic conditions such as hypertension, failure to reach the therapeutic target, e.g. blood pressure, could be due to a sub-optimal drug regime or non-adherence to the prescribed regime. Most doctors are fully aware that up to half of their patients are not adhering to their medication and their ability to identify non-adherence will be a major factor in the effective drug management of hypertension.

In the absence of objective evidence, doctors frequently overestimate the level of their patient's adherence to medication and other treatment [1-4] and there is no published work looking at what factors influence the doctor's perceptions of medication adherence by hypertensive patients, although a dissonance in the views of doctors and patients about the benefits of treatment and risks of hypertension has been reported [5].

Method

A ten-item questionnaire was developed to elicit the doctor's perception of adherence and their perceptions of the patient's treatment and overall condition. The questionnaire was adapted from a published method [45] which was used to compare self-reported adherence and doctor perceptions in outpatients being treated for pulmonary disease. The questionnaire in figure 1 was arrived at through a process of discussion with health center doctors and a pilot study to ensure that the doctors understood each item and the meaning of the possible responses. A seven item Arabic / English self-reported adherence measure based on the Morisky scale [6] was developed locally and has been shown to have good internal reliability and concurrent validity (reported earlier, in press), and this was used to determine the patient's perceptions of their adherence to the hypertensive medication.

The study was performed in two outpatient government health centres in Abu Dhabi, UAE. The Ministry of Health granted ethics approval. The sample included any hypertensive adult who attended the health centre for the routine management of their hypertension, who had been on their current antihypertensive medication for at least three months and who verbally consented to participate.

Upon arrival at the health centre the patient was screened for recruitment by a nurse and invited to participate. A nurse or a pharmacist, depending upon the health centre, read the items to the patient in the patient's preferred language (usually Arabic). The nurse attached a copy of the doctor's questionnaire to the patient's medical record for completion by the doctor after the consultation. The doctor did not see the self-reported adherence report.

Current blood pressure was the average of the last three measurements in the medical record. The standard operating procedures of the health centres adhere to British Hypertension Society (BHS) guidelines for the measurement of blood pressure [7-8]. The target blood pressure was taken from the JNC VI recommendations of not more than 140/90mmHg or not more than 135/85mmHg for diabetics [9]. If both

the systolic or diastolic pressure were at or below these limits the patient was considered to have reached their target blood pressure.

The responses to each item plus an array of blood pressure measurements and demographic data (from the medical record) were entered into a Microsoft Excel 2000 workbook and analysed using Excel or SPSS version 10. The doctor's evaluation was compared with the patient's self-reported adherence and the attainment of target blood pressure.

Results

There were eight doctors involved at the two health centres. Adherence assessments (items 1-4) were available for 200 consultations and responses to all ten items were available for 198 consultations. The doctor's estimate of adherence was compared with the achievement of the target blood pressure (according to JNC VI). The doctor's evaluation of different aspects of the medical situation of each patient was compared with the doctor's adherence estimate and patient self-reported adherence.

The doctors estimated adherence to be high (taking more than 80% of doses) in 141 (71%) of patients compared with 103 (52%) patients who reported high adherence. While the doctor could identify 75% ($^{77}/_{103}$) of high adherence, they identified only 34% of those patients who self-reported medium or low adherence. Of the patients who the doctor estimated to have medium to low adherence, 33 (56%) had reported high adherence. There was no significant relationship between the doctor's evaluation of adherence and the patient's self-reported adherence. In the 59 patients perceived as having medium or low adherence, the most common reason cited was forgetting (20, 34%) or a mixture of all reasons (19, 32%). No reason was proposed for 16 (27%) of cases. Although around half of the doctor's estimates were accurate, the large number of patients who were estimated to have high adherence and the large number whom self-reported medium or low adherence skews the accuracy in real terms. The 141 subjects perceived by their doctor as having high adherence achieved target blood pressure in 63 (45%) of those cases. Of the 59 patients assessed by the doctor as having medium to low adherence, 42 (71%) had not reached target blood pressure.

The doctor was asked to evaluate the effectiveness of the anti-hypertensive treatment, quality of doctor-patient communication, the patient's knowledge of their hypertension and medication, and the seriousness of the medical situation. These evaluations are shown in table 1.

The doctors estimated that 57% of the patients had effective antihypertensive drug treatment and 57% had an excellent understanding of their hypertension and its' treatment. They estimated that 58% of their patients had a low five-year risk of a major cardiovascular event. No more than 8% of patients were evaluated as having a "poor" or "high risk" rating on any of the criteria.

The doctor's assessment of treatment effectiveness was compared with the achieving of the target blood pressure. As shown in table 2, of the 114 patients whose treatment was assessed as being good, 51 (45%) had not reached the target blood pressure recommended by JNC VI. The doctor's assessment of partial and poor effectiveness correlated far better with the JNC VI criteria, although 19% of these ($^{16}/_{(75+9)}$) had reached the JNC VI target.

The doctor was also asked to select one of three reasons for the patient not reaching their target blood pressure (Item 9), non-adherence, non-ideal regime or other reason. Non-adherence was selected as the reason in 34 (41%) and a non-ideal drug regime in 22 (26%). "Other reasons" or no reason was selected for 28 (31%) subjects.

All four estimates of patient related characteristics were significantly correlated with the doctor's estimates of the adherence, Gamma statistic ranging from 0.40-0.42, $p < 0.05$, see table 2. Higher adherence was more likely to be perceived by the doctor if the doctor also considered that: the patient's treatment was effective; the doctor-patient communication was excellent; the patients knowledge of their hypertension was excellent and if the patient was perceived as having a low five-year cardiovascular risk.

However, for all but one characteristic, the doctor's evaluation had no significant correlation with the patient's self-reported adherence. The doctor's assessment of good treatment effectiveness, excellent quality of communication and excellent patient knowledge, was associated with around half of the patients who reported high adherence.

Only the doctor's evaluation of the seriousness of the medical situation showed a significant correlation with the self-reported adherence and this was in the opposite direction (Gamma statistic –0.32, $p<0.05$). The doctor's perceived that those patients with the lower five-year cardiovascular risk would have the higher adherence, while in fact, patients who the doctors perceived as having a high to medium five year cardiovascular risk reported higher adherence.

The doctor was asked to record if they had changed the antihypertensive medication at that consultation (item 10a), and if so, why (item 10b)? This question was

answered for 177 consultations and showed that the regime was changed at 24 (14%) of those consultations, the majority of which were in patients with sub-optimal blood pressure control. Out of the 53 patients with partial or poor control, 18 (34%) had their regime changed. Item 10b was answered for 23 of the 24 instances where the regime was changed. In 20 of these cases, the reason for changing the medication was "to improve control" and 2 cases of changes being due to side effects, or other reasons (1 case) or not stated (1 case).

Discussion

The doctor's ability to distinguish between non-adherence and the need to change the regime is at the heart of successful hypertension management and the identification of non-adherence is the first step towards improving adherence.

The doctor's estimated 71% of the patients to have high adherence, which was far greater than the 52% of patients who reported high adherence. Furthermore, the doctors selected "forgetting" as the most common reason for non-adherence. Current research suggests that unintentional non-adherence is a relatively minor and oversimplified cause of non-adherence to chronic drug regimes and that mistaken health beliefs about the necessity of treatment lie behind non-adherence in chronic disease [10]. In hypertension, research among diverse patient groups suggests that these beliefs are often influenced by a misperception that physical symptoms can indicate when the blood pressure is under control [11-17] or the fear of, or experience of side-effects[18-19].

Failure to reach the JNC VI target for blood pressure control did not appear to be a significant factor influencing their estimate of the adherence. This would appear to be due to the doctor's threshold for "control" tending to be being less rigorous than the JNC VI criteria. Only 45% of those patients considered by the doctor to have "Good" blood pressure control were achieving the JNC VI levels of control, while 81% of those considered to have "Partial to Poor" blood pressure control had not reached JNC VI targets. Therefore, this study highlights that there are clear continuing education needs relating to the blood pressure targets for drug treatment. In most cases, when a doctor estimated there to be a high to increased risk of suffering a serious cardiovascular event, the doctor also reported that these patients had medium to low adherence, which was the complete opposite to what the patient was reporting.

No causal association can be proved from this data, but the overall impression is that the doctor's estimate of adherence is more closely related to their overall sense of well being about a case than objective data, e.g. blood pressure control. There was

a reluctance to assess a patient characteristic as having a particularly adverse rating. This "rosy" view of a case may arise from a lack of rigorous clinical audit and may be compounded by an instinctive reluctance for the Arab expatriate doctors to avoid reporting anything that would make them look less than a successful family physician for risk of there being action taken against them by the employer.

The doctor's estimate of medium to low adherence coincided with 40% of the 84 assessments of "Partial to Poor" treatment effectiveness, 48% of which were attributed by the doctor to non-adherence. While 52% of patients in this group self-reported medium to low adherence, this similarity to the doctor's figure was a coincidence as the doctor's evaluation of non-adherence (medium to low) agreed with the self-reported adherence only 34% of the time.

These results are remarkably similar to those reported in the paper from which the doctor's questionnaire was reported [3]. In that study 138 pulmonary disease patients were studied at an outpatient health centre and the doctors over estimated adherence and also associated a less serious condition, effective treatment, excellent quality of communication and excellent knowledge to high adherence. They were also wrong about the effect of a serious condition upon adherence. In the Goldberg study those patients with the worst prognosis reported higher adherence.

The UAE study design did not provide a way of validating the doctor's perceptions of factors other than adherence and blood pressure control. It would have been interesting to compare the doctor's estimates of the patient related characteristics with the patient's perceptions of quality of communication and their own knowledge. It may well be that, like adherence, the doctor's perception of these factors were at variance with the patient's perceptions. A qualitative study of patient-doctor communication at hypertension consultations in Sweden reported that doctors and patients often have very different discussion priorities with the doctor focussing on the medication and the patient wishing to talk about their experience of taking the drug [20]. Miscommunication may be the main factor behind the lack of association between doctor perceptions and other patient outcomes.

The patient's risk of suffering a major cardiovascular event depends upon a range of cardiovascular risks, of which blood pressure is only one. If more clinical data had been recorded, especially blood lipid data, then the cardiovascular risk could have been estimated post hoc using one of the available tools such as the Framingham risk equations [21], Dundee Coronary Risk equation [22] or the PROCAM risk equation [23]. This could then have been used to validate the doctor's estimates of disease risk. However, lipid-screening data was not routinely available and the validity of these

equations in a Gulf Arab or sub-continental population has not been demonstrated. Furthermore, the doctors were asked to estimate the absolute risk over the next five years (five years was chosen after discussion with the doctors at the first health centre as a more practical, medium term time frame). Validation would have required careful re-wording of the item as some tools provide an estimate of risk over a 10-year period (e.g. Framingham) or their relative risk (e.g. Dundee Coronary Risk equation) or would not have been validated for use in women (e.g. PROCAM risk equation or the British regional Heart Study Risk equation).

Failure to identify non-adherence will make it difficult for the doctor to distinguish between the need for a regimen / dose change and the need for a review of the patient's motivations and beliefs relating to the drug therapy. An easy to use self-reporting measure would have greatly improved the doctor's assessment of adherence. Consequently, many regime changes will be made in patients who already have poor adherence and the change is unlikely to improve blood pressure control.

Conclusion

The doctors consistently exaggerated the level of adherence and also over estimated the quality of blood pressure control compared with JNC VI criteria. The doctors' estimates of adherence were related to their perceptions of treatment effectiveness, quality of communication, patient knowledge and the seriousness of the condition. These did not relate with the patients self reported adherence. The doctors estimated adherence to be low in most patients who they perceived as having a more serious condition, whereas those patients reported relatively high levels of adherence. The practical assessment of adherence and drug management would have been greatly enhanced if the results of the Arabic / English self-reporting measure had been available to the doctors in the course of routine practice.

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Figure 47 Doctor's questionnaire

1. Please give your estimate of this patient's adherence to their blood pressure medication

High adherence	Takes more than 80% of the doses as prescribed	☐	*tick one*
Medium Adherence	Takes between 60 and 80% of the doses as prescribed	☐	
Low Adherence	Takes less than 60% of doses as prescribed	☐	

2. Do you think that this patient ever forgets to take a dose of their blood pressure drugs? ☐ Yes ☐ No

3. Do you think that this patient sometimes stops taking or reduces the dose of their blood pressure drugs because they feel better or because they feel that their blood pressure is under control? ☐ Yes ☐ No

4. Do you think that this patient sometimes stops taking or reduces the dose of their blood pressure drugs because they feel worse, e.g. due to side effects? ☐ Yes ☐ No

Figure 1 continued

5. How would you describe the effectiveness of this patient's current antihypertensive medication? (tick one box)

☐ Good -Patient has reached their target BP ☐ Partial - Some reduction in the BP since starting but not enough ☐ Poor - No improvement in the BP since starting this regime

6. How do you rate the communication and openness between you and this patient? (tick one box)

☐ Excellent ☐ OK ☐ Poor

7. How do you rate this patient's knowledge of their hypertension and of their BP medication? (tick one box)

☐ Excellent ☐ OK ☐ Poor

8. After considering the patient's age and sex, how do you rate this patient's risk of suffering a major cardiovascular event in the next 5 years? (tick one box)

☐ Unlikely ☐ Increased risk ☐ Greatly increased risk

9. If the patient's BP is NOT controlled, what do you think is the main reason? (tick one box)

☐ Non-adherence ☐ Non-ideal drug regime ☐ Other reason e.g. worsening pathology

10. a) Have you changed the blood pressure regime today? (tick one box) ☐ Yes ☐ No

10. b) If "Yes", why? (tick one box) ☐ To improve control ☐ Because of side effects ☐ Other reason

Table 47 Doctor's evaluation of four patient-related characteristics

Doctor's evaluation (198 patients)			
Effectiveness of anti-hypertensive treatment	Good 114 (57%)	Partial 75 (38%)	Poor 9 (5%)
Quality of communication	Excellent 114 (57%)	OK 72 (36%)	Poor 12 (6%)
Patient knowledge	Excellent 75 (37.5%)	OK 107 (54%)	Poor 16 (8%)
Seriousness of condition (5 year risk of major CV event)	High risk 11 (6%)	Increased risk 71 (36%)	Low risk 116 (58%)

Table 48 Relation of Doctor's assessment of treatment effectiveness with the achieving of target blood pressure (n=198)

		Doctor's estimate of treatment effectiveness			
		Good[1]	Partial[2]	Poor[3]	Total
Achieved target blood pressure?	Yes	63 (55%)	16 (19%)	0	79
	No	51 (45%)	59 (81%)	9	119
		114	75	9	198

[1] Patient has reached their target blood pressure

[2] Some reduction in the blood pressure since starting but not enough

[3] No improvement in the blood pressure since starting this regime

Table 49 Relation of the doctor's evaluation of the medical situation to the doctor's evaluation of adherence and the self-reported adherence

	Doctor's		Patient Self report	
Doctor's evaluation (n=198)	% High adherence	Gamma	% High adherence	Gamma
Adherence				
High	71		55	
			43	0.21
Effectiveness of treatment				
Good (114)	79		54	
Partial-Poor (84)	60	0.42*	48	0.14
Quality of communication				
Excellent (114)	78		51	
OK-Poor (84)	61	0.40*	52	-0.03
Patient knowledge				
Excellent (75)	81		51	
OK-Poor (123)	64	0.42*	52	-0.03
Seriousness of medical situation				
Low CV risk (116)	77		45	
High-Increased CV risk (82)	58	0.42*	61	-0.32*

* = $p < 0.05$

References (Annex 8 – Paper 2)

1. Al Mushlin, Appel FA. Diagnosing potential noncompliance. Physicians' ability in a behavioral dimension of medical care. Arch Int Med 1977;137(3):318-321.
2. JR Gilbert, Evans CE, Haynes RB, Tugwell P. Predicting compliance with a regimen of digoxin therapy in family practice. Can Med Assoc J 1980;123(2):119-22.
3. Al Goldberg, Cohen G, Rubin AH. Physician assessments of patient compliance with medical treatment. Soc Sci Med 1998;47(11):1873-6.

4. RH Feierabend. Physician ability to predict appointment-keeping behavior of prenatal patients. J Fam Pract 1996;42(5):482-6.

5. KI Kjellgren, Ahlner J, Dahlof B, Gill H, Hedner T, Saljo R. Patients' and physicians' assessment of risks associated with hypertension and benefits from treatment. J Cardiovasc Risk 1998;5(3):161-6.

6. DE Morisky, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care 1986;24(1):67-74.

7. G Beevers, Lip GY, O_Brien E. ABC of hypertension: Blood pressure measurement. Part II-conventional sphygmomanometry: technique of auscultatory blood pressure measurement. BMJ (Clinical Research Ed) 2001;322(7293):1043-7.

8. British Hypertension Society. Blood Pressure Measurement - Recommendations of the British Hypertension Society. 3rd ed, 1997.

9. Joint National Committee on Prevention Detection Evaluation and Treatment of High Blood Pressure. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. Archives of Internal Medicine 1997;157:2413-46.

10. R Horne, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J Psychosom Res 1999;47(6):555-67.

11. D Meyer, Leventhal H, Gutmann M. Common-sense models of illness: the example of hypertension. Health Psychol 1985;4(2):115-35.

12. LJ Baumann, Leventhal H. "I can tell when my blood pressure is up, can't I?". Health Psychol 1985;4(3):203-18.

13. CM Sharkness, Snow DA. The patient's view of hypertension and compliance. Am J Prev Med 1992;8(3):141-6.

14. M Morgan, Watkins C. Managing hypertension: beliefs and responses to medication among cultural groups. Social Health and Illness 1988;10:561-78.

15. SA Khalil, Elzubier AG. Drug compliance among hypertensive patients in Tabuk, Saudi Arabia. J Hypertens 1997;15(5):561-5.

16. J Curb, Borhani NO, Blaszkowski T, Zimbaldi N, Foitu S, Williams W. Patient-perceived side effects to antihypertensive drugs. Am J Prev Med 1985;1:36-40.

17. H Guo, He H, Jiang J. [Study on the compliance of antihypertensive drugs in patients with hypertension]. Zhonghua Liu Xing Bing Xue Za Zhi 2001;22(6):418-20.

18. H Enlund, Jokisalo E, Wallenius S, Korhonen M. Patient-perceived problems, compliance, and the outcome of hypertension treatment. Pharm World Sci 2001;23(2):60-4.

19. S Svensson, Kjellgren KI, Ahlner J, Saljo R. Reasons for adherence with antihypertensive medication. Int J Cardiol 2000;76(2-3):157-63.

20. KI Kjellgren, Svensson S, Ahlner J, Saljo R. Antihypertensive medication in clinical encounters. Int J Cardiol 1998;64(2):161-9.

21. P Wilson, D'Agostino R, Levy D, Belanger A, Silbershatz H, Kannel WB.

Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837-47.

22. H Tunstall-Pedoe. The Dundee coronary risk-disk for management of change in risk factors. BMJ 1991;303:744-7.

23. I Haq, Ramsay L, Yeo WW, Jackson P, Wallis E. Is the Framingham risk function valid for northern European populations? A comparison of methods for estimating absolute coronary risk in high risk men. Heart 1999;81:40-6.

Bibliography

1. Royal Pharmaceutical Society of Great Britain. From Compliance to Concordance. Achieving shared goals in medicine taking. London: Royal Pharmaceutical Society of Great Britain, 1997.
2. Blackwell B. Treatment adherence: a contemporary viewpoint. *Psychosematics* 1979;20:27-35.
3. Stimson G. Obeying the doctor's orders: a view from the other side. *Social Science and Medicine* 1974;8:97-104.
4. Sackett D, Snow J. The magnitude of compliance and non-compliance. In: Haynes R, Taylor D, Sackett D, editors. *Compliance in Healthcare*. 2nd ed. Baltimore: Johns Hopkins University Press, 1981:11-22.
5. Gordis L. Methodologic issues in the measurement of patient compliance. In: Sackett DL HR, editor. *Compliance with therapeutic regimens*. Baltimore & London: Johns Hopkins University Press, 1976:51-66.
6. McGavock H, Britten N, Weinman J. A Review of the Literature on Drug Adherence. Belfast: Queen's University, 1996.
7. Kruse W. Compliance with treatment of hyperlipoproteinaemia in medical practice and clinical trials. In: Cramer JA SB, editor. *Patient compliance in medical practice and clinical trials*. New York: Raven Press, 1991:175-86.
8. Rudd P, Ahmed S, Zachary V, et al. Issues in patient compliance: the search for therapeutic sufficiency. *Cardiology* 1992;80(Suppl 1):2-10.
9. Waeber B, Brunner H, Metry J. Compliance with Antihypertensive Treatment: Implications for Practice. *Blood Pressure* 1997;6:326-331.
10. Weintraub M. Compliance in the elderly. *Clinics in Geriatric Medicine* 1990;6:445-452.
11. Cooper J, Love D, Raffoul P. Intentional prescription non-adherence (non-compliance) in the elderly. *Journal of the American Geriatric Society* 1982;30:329-33.
12. Beardon PH, McGilchrist MM, McKendrick AD, McDevitt DG, MacDonald TM. Primary non-compliance with prescribed medication in primary care. *British Medical Journal* 1993;307(6908):846-8.
13. Jones I, Britten N. Why do some patients not cash their prescriptions? *British Journal of General Practice* 1998;48(426):903-5.
14. American Association of Retired Persons. Prescription drugs: a survey of consumer use, attitudes and behavior. Washington DC: American Association of Retired Persons, 1984.
15. Market Facts Inc. National Prescription Buyers' Survey. Kalamazoo, Michigan: The Upjohn Company, 1985.
16. Schering L. The forgetful patient: the high cost of improper patient compliance. Schering Report IX. Kenilworth, New Jersey: Schering Laboratories, 1987.
17. Ahluwalia J, McNagny S, Kanuru N. A randomized trial to improve follow-up care in severe uncontrolled hypertensives at an inner-city walk-in clinic. *Journal of Health Care for the Poor & Undeserved* 1996;7(4):377-89.
18. Horne R. One to Be Taken as Directed: Reflections on Non-adherence (Non-compliance). *Journal of Social and Administrative Pharmacy* 1993;10(4):150-156.
19. Donovan JL, Blake DR. Patient non-compliance: deviance or reasoned decision-making? *Social Science and Medicine* 1992;34(5):507-13.
20. Conrad P. The meaning of medications: another look at compliance. *Social Science and Medicine* 1985;20(1):29-37.
21. Horne R. Representations of medication and treatment: Advances in theory and measurement. In: Petrie KJ, Weinman J, editors. *Perceptions of health and illness: current research and applications*: Harwood Academic Publishers, 1997:155-188.
22. Arluke A. Judging drugs: patients' conceptions of therapeutic efficacy in the treatment of arthritis. *Human Organisation* 1980;39:84-8.
23. Enlund H, Jokisalo E, Wallenius S, Korhonen M. Patient-perceived problems, compliance, and the outcome of hypertension treatment. *Pharmacy World and Science* 2001;23(2):60-4.
24. Verbeek-Heida P. Patient's views on doctor's prescriptions: management of illness episodes involving antibiotic prescriptions in daily life. [PhD]. University of Amsterdam, 1992.

25. New S, Senior M. I"I don't believe in needles": qualitative aspects of a study into the uptake of infant immunisation in two English Health Authorities. *Social Sciences in Medicine* 1991;33:509-18.
26. Rogers A, Pilgrim D. Rational non-compliance with childhood immunisation: personal accounts of parents and primary health care professionals. *Uptake of immunisation: issues for health educators*. London: Health Education Authority, 1994.
27. Gabe J, Lipshitz-Phillips S. Evil necessity? The meaning of benzodiazepine use for women patients from one general practice. *Social Health and Illness* 1982;4:201-23.
28. Gabe J, Thorogood N. Prescribed drug use and the management of everyday life: the experiences of black and white working-class women. *Social Reviews* 1986;34:737-72.
29. Morgan M, Watkins C. Managing hypertension: beliefs and responses to medication among cultural groups. *Social Health and Illness* 1988;10:561-78.
30. Britten N. Patients' ideas about medicines: a qualitative study in a general practice population. *British Journal of General Practice* 1994;44(387):465-8.
31. Calnan M. Lay evaluation of medicine and medical practice: report of a pilot study. *International Journal of Health Services* 1988;18(2):311-22.
32. WOSCOPS Group. Compliance and adverse event withdrawal: their impact on the West of Scotland Coronary Prevention Study. *European Heart Journal* 1997;18(11):1718-24.
33. Morgan M. Beliefs and responses to hypertension: patients' and practitioners' perspectives [PhD thesis]. University of London, 1993.
34. Morgan M. The significance of ethicity for health promotion: patient's use of anti-hypertensive drugs in inner London. *International Journal of Epidemiology* 1995;24(suppl 1):S79-84.
35. Horne R, Clatworthy J, Polmear A, Weinman J. Do hypertensive patients' beliefs about their illness and treatment influence medication adherence and quality of life? *Journal of Human Hypertension* 2001;15 Suppl 1:S65-8.
36. Svensson S, Kjellgren KI, Ahlner J, Saljo R. Reasons for adherence with antihypertensive medication. *International Journal of Cardiology* 2000;76(2-3):157-63.
37. Benson J, Britten N. Patients' decisions about whether or not to take antihypertensive drugs: qualitative study. *British Medical Journal* 2002;325:873-7.
38. Sackett DL, Haynes RB, Gibson ES, Hackett BC, Taylor DW, Roberts RS, et al. Randomised clinical trial of strategies for improving medication compliance in primary hypertension. *Lancet* 1975;1(7918):1205-7.
39. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Medical Care* 1986;24(1):67-74.
40. Pineiro CF, Gil GVF, Donis OM, Orozco BD, Pastor LR, Merino SJ. [The validity of 6 indirect methods for assessing drug treatment compliance in arterial hypertension]. *Atencion Primaria* 1997;19(7):372-4, 376.
41. Pineiro CF, Gil GVF, Donis OM, Orozco BD, Pastor LR, Merino SJ. [Validity of 6 indirect methods in the evaluation of compliance to drug treatment of non-insulin dependent diabetes mellitus]. *Revista Clinica Espanola* 1997;197(8):555-9.
42. Pineiro CF, Gil GVF, Donis OM, Orozco BD, Torres MT, Merino SJ. [The validity of 6 indirect methods for assessing compliance with pharmacological treatment in dyslipidemias]. *Atencion Primaria* 1997;19(9):465-8.
43. Gilbert JR, Evans CE, Haynes RB, Tugwell P. Predicting compliance with a regimen of digoxin therapy in family practice. *Canadian Medical Association Journal* 1980;123(2):119-22.
44. Maenpaa H, Manninen V, Heinonen OP. Compliance with medication in the Helsinki Heart Study. *European Journal of Clinical Pharmacology* 1992;42(1):15-9.
45. Goldberg AI, Cohen G, Rubin AH. Physician assessments of patient compliance with medical treatment. *Social Science and Medicine* 1998;47(11):1873-6.
46. Engelland AL, Alderman MH, Powell HB. Blood pressure control in private practice: a case report. *American Journal of Public Health* 1979;69(1):25-9.
47. Gillum RF, Neutra RR, Stason WB, Solomon HS. Determinants of dropout rate among hypertensive patients in an urban clinic. *Journal of Community Health* 1979;5(2):94-100.
48. Degoulet P, Menard J, Vu HA, Golmard JL, Devries C, Chatellier G, et al. Factors predictive of attendance at clinic and blood pressure control in hypertensive patients. *British Medical Journal (Clinical Research Ed.)* 1983;287(6385):88-93.

49. Pullar T, Kumar S, Tindall H, Feely M. Time to stop counting tablets? *Clinical Pharmacology and Therapeutics* 1989;46:163-8.
50. Rudd P, Byyny RL, Zachary V, LoVerde ME, Mitchell WD, Titus C, et al. Pill count measures of compliance in a drug trial: variability and suitability. *American Journal of Hypertension* 1988;1(3 Pt 1):309-12.
51. Roth HP, Caron HS, Hsi BP. Measuring intake of a prescribed medication. A bottle count and a tracer technique compared. *Clinical Pharmacology and Therapeutics* 1970;11(2):228-37.
52. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. *Journal of the American Medical Association* 1989;261(22):3273-7.
53. George CF, Peveler RC, Heiliger S, Thompson C. Compliance with tricyclic antidepressants: the value of four different methods of assessment. *British Journal of Clinical Pharmacology* 2000;50(2):166-71.
54. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344(8934):1383-9.
55. Inui TS, Carter WB, Pecoraro RE, Pearlman RA, Dohan JJ. Variations in patient compliance with common long-term drugs. *Medical Care* 1980;18(10):986-93.
56. Raynor D, Nicolson M, Nunney J, Petty D, Vail A, Davies L. The development and evaluation of an extended adherence support programme by community pharmacists for elderly patients at home. *International Journal of Pharmacy Practice* 2000;8:157-64.
57. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *Journal of Clinical Epidemiology* 1997;50(1):105-16.
58. Wannemacher AJ, Schepers GP, Townsend KA. Antihypertensive Medication Compliance in a Veterans Affairs Healthcare System. *Annals of Pharmacotherapy* 2002;36:986-91.
59. Urquhart J, de Klerk E. Contending paradigms for the interpretation of data on patient compliance with therapeutic drug regimens. *Statistics in Medicine* 1998;17(3):251-67; discussion 387-9.
60. Raynor D. Patient compliance: the pharmacist's role. *International Journal of Pharmacy Practice* 1992;1:126-135.
61. Wendel CS, Mohler MJ, Kroesen K, Ampel NM, Gifford AL, Coons SJ. Barriers to use of electronic adherence monitoring in an HIV clinic. *Annals of Pharmacotherapy* 2001;35(9):1010-5.
62. Haynes RB, Taylor DW, Sackett DL, Gibson ES, Bernholz CD, Mukherjee J. Can simple clinical measurements detect patient noncompliance? *Hypertension* 1980;2(6):757-64.
63. Urquhart J. Role of patient compliance in clinical pharmacokinetics. A review of recent research. *Clinical Pharmacokinetics* 1994;27(3):202-15.
64. Bignell CJ, Mulcahy FM, Peaker S, Pullar T, Feely MP. Measuring treatment compliance of men with non-gonococcal urethritis receiving oxytetracycline combined with low dose phenobarbitone. *Genitourinary Medicine* 1988;64(5):312-5.
65. Wolff K, Hay AA, Raistrick D, Feely M. Use of 'very low-dose phenobarbital' to investigate compliance in patients on reducing doses of methadone (detoxification). *Journal of Substance Abuse Treatment* 1993;10(5):453-8.
66. Wolff K, Hay A, Raistrick D, Calvert R, Feely M. Measuring compliance in methadone maintenance patients: use of a pharmacologic indicator to "estimate" methadone plasma levels. *Clinical Pharmacology and Therapeutics* 1991;50(2):199-207.
67. Maenpaa H, Manninen V, Heinonen OP. Comparison of the digoxin marker with capsule counting and compliance questionnaire methods for measuring compliance to medication in a clinical trial. *European Heart Journal* 1987;8 Suppl I:39-43.
68. Karbwang J, Fungladda W, Pickard CE, Shires S, Hay A, Feely M. Initial evaluation of low-dose phenobarbital as an indicator of compliance with antimalarial drug treatment. *Bulletin of the World Health Organization* 1998;76 Suppl 1:67-73.
69. Anon. Patient compliance in therapeutic trials. *Lancet* 1991;337(8745):823-4.
70. King JB. The impact of patients perceptions of high blood pressure on attendance at screening: an attributional extension of the health belief model. *Social Science and Medicine* 1982;16:1079-91.
71. Miaskowski C, Dodd MJ, West C, Paul SM, Tripathy D, Koo P, et al. Lack of adherence with the analgesic regimen: a significant barrier to effective cancer pain management. *Journal of Clinical Oncology* 2001;19(23):4275-9.

72. Meyer D, Leventhal H, Gutmann M. Common-sense models of illness: the example of hypertension. *Health Psychology* 1985;4(2):115-35.
73. Vaur L, Vaisse B, Genes N, Elkik F, Legrand C, Poggi L. Use of electronic pill boxes to assess risk of poor treatment compliance: results of a large-scale trial. *American Journal of Hypertension* 1999;12(4 Pt 1):374-80.
74. Shulman N, Cutter G, Daugherty R, Sexton M, Pauk G, Taylor MJ, et al. Correlates of attendance and compliance in the hypertension detection and follow-up program. *Controlled Clinical Trials* 1982;3(1):13-27.
75. Black DM, Brand RJ, Greenlick M, Hughes G, Smith J. Compliance to treatment for hypertension in elderly patients: the SHEP pilot study. Systolic Hypertension in the Elderly Program. *Journal of Gerontology* 1987;42(5):552-7.
76. Sherbourne CD, Hays RD, Ordway L, DiMatteo MR, Kravitz RL. Antecedents of adherence to medical recommendations: results from the Medical Outcomes Study. *Journal of Behavioral Medicine* 1992;15(5):447-68.
77. Richardson MA, Simons-Morton B, Annegers JF. Effect of perceived barriers on compliance with antihypertensive medication. *Health Education Quarterly* 1993;20(4):489-503.
78. Morrell RW, Park DC, Kidder DP, Martin M. Adherence to antihypertensive medications across the life span. *Gerontologist* 1997;37(5):609-19.
79. Pineiro Chousa F, Gil Guillen VF, Pastor Lopez R, Merino Sanchez J. [Non-compliance with scheduled appointments in hypertensive patients: profile of the non-compliant patient]. *Revista Clinica Espanola* 1998;198(10):669-72.
80. Coons SJ, Sheahan SL, Martin SS, Hendricks J, Robbins CA, Johnson JA. Predictors of medication noncompliance in a sample of older adults. *Clinical Therapeutics* 1994;16(1):110-7.
81. Joshi PP, Salkar RG, Heller RF. Determinants of poor blood pressure control in urban hypertensives of central India. *Journal of Human Hypertension* 1996;10(5):299-303.
82. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Archives of Internal Medicine* 2000;160(14):2101-7.
83. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clinical Therapeutics* 2001;23(8):1296-310.
84. Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR. The effect of prescribed daily dose frequency on patient medication compliance. *Archives of Internal Medicine* 1990;150(9):1881-4.
85. Eisen SA, Woodward RS, Miller D, Spitznagel E, Windham CA. The effect of medication compliance on the control of hypertension. *Journal of General Internal Medicine* 1987;2(5):298-305.
86. Bloom BS. Continuation of initial antihypertensive medication after 1 year of therapy. *Clinical Therapeutics* 1998;20(4):671-81.
87. Murphy DA, Rotheram_Borus MJ, Joshi V. HIV-infected adolescent and adult perceptions of tuberculosis testing, knowledge and medication adherence in the USA. *Aids Care* 2000;12(1):59-63.
88. Monane M, Bohn RL, Gurwitz JH, Glynn RJ, Avorn J. Noncompliance with congestive heart failure therapy in the elderly. *Archives of Internal Medicine* 1994;154(4):433-7.
89. Billups SJ, Malone DC, Carter BL. The relationship between drug therapy noncompliance and patient characteristics, health-related quality of life, and health care costs. *Pharmacotherapy* 2000;20(8):941-9.
90. Shalansky SJ, Levy AR. Effect of Number of Medications on Cardiovascular Therapy Adherence. *Annals of Pharmacotherapy* 2002;36:1532-9.
91. DiMatteo MR, Sherbourne CD, Hays RD, Ordway L, Kravitz RL, McGlynn EA, et al. Physicians' characteristics influence patients' adherence to medical treatment: results from the Medical Outcomes Study. *Health Psychology* 1993;12(2):93-102.
92. Dunbar-Jacob J, Dwyer K, Dunning EJ. Compliance with anti-hypertensive regimen: a review of the research in the 1980's. *Annals of Behavioral Medicine* 1991;13(1):31-39.
93. Stanton AL. Determinants of adherence to medical regimens by hypertensive patients. *Journal of Behavioral Medicine* 1987;10(4):377-94.
94. McElnay JC, McCallion CR, al-Deagi F, Scott M. Self-reported medication non-compliance in the elderly. *European Journal of Clinical Pharmacology* 1997;53(3-4):171-8.

95. Cochran SD, Gitlin MJ. Attitudinal correlates of lithium compliance in bipolar affective disorders. *Journal of Nervous and Mental Disease* 1988;176(8):457-64.
96. Meryn S. Improving doctor-patient communication. *British Medical Journal* 1998;316(27 June):1922.
97. Donovan JL. Patient decision making. The missing ingredient in compliance research. *International Journal of Technology Assessment in Health Care* 1995;11(3):443-55.
98. Simpson M, Buckman R, Stewart M, Maguire P, Lipkin M, Novack D, et al. Doctor-patient communication: the Toronto consensus statement. *British Medical Journal* 1991;303(6814):1385-7.
99. Stewart MA. Effective physician-patient communication and health outcomes: a review. *Canadian Medical Association Journal* 1995;152(9):1423-33.
100. Hays RD, Kravitz RL, Mazel RM, Sherbourne CD, DiMatteo MR, Rogers WH, et al. The impact of patient adherence on health outcomes for patients with chronic disease in the Medical Outcomes Study. *Journal of Behavioral Medicine* 1994;17(4):347-60.
101. Ley P. *Communicating with patients: improving communication, satisfaction and compliance.* London: Croom Helm, 1988.
102. Lewis FM, Morisky DE, Flynn BS. A test of the construct validity of health locus of control: effects on self-reported compliance for hypertensive patients. *Health Education Monographs* 1978;6(2):138-48.
103. Kendrick R, Bayne JR. Compliance with prescribed medication by elderly patients. *Canadian Medical Association Journal* 1982;127(10):961-2.
104. Larrat EP, Taubman AH, Willey C. Compliance-related problems in the ambulatory population. *American Pharmacy* 1990;NS30(2):18-23.
105. Pullar T, Birtwell AJ, Wiles PG, Hay A, Feely MP. Use of a pharmacologic indicator to compare compliance with tablets prescribed to be taken once, twice, or three times daily. *Clinical Pharmacology and Therapeutics* 1988;44(5):540-5.
106. Kruse W, Rampmaier J, Ullrich G, Weber E. Patterns of drug compliance with medications to be taken once and twice daily assessed by continuous electronic monitoring in primary care. *International Journal of Clinical Pharmacology and Therapeutics* 1994;32(9):452-7.
107. Brun J. Patient compliance with once-daily and twice-daily oral formulations of 5-isosorbide mononitrate: a comparative study. *Journal of International Medical Research* 1994;22(5):266-72.
108. Leenen FH, Wilson TW, Bolli P, Larochelle P, Myers M, Handa SP, et al. Patterns of compliance with once versus twice daily antihypertensive drug therapy in primary care: a randomized clinical trial using electronic monitoring. *Canadian Journal of Cardiology* 1997;13(10):914-20.
109. Caro JJ, Speckman JL, Salas M, Raggio G, Jackson JD. Effect of initial drug choice on persistence with antihypertensive therapy: the importance of actual practice data. *Canadian Medical Association Journal* 1999;160(1):41-6.
110. Kaplan SH, Greenfield S, Ware JE. Assessing the effects of physician-patient interactions on the outcomes of chronic disease. *Medical Care* 1989;27(3 Suppl):S110-27.
111. McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. *Journal of the American Medical Association* 2002;288(22):2868-79.
112. Hoel D, Howard R. Hypertension, Stalking the silent killer. *Postgraduate Medicine* 1997;101(Feb).
113. WHO/ISH. 1993 Guidelines for the management of mild hypertension: memorandum from a WHO/ISH meeting. *Bulletin of the World Health Organization* 1993;71:503-517.
114. Joint National Committee on Detection E, and Treatment of High Blood Pressure. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Archives of Internal Medicine* 1993;153:154-183.
115. Joint National Committee on Prevention D, Evaluation and Treatment of High Blood Pressure,. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Archives of Internal Medicine* 1997;157:2413-46.
116. WHO-ISH. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee. *Journal of Hypertension* 1999;17(2):151-83.

117. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998;351(9118):1755-62.
118. Kannel W, Dawber T, McGee D. Perspectives on systolic hypertension: the Framingham Study. *Circulation* 1986;61:1179-1182.
119. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. *Archives of Internal Medicine* 1993;153(5):598-615.
120. Izzo JL, Levy D, Black HR. Clinical Advisory Statement. Importance of systolic blood pressure in older Americans. *Hypertension* 2000;35(5):1021-4.
121. Psaty BM, Furberg CD, Kuller LH, Cushman M, Savage PJ, Levine D, et al. Association between blood pressure level and the risk of myocardial infarction, stroke, and total mortality: the cardiovascular health study. *Archives of Internal Medicine* 2001;161(9):1183-92.
122. Benetos A, Thomas F, Bean K, Gautier S, Smulyan H, Guize L. Prognostic value of systolic and diastolic blood pressure in treated hypertensive men. *Archives of Internal Medicine* 2002;162(5):577-81.
123. Port S, Demer L, Jennrich R, Walter D, Garfinkel A. Systolic blood pressure and mortality. *Lancet* 2000;355(9199):175-80.
124. Pickering TG, James GD, Boddie C, Harshfield GA, Blank S, Laragh JH. How common is white coat hypertension? *Journal of the American Medical Association* 1988;259(2):225-8.
125. Mancia G, Zanchetti A. White-coat hypertension: misnomers, misconceptions and misunderstandings. What should we do next? *Journal Of Hypertension* 1996;14(9):1049-52.
126. Lerman CE, Brody DS, Hui T, Lazaro C, Smith DG, Blum MJ. The white-coat hypertension response: prevalence and predictors. *Journal of General Internal Medicine* 1989;4(3):226-31.
127. Siegel WC, Blumenthal JA, Divine GW. Physiological, psychological, and behavioral factors and white coat hypertension. *Hypertension* 1990;16(2):140-6.
128. Mancia G, Parati G, Pomidossi G, Grassi G, Casadei R, Zanchetti A. Alerting reaction and rise in blood pressure during measurement by physician and nurse. *Hypertension* 1987;9(2):209-15.
129. Mancia G, Sega R, Milesi C, Cesana G, Zanchetti A. Blood-pressure control in the hypertensive population. *Lancet* 1997;349(9050):454-7.
130. American Heart Association. 1999 Heart and Stroke A to Z Guide. Dallas TX, 1999.
131. Gillum RF. Stroke mortality in blacks. Disturbing trends. *Stroke* 1999;30(8):1711-5.
132. Alwan A. Noncommunicable diseases: a major challenge to public health in the Region. *Eastern Mediterranean Health Journal* 1997;3(1):6-16.
133. Dipiro J, Talbert R, Yee G, editors. *Pharmacotherapy : A Pathophysiologic Approach*. 3rd Edition ed: McGraw-Hill Professional Publishing, 1998.
134. Beevers G, Lip GY, O'Brien E. *ABC of Hypertension*. 4th Edition ed: BMJ Books, 2001.
135. Beevers G, Lip GY, O_Brien E. ABC of hypertension: The pathophysiology of hypertension. *BMJ (Clinical Research Ed.)* 2001;322:912-916.
136. Intersalt Cooperative Research Group. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. *BMJ (Clinical Research Ed.)* 1988;297(6644):319-28.
137. Elliott P, Stamler J, Nichols R, Dyer AR, Stamler R, Kesteloot H, et al. Intersalt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. Intersalt Cooperative Research Group. *British Medical Journal (Clinical Research Ed.)* 1996;312(7041):1249-53.
138. Cutler JA, Follmann D, Allender PS. Randomized trials of sodium reduction: an overview. *American Journal of Clinical Nutrition* 1997;65(2 Suppl):643S-651S.
139. Midgley JP, Matthew AG, Greenwood CM, Logan AG. Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomized controlled trials. *Journal of the American Medical Association* 1996;275(20):1590-7.
140. Cappuccio FP, Elliott P, Allender PS, Pryer J, Follman DA, Cutler JA. Epidemiologic association between dietary calcium intake and blood pressure: a meta-analysis of published data. *American Journal of Epidemiology* 1995;142(9):935-45.

141. Whelton PK, Kumanyika SK, Cook NR, Cutler JA, Borhani NO, Hennekens CH, et al. Efficacy of nonpharmacologic interventions in adults with high-normal blood pressure: results from phase 1 of the Trials of Hypertension Prevention. Trials of Hypertension Prevention Collaborative Research Group. *American Journal of Clinical Nutrition* 1997;65(2 Suppl):652S-660S.
142. Whelton PK, He J, Cutler JA, Brancati FL, Appel LJ, Follmann D, et al. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. *Journal of the American Medical Association* 1997;277(20):1624-32.
143. Stamler J, Caggiula AW, Grandits GA. Relation of body mass and alcohol, nutrient, fiber, and caffeine intakes to blood pressure in the special intervention and usual care groups in the Multiple Risk Factor Intervention Trial. *American Journal of Clinical Nutrition* 1997;65(1 Suppl):338S-365S.
144. Pravenec M, Wallace C, Aitman TJ, Kurtz TW. Gene Expression Profiling in Hypertension Research: A Critical Perspective. *Hypertension* 2003;41(1):3-8.
145. Bonita R. Epidemiology of stroke. *Lancet* 1992;339(8789):342-4.
146. Shaper AG, Phillips AN, Pocock SJ, Walker M, Macfarlane PW. Risk factors for stroke in middle aged British men. *British Medical Journal* 1991;302(6785):1111-5.
147. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335(8692):765-74.
148. Chalmers J, MacMahon S, Anderson C, Neal B, Rodgers A. *Clinicians Manual on Blood Pressure and Stroke Prevention*. 2nd ed. London: Science Press Ltd, 1997.
149. Eastern stroke and Coronary Heart Disease Collaborative Research Group. Blood pressure, cholesterol, and stroke in eastern Asia. Eastern Stroke and Coronary Heart Disease Collaborative Research Group. *Lancet* 1998;352(9143):1801-7.
150. Stamler J, Neaton JD, Wentworth DN. Blood pressure (systolic and diastolic) and risk of fatal coronary heart disease. *Hypertension* 1989;13(5 Suppl):I2-12.
151. Kannel W, Belanger A. Epidemiology of heart failure. *American Heart Journal* 1991;121:951-957.
152. Lauer MS, Anderson KM, Kannel WB, Levy D. The impact of obesity on left ventricular mass and geometry. The Framingham Heart Study. *Journal of the American Medical Association* 1991;266(2):231-6.
153. Levy D, Larson MG, Vasan R, Kannel WB, Ho K. The progression from hypertension to congestive heart failure. *Journal of the American Medical Association* 1996;275:1557-1562.
154. Kannel WB, Castelli WP, McNamara PM, McKee PA, Feinleib M. Role of blood pressure in the development of congestive heart failure. The Framingham study. *New England Journal of Medicine* 1972;287(16):781-7.
155. McKee P, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham Study. *New England Journal of Medicine* 1971;285:1441-1446.
156. World Health Organization. Implementation of the Global Strategy for Health for All by the Year 2000. Second evaluation: eighth report on the world health situation. Geneva, 1993.
157. Murray C, AD L. *The global burden of disease*. London: Harvard University Press, 1996.
158. Howard G, Howard VJ, Katholi C, Oli MK, Huston S, Asplund K. Decline in US Stroke Mortality: An Analysis of Temporal Patterns by Sex, Race, and Geographic Region Editorial Comment: An Analysis of Temporal Patterns by Sex, Race, and Geographic Region. *Stroke* 2001;32(10):2213-2220.
159. Tunstall_Pedoe H, Kuulasmaa K, Mahonen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. *Lancet* 1999;353(9164):1547-57.
160. Mihalka L, Smolanka V, Bulecza B, Mulesa S, Bereczki D. A Population Study of Stroke in West Ukraine: Incidence, Stroke Services, and 30-Day Case Fatality. *Stroke* 2001;32(10):2227-2220.
161. Tunstall_Pedoe H, Vanuzzo D, Hobbs M, Mahonen M, Cepaitis Z, Kuulasmaa K, et al. Estimation of contribution of changes in coronary care to improving survival, event

rates, and coronary heart disease mortality across the WHO MONICA Project populations. *Lancet* 2000;355(9205):688-700.
162. British Hypertension Society. *Blood Pressure Measurement - Recommendations of the British Hypertension Society*. 3rd ed, 1997.
163. American Society of Hypertension. Recomendations for routine blood pressure measurement by indirect cuff sphygmomanometry. *American Journal of Hypertension* 1992;5:207-209.
164. Perloff D, Grim C, Flack J, al e. Human blood pressure determination by sphygmomanometry. *Circulation* 1993;88:2460-2467.
165. Enstrom I, Thulin T, Lindholm L. How good are standardized blood pressure recordings for diagnosing hypertension? A comparison between office and ambulatory blood pressure. *Journal of Hypertension* 1991;9(6):561-6.
166. Toyoshima T, Kuwajima I, Suzuki Y, Ohkawa S, Matsushita S, Ozawa T. [The relationship between office and ambulatory blood pressure in elderly patients in a non-academic setting]. *Nippon Ronen Igakkai Zasshi. Japanese Journal of Geriatrics* 1996;33(2):78-83.
167. Selenta C, Hogan BE, Linden W. How often do office blood pressure measurements fail to identify true hypertension? An exploration of white-coat normotension. *Archives of Family Medicine* 2000;9(6):533-40.
168. Liu JE, Roman MJ, Pini R, Schwartz JE, Pickering TG, Devereux RB. Cardiac and arterial target organ damage in adults with elevated ambulatory and normal office blood pressure. *Annals of Internal Medicine* 1999;131(8):564-72.
169. O'Brien E, O'Malley K. Twenty-four-hour ambulatory blood pressure monitoring: a review of validation data. *Journal of Hypertension. supplement* 1990;8(6):S11-6.
170. White WB, Berson AS, Robbins C, Jamieson MJ, Prisant LM, Roccella E, et al. National standard for measurement of resting and ambulatory blood pressures with automated sphygmomanometers. *Hypertension* 1993;21(4):504-9.
171. Sternberg H, Rosenthal T, Shamiss A, Green M. Altered circadian rhythm of blood pressure in shift workers. *Journal of Human Hypertension* 1995;9(5):349-53.
172. Appel LJ, Stason WB. Ambulatory blood pressure monitoring and blood pressure self-measurement in the diagnosis and management of hypertension [see comments]. *Annals of Internal Medicine* 1993;118(11):867-82.
173. Perloff D, Sokolow M, Cowan RM, Juster RP. Prognostic value of ambulatory blood pressure measurements: further analyses. *Journal of Hypertension. Supplement* 1989;7(3):S3-10.
174. Pickering T. Recommendations for the use of home (self) and ambulatory blood pressure monitoring. American Society of Hypertension Ad Hoc Panel. *American Journal of Hypertension* 1996;9(1):1-11.
175. Tsuji I, Imai Y, Nagai K, Ohkubo T, Watanabe N, Minami N, et al. Proposal of reference values for home blood pressure measurement: prognostic criteria based on a prospective observation of the general population in Ohasama, Japan. *American Journal of Hypertension* 1997;10(4 Pt 1):409-18.
176. Nesselroad JM, Flacco VA, Phillips DM, Kruse J. Accuracy of automated finger blood pressure devices. *Family Medicine* 1996;28(3):189-92.
177. O'Brien E, O'Malley K. Evaluation of blood pressure measuring devices with special reference to ambulatory systems. *Journal of Hypertension. supplement* 1990;8(7):S133-9.
178. Morgan T, Menard J, Brunner H. Twenty-four hour blood pressure control and trough to peak ratio: who, when, how and why? *Journal of Human Hypertension* 1998;12(1):45-8.
179. Morgan T, Menard J, Brunner H. Trough to peak ratio as a guide to BP control: measurement and calculation. *Journal of Human Hypertension* 1998;12(1):49-53.
180. Ramsay L, Williams B, Johnston G, MacGregor G, Poston L, Potter J, et al. Guidelines for management of hypertension: report of the third working party of the British Hypertension Society. *J Hum Hypertens* 1999;13(9):569-592.
181. Mulrow CD, Pigone M. What are the elements of good treatment for hypertension? In: Mulrow CD, editor. *Evidence-based Hypertension*: BMJ Books, 2001:81-116.
182. Pignone M, Sheridan S, Mulrow CD. How do we individualize antihypertensive therapy for patients with specific comorbid conditions? In: Mulrow CD, editor. *Evidence-based Hypertension*. London: BMJ Books, 2001:131-159.

183. Furberg CD, Psaty BM, Pahor M, Alderman MH. Clinical Implications of Recent Findings from the Antihypertensive and Lipid-Lowering Treatment To Prevent Heart Attack Trial (ALLHAT) and Other Studies of Hypertension. *Annals of Internal Medicine* 2001;135(12):1074-8.
184. Hansson L, Lindholm LH, Ekbom T, Dahlof B, Lanke J, Schersten B, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999;354(9192):1751-6.
185. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999;353(9153):611-6.
186. Hansson L, Hedner T, Lund-Johansen P, Kjeldsen SE, Lindholm LH, Syvertsen JO, et al. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet* 2000;356:359-65.
187. Brown M, Plamer C, Castaigne A, al e. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 2000;356:366-372.
188. UKPDS study group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. *British Medical Journal* 1998;317(7160):713-20.
189. Tatti P, Pahor M, Byington RP, Di_Mauro P, Guarisco R, Strollo G, et al. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 1998;21(4):597-603.
190. Anon. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). ALLHAT Collaborative Research Group. *Journal of the American Medical Association* 2000;283(15):1967-75.
191. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Journal of the American Medical Association* 2002;288(23):2981-97.
192. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *The New England Journal of Medicine* 2000;342(3):145-53.
193. Parving H-H, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P, et al. The Effect of Irbesartan on the Development of Diabetic Nephropathy in Patients with Type 2 Diabetes. *New England Journal of Medicine* 2001;345(12):870-878.
194. Weber M. Clinical safety and tolerability of losartan. *Clinical Therapeutics* 1997;19(4):604-16.
195. Andersson OK. Tolerability of a modern antihypertensive agent: candesartan cilexetil. *Basic Research in Cardiology* 1998;93(Suppl 2):54-8.
196. Davis BR, Cutler JA, Furberg CD, Wright JT, Farber MA, Felicetta JV, et al. Relationship of antihypertensive treatment regimens and change in blood pressure to risk for heart failure in hypertensive patients randomly assigned to doxazosin or chlorthalidone: further analyses from the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial. *Annals of Internal Medicine* 2002;137(5 Part 1):313-20.
197. Moser M. Current recommendations for the treatment of hypertension: are they still valid? *Journal of Hypertension* 2002;20 Suppl 1:S3-10.
198. Nuesch R, Schroeder K, Dieterle T, Martina B, Battegay E. Relation between insufficient response to antihypertensive treatment and poor compliance with treatment: a prospective case-control study. *British Medical Journal (Clinical Research Ed.)* 2001;323(7305):142-6.
199. Urquhart J. Patient non-compliance with drug regimens: measurement, clinical correlates, economic impact. *European Heart Journal* 1996;17 Suppl A:8-15.

200. Jones JK, Gorkin L, Lian JF, Staffa JA, Fletcher AP. Discontinuation of and changes in treatment after start of new courses of antihypertensive drugs: a study of a United Kingdom population. *British Medical Journal* 1995;311(7000):293-5.
201. Caro JJ, Salas M, Speckman JL, Raggio G, Jackson JD. Persistence with treatment for hypertension in actual practice. *Canadian Medical Association Journal* 1999;160(1):31-7.
202. Caro J, Jackson J, Speckman J, Salas M, Raggio G. Compliance as a function of initial choice of antihypertensive drug. *American Journal of Hypertension* 1997;10(Apr):141A.
203. Degli-Esposti E, Sturani A, Di Martino M, Falasca P, Novi MV, Baio G, et al. Long-term persistence with antihypertensive drugs in new patients. *Journal of Human Hypertension* 2002;16(6):439-44.
204. Gregoire JP, Moisan J, Guibert R, Ciampi A, Milot A, Cote I, et al. Tolerability of antihypertensive drugs in a community-based setting. *Clinical Therapeutics* 2001;23(5):715-26.
205. Gregoire JP, Moisan J, Guibert R, Ciampi A, Milot A, Gaudet M, et al. Determinants of discontinuation of new courses of antihypertensive medications. *Journal of Clinical Epidemiology* 2002;55:728-735.
206. Marentette MA, Gerth WC, Billings DK, Zarnke KB. Antihypertensive persistence and drug class. *Canadian Journal of Cardiology* 2002;18(6):649-56.
207. Curb J, Borhani NO, Blaszkowski T, Zimbaldi N, Foitu S, Williams W. Patient-perceived side effects to antihypertensive drugs. *American Journal of Preventive Medicine* 1985;1:36-40.
208. Ward HJ, Morisky DE, Lees NB, Fong R. A clinic and community-based approach to hypertension control for an underserved minority population: design and methods. *American Journal of Hypertension* 2000;13(2):177-83.
209. Morisky DE. Description of the amended self-reported adherence measure. In: Fahey M, editor, 2000.
210. Pratt RJ, Robinson N, Loveday HP, Pellowe CM, Franks PJ, Hankins M, et al. Adherence to antiretroviral therapy: appropriate use of self-reporting in clinical practice. *HIV Clinical Trials* 2001;2(2):146-59.
211. Horne R. The Nature, Determinants and Effects of Medication Beliefs in Chronic Illness. University of London, 1997.
212. Cramer JA, Scheyer RD, Mattson R. Compliance declines between clinic visits. *Archives of Internal Medicine* 1990;150(7):1509-1510.
213. Hecht F, Colfax G, Swanson M, Chesney M. Adherence and effectiveness of protease inhibitors in clinical practice. *Proceedings of the Fifth conference on Retroviruses and Opportunistic infections* 1998;Abstract 51.
214. Morisky DE, Levine DM, Green LW, Shapiro S, Russell RP, Smith CR. Five-year blood pressure control and mortality following health education for hypertensive patients. *American Journal of Public Health* 1983;73(2):153-62.
215. Neaton JD, Grimm RH, Jr., Prineas RJ, Stamler J, Grandits GA, Elmer PJ, et al. Treatment of Mild Hypertension Study. Final results. Treatment of Mild Hypertension Study Research Group. *Journal of the American Medical Association* 1993;270(6):713-24.
216. Mushlin AI, Appel FA. Diagnosing potential noncompliance. Physicians' ability in a behavioral dimension of medical care. *Archives of Internal Medicine* 1977;137(3):318-321.
217. Kjellgren KI, Svensson S, Ahlner J, Saljo R. Antihypertensive medication in clinical encounters. *International Journal of Cardiology* 1998;64(2):161-9.
218. Wilson P, D'Agostino R, Levy D, Belanger A, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837-47.
219. Tunstall-Pedoe H. The Dundee coronary risk-disk for management of change in risk factors. *British Medical Journal* 1991;303:744-7.
220. Haq I, Ramsay L, Yeo WW, Jackson P, Wallis E. Is the Framingham risk function valid for northern European populations? A comparison of methods for estimating absolute coronary risk in high risk men. *Heart* 1999;81:40-6.
221. Ong LM, de Haes JC, Hoos AM, Lammes FB. Doctor-patient communication: a review of the literature. *Social Science and Medicine* 1995;40(7):903-18.
222. Unger T. Patient-doctor interactions in hypertension. *Journal of Human Hypertension* 1995;9(1):41-5.

223. Little P, Everitt H, Williamson I, Warner G, Moore M, Gould C, et al. Observational study of effect of patient centredness and positive approach on outcomes of general practice consultations. *British Medical Journal* 2001;323(7318):908-911.
224. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. *Journal of Clinical Pharmacy and Therapeutics* 2001;26:331-342.
225. Maronde R, Chan L, Larsen F, et al. Underutilization of antihypertensive drugs and associated hospitalization. *Medical Care* 1989;27(12):1159-66.
226. Thrift AG, McNeil JJ, Forbes A, Donnan GA. Three important subgroups of hypertensive persons at greater risk of intracerebral hemorrhage. Melbourne Risk Factor Study Group. *Hypertension* 1998;31(6):1223-9.
227. Antihypertensive compliance and stroke risk. *Pharmaceutical Journal* 2000;265(7120):642.
228. Rizzo JA, Simons WR. Variations in compliance among hypertensive patients by drug class: implications for health care costs. *Clinical Therapeutics* 1997;19(6):1446-57; discussion 1424-5.
229. Hughes D, McGuire A. The direct costs to the NHS of discontinuing and switching prescriptions for hypertension. *Journal of Human Hypertension* 1998;12(8):533-7.
230. Degli Esposti E, Sturani A, Degli_Esposti L, Macini PL, Falasca P, Valpiani G, et al. Pharmacoutilization of antihypertensive drugs: a model of analysis. *International Journal of Clinical Pharmacology and Therapeutics* 2001;39(6):251-8.
231. Berto P, Degli Esposti E, Ruffo P, Buda S, Esposti LD, Sturani A, et al. The pandora project: cost of hypertension from a general practitioner database. *Blood Pressure* 2002;11(3):151-6.
232. Hansson L. Medical and cost-economy aspects of modern antihypertensive therapy--with special reference to 2 years of clinical experience with losartan. *Blood Pressure. Supplement* 1997;1:52-5.
233. Ambrosioni E. Pharmacoeconomic challenges in disease management of hypertension. *Journal of Hypertension* 2001;19(3):S33-40.
234. The Task Force for Compliance. Noncompliance with Medications: An Economic Tragedy with Important Implications for Health Care Reform. Reston, VA: National Pharmaceutical Council, 1994:1-32.
235. Houston Miller N, Hill M, Kottke T, Ockene IS. The Multilevel Compliance Challenge: Recommendations for a Call to Action. *Circulation* 1997;95:1085-1090.
236. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. *American Journal of Hospital Pharmacy* 1990;47(3):533-43.
237. Ellis SL, Billups SJ, Malone DC, Carter BL, Covey D, Mason B, et al. Types of interventions made by clinical pharmacists in the IMPROVE study. Impact of Managed Pharmaceutical Care on Resource Utilization and Outcomes in Veterans Affairs Medical Centers. *Pharmacotherapy* 2000;20(4):429-35.
238. Malone DC, Carter BL, Billups SJ, Valuck RJ, Barnette DJ, Sintek CD, et al. An economic analysis of a randomized, controlled, multicenter study of clinical pharmacist interventions for high-risk veterans: the IMPROVE study. Impact of Managed Pharmaceutical Care Resource Utilization and Outcomes in Veterans Affairs Medical Centers. *Pharmacotherapy* 2000;20(10):1149-58.
239. Ellis SL, Carter BL, Malone DC, Billups SJ, Okano GJ, Valuck RJ, et al. Clinical and economic impact of ambulatory care clinical pharmacists in management of dyslipidemia in older adults: the IMPROVE study. Impact of Managed Pharmaceutical Care on Resource Utilization and Outcomes in Veterans Affairs Medical Centers. *Pharmacotherapy* 2000;20(12):1508-16.
240. Bero LA, Mays NB, Barjesteh K, Bond C. Expanding the roles of outpatient pharmacists: effects on health services utilisation, costs, and patient outcomes. *Cochrane Database of Systematic Reviews (Online : Update Software)* 2000(2):CD000336.
241. Goodyer LI, Miskelly FG. The clinical benefits of counselling in elderly patients with stable chronic heart failure. *Pharmaceutical Journal* 1993;251:Suppl R7.
242. Haynes RB, Montague P, Oliver T, McKibbon KA, Brouwers M, Kanani R. Interventions for helping patients to follow prescriptions for medications (Cochrane Review). *The Cochrane Library*. Oxford: Update Software, 2002.

243. Willey C, Redding C, Stafford J, Garfield F, Geletko S, Flanigan T, et al. Stages of change for adherence with medication regimens for chronic disease: development and validation of a measure. *Clinical Therapeutics* 2000;22(7):858-71.
244. McAnaw J, McGregor A-M, Hudson S. The pharmaceutical care of patients with hypertension: an examination of service models in primary care in the US. *Pharmacy World and Science* 2001;23(5):189-194.
245. Friedman RH, Kazis LE, Jette A, Smith MB, Stollerman J, Torgerson J, et al. A telecommunications system for monitoring and counseling patients with hypertension. Impact on medication adherence and blood pressure control. *American Journal of Hypertension* 1996;9(4 Pt 1):285-92.
246. Can a computerized telephone-based tracking system improve compliance and increase the percentage of secondary prevention patients achieving target LDL levels in a large private cardiology practice? American Heart Association 71st Scientific Sessions; 1998. Medscape Inc.
247. Guthrie RM. The effects of postal and telephone reminders on compliance with pravastatin therapy in a national registry: results of the first myocardial infarction risk reduction program. *Clinical Therapeutics* 2001;23(6):970-80.
248. Garson D. Factor analysis. *Social Science Computer Review* 2002;Web page(Last accessed 16th February 2002):www2.chass.ncsu.edu/garson/pa765/factor.htm.
249. Edouard L, Senthilselvan A. Observer error and birthweight: digit preference in recording. *Public Health* 1997;111(2):77-9.
250. Beevers G, Lip G, O'Brien E. *ABC of hypertension*. 4th ed: BMJ Books, 2001.
251. Patterson HR. Sources of error in recording the blood pressure of patients with hypertension in general practice. *British Medical Journal (Clinical Research Ed.)* 1984;289(6459):1661-4.
252. Stoneking HT, Hla KM, Samsa GP, Feussner JR. Blood pressure measurements in the nursing home: are they accurate? *The Gerontologist* 1992;32(4):536-40.
253. Wen SW, Kramer MS, Hoey J, Hanley JA, Usher RH. Terminal digit preference, random error, and bias in routine clinical measurement of blood pressure. *Journal of Clinical Epidemiology* 1993;46(10):1187-93.
254. Wingfield D. Observational precision in general practice data: a technique for analysis and audit. *Mathematical Medicine and Biology (Formerly the Journal of Mathematics Applied in Medicine and Biology)* 1995;12(3-4):275-81.
255. Kuulasmaa K, Hans-Werner H, Tolonen H. Quality Assessment of Data on Blood Pressure in the WHO MONICA Project: MONICA Data Centre, National Public Health Institute, Helsinki, Finland, 1998.
256. Armstrong RS. Nurses' knowledge of error in blood pressure measurement technique. *International Journal of Nursing Practice* 2002;8(3):118-26.