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THE CONDUCT AND MANAGEMENT OF LARGE CLINICAL TRIALS IN HYPERTENSION

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This thesis is submitted in accordance with the requirements for the degree of Doctor of Medicine of the University of Adelaide.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any University.

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John Marley

June 7th 1992

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APPENDICES

PREFACE

Studies which constitute this thesis have been published in;

The Journal of the Royal Society of Medicine

The British Medical Journal

The British Journal of Clinical Practice

The Lancet

The International Journal of Clinical Research.

Presentations of data from Studies in this Thesis have been made at international meetings in four continents.

Full details of these publications and presentations are given in Appendix 9 of this thesis.

ABSTRACT

Large multicentre studies are difficult to conduct and are expensive in both human and financial resources, yet they are essential in common conditions such as hypertension and hyperlipidaemia if important questions of morbidity and mortality of the condition and its treatment are to be answered. They must also be able to gather large amounts of data before the therapy being studied becomes outdated.

The first Study in this thesis describes and evaluates an economical method of collecting a large amount of data on thousands of patients suffering from essential hypertension. It establishes the reliability of the data collected in this way. The tolerability of antihypertensive drugs was assessed by comparison of the prevalence of adverse medical events reported by treated hypertensive patients and those who were untreated. This confirmed the impression that patients suffering from a symptomless condition, essential hypertension, did not tolerate the medications studied well.

The study also provided the largest single volume of information on the tolerability and effectiveness of nifedipine, at the time, the second most commonly prescribed antihypertensive drug. These data caused the world wide prescribing information for nifedipine to be changed.

The relationship between body mass index and diastolic blood pressure was explored in this large population and only a weak positive correlation between the two was found.

The generally poor tolerability of antihypertensive drugs led to the consideration of whether doctors neglected the non-pharmacological treatments for hypertension. The Study described in Chapter 4, shows that the provision of this advice could be better and more consistent.

Studies conducted as part of the development of new medicines are now required to be conducted to the standards of "Good Clinical Practice" as described by the Food and Drug Administration of the United States. A computerised system for patient tracking and the successful management of such clinical trials is described and evaluated in Chapter 3.

INTRODUCTION

General practice has a long and honourable tradition of research. One of the major triumphs of twentieth century medicine, the eradication of smallpox from the world, started with the work of Edward Jenner, a country general practitioner. General practitioners are ideally placed to be pioneers in medical research being able to observe the beginnings of an illness, follow it through its stages and see it in its true perspective.

During the course of the year, every general practitioner makes a note of several thousand independent observations, each of which makes minimal demands on his or her time and energy. These records, kept for the purpose of investigating and treating disease, can, with very little modification be used for research. In Australia, 80% of the population consults a doctor at least once every twelve months and 78% of doctor consultations are with general practitioners (1). The majority of persons, (ie around 90%), can identify a particular general practitioner to whom they would turn when sick (2). In the United Kingdom, the general practitioner's records are, technically at least, the property of the Secretary of State for Health. As such, the one record follows each patient wherever that patient might move, from general practitioner to general practitioner, and so provides a comprehensive and complete record of that patient from birth to death.

Careful and minute observation of patients in general practice has lead to the development of complete, effective management systems, such as the treatment of back pain by spinal manipulation (3), for widespread disabling conditions.

Effective associations have been formed between general practice and clinical pharmacology and have been able to describe, for example; the psychological distress induced in chronic conditions such as hypertension and asthma and its effect on patient compliance (4) and, that control of blood pressure will at least be maintained and may even be improved, when patients are returned to their general practitioners at the completion of a clinical trial (5).

General practitioners then, are the holders of vast amounts of medical information; information, which is, at least for four fifths of the population, updated at a maximum interval of one year. The problem to date has been the accessing of this information.

In common with many other branches of medicine, the clinical and administrative workloads in general practice at times are overwhelming, so that any system of information retrieval should not add to those burdens. The system must be easy to use, take little extra time to enter and retrieve data and must collect data which are reliable.

Large studies have been conducted in general practice. The Medical Research Council Study of mild to moderate hypertension (6), collected data on 17,354 patients. Recruitment took place over nine years from March 1973 to February 1982. It was performed by teams visiting general practices, often using a caravan when suitable rooms were not available. The time taken for screening and recruitment meant that by the time the Study was first reported in 1985, the drugs studied, propranolol and bendrofluazide, were no longer the most commonly used drugs for the treatment of mild to moderate hypertension.

The Medical Research Council and the Royal College of General Practitioners study on the relationship between oral contraceptives and thrombo-embolic disease (7), a case control study which identified the association between venous thromboembolism and oral contraceptive use, collected data on 399 patients with two matched controls for every patient. The study reached a successful conclusion in spite of difficulty with data collection and inadequate or missing records.

Postmarketing surveillance of the safety of cimetidine was also undertaken in general practice (8). That study commenced in 1977 and was eventually reported in 1983. Cimetidine takers were identified by prescription data from 254 pharmacies. The general practitioners in 327 practices were

contacted, visited by research personnel who recorded patient's medical details and together with the general practitioners identified matched controls. A total of 9928 patients taking cimetidine and 9351 controls were recruited and followed for one year. All, except 1.2% of the takers and 1.6% of the controls, were successfully followed for that period. This study reached a successful conclusion; however it took a considerable time to perform and the authors state, "A more important limitation of our method is its dependence on skilled research assistants for the collection of much of the data. This means that costs are high and that only widely used drugs may be studied. Each research assistant can only cover a restricted geographical area" (8).

These examples of large, successful general practice studies share several common features:

a) They are difficult and elaborate to set-up

b) They have a long time-course and are expensive

and

c) They consume large financial and personnel resources.

For the future of general practice research, whilst capitalising on its strength of numbers of patients, it is important to develop methods which collect large volumes of data quickly and reliably. This will enable large projects,

such as post-marketing surveillance studies of new drugs, to be undertaken.

Postmarketing surveillance

A generation after thalidomide there are still no clear guidelines for risk assessment of new drugs in any country operating a regulatory scheme. Major catastrophes, as with practolol, have occurred in spite of elaborate regulatory machinery (9). Pre-licensing clinical trials of new drugs involve small numbers of closely monitored patients, for example 2000, but once a licence is granted, prescriptions may run into millions. To identify rare or unusual events may require the observation of large numbers of patients. To detect an adverse event at an incidence of 1 in 5000 against a spontaneous background of 1 in 100, requires a minimum of 3,255,000 patients to be exposed. Already, one government working party has issued guidelines suggesting that for new drugs destined for widespread or prolonged use, grant of a product licence may be conditional on the postmarketing surveillance of 10,000 patients for two years (10). It is likely that most countries having a regulatory system will follow this principle in future years. Because such large patient numbers are involved, these surveillance studies can only be performed in general practice (11).

The requirements for good postmarketing surveillance are that:

i) In prospective studies the patient should only be included in the study after the decision to prescribe the drug has been made.

ii) The study design should not influence the way the drug is used, ie the drug should not be used in the narrow directed framework of a clinical trial, since the object is to monitor its safety in everyday practice.

iii) All adverse medical events should be recorded, not just the suspected adverse drug reactions.

iv) No inducement should be offered to doctors to use the drug because this may alter prescribing practice.

v) The study should be a safety assessment not a promotional exercise, and it should include controls.

vi) A large enough number of patients should be followed for a sufficiently long period of time and the outcome must be known in all patients for safety assessments to be valid.

For effective postmarketing surveillance, methods which will collect and handle large amounts of reliable data, with the necessary speed essential for safety information, are essential.

The advent of computers should thus facilitate the performance of such large studies, and the expansion of postmarketing surveillance which may be expected in general practice.

Computers in Medicine

There have been three great information revolutions in the history of the world. These are:

1) The first use of hieroglyphics by the ancient Egyptians.

2) The invention of the printing press by Thomas Caxton.

3) The coming of the computer.

The first computer appeared in February 1946, when IBM introduced the ENIAC programmable calculator with memory, at the University of Pennsylvania. Professor Douglas Hartree of Cambridge University, who played a part in its development stated that it originated from an idea to assist gunnery in the second world war (12).

Computer based medical history taking was attempted in 1966 (13) and the first computer was used in a general practice consulting room by John Preece in 1969 (14). However, proper development in this area started with the initial programmes of the 1970s. These programmes focused on a strictly limited number of objectives, for example, computer held medical records in hypertension (15), or computer guided hypertension treatment protocols (16). Computers have been used as tools for patient care, for example in upper gastrointestinal endoscopy (17), the management of burn patients (18) and in the assessment of fluid status in premature neonates

(19). They have been used to facilitate clinical research, for example in The Cardiac Arrhythmia Suppression Trial (20), the National Polyp Study (21) and in the provision of nutrition analysis (22). Continuing medical education is provided by on-line programmes, such as the "Check Up" programme of the Royal Australian College of General Practitioners (RACGP), available in all parts of Australia through Telecom Viatel. Computer Assisted Learning, using Hypertext high resolution graphic imagery and sound (23), may be used for undergraduate teaching. Medical information may be made instantly available in hospital clinical settings (21) and in Family Practice (25).

The possibility of storing, sorting and retrieving large amounts of information by computers has lead to the development of databases dedicated to particular areas of medicine. For example, in dermatology, a database with the complete composition of pharmaceutical products and some cosmetics enabled patients to avoid specific allergens (26); vulval lesions have been classified and documented in gynaecology (27); in virology, computers have been used to store viral information to improve the accuracy of reported results (28).

The principal factor in the introduction of computers into Australian general practice has been their use for patient billing. In 1988, a survey of a randomly chosen sample of 1000 RACGP members (29) revealed that 41%

of the respondent practices used a computer for some aspect of their practice, the commonest uses being accounting (71%) and word processing (60%). Unfortunately, the potential for the practice computer to provide a database for research seems to be little used. Computing in British general practice started in 1975 with a government funded project to establish links between records held in a surgery and the local hospital, thus providing an opportunity for electronic shared care. This idea was not developed further at the time. Currently, 20% of British general practitioners use computers in their practices (30). Prescription writing by computer has been in use in Britain for some time and is becoming available in Australia. It has the advantages of legibility and automatic dose and drug interaction checking. In the United States of America and in Canada, the establishment of Health Maintenance Organisations has in turn created large computerised patient databases, which are used for record linkage.

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Record Linkage

Record linkage is the collecting together of all the information, from all sources, about a patient. This means that the hospital discharge data, the general practitioners "reason for encounter" and all drugs prescribed for the individual are kept in one central record. It is particularly useful for the evaluation of possible adverse reactions to drugs, since all medical events are entered, not just the suspected "side-effects". The potential of record linkage for the detection of adverse drug reactions was first shown in the Oxford Community Health Record (31). The Tayside Record Linkage Scheme, (MEMO), makes use of the fact that each resident in the Tayside area has been allocated a unique community health number (32). All hospital discharge data are coded by the Area Health Authority and may be accessed through the patient's community health number. The safety of cimetidine was once again assessed in that scheme. Twelve thousand eight hundred and sixty one prescriptions were traced to 3802 patients whose discharge data were compared with those of controls matched for age, sex and general practitioner.

The advantages of using this method are;

a) economy, the cost of the study was £12,000.

b) the duration of follow-up could be made indefinite, simply by searching the community health numbers again for new discharge data.

The disadvantages of the Tayside scheme are;

a) prescription data have to be obtained from the Prescription Pricing Authority, as they are not entered at the time of dispensing.

b) information from general practice is not entered.

c) being hospital discharge reports, only major morbidity data are available.

Beginning in the mid-1970s medical care organisations in America have relied heavily on computer support for administrative efficiency, economy, billing and costing. This has resulted in the emergence of several large computer-supported pharmacy files in which every prescription with prescribing details is entered for each member of the insured or served group, along with a patient-identification number. In the same health plans, hospitals have automated their information systems in a way that allows full entry of every hospital discharge diagnosis and again an associated patient identification number. In one such setting, the Group Health Cooperative of Puget Sound (a large prepaid group practice in Seattle with 330,000 enrollees) automated the data entry on pharmacy dispensed prescriptions in 1976. Since then, every prescription for the entire population has been entered into an automated database and can be linked to membership files for the identification of demographic information, and hospital files for events significant enough to result in hospitalisation. The latter includes most adverse drug reactions of major significance. The American and Canadian databases are shown in Table 1.

Table 1. Database resources USA/Canada (1986)

Database	Population	Data collection commenced
Group health Cooperative	330,000	1976
Medicaid -COMPASS -Tennessee	 6,000,000 400,000	 1980
Kaiser-Permanente Health Plans -Los Angeles -Portland -other	 1,600,000 175,000 100,000	 1983
Saskatchewan Provincial Drug Plan	1,000,000	1986
Minneapolis Consortium	500,000	1982
Trimis Dept of Defence	>1,000,000	1980 (approx.)
Blue Cross (Rhode Island)	1,000,000	1980 (approx.)

Under reporting of adverse drug events in spontaneous reporting systems is very common. In a survey of 100 doctors in 24 training general practices in Britain, of the total of 638 adverse drug reactions seen over the four week monitoring period, only 35 were reported (33). Of ten suspected serious events, only five had been reported to the Committee on the Safety of Medicines. With such profound and variable under reporting, the numerator of any risk fraction based on such data is highly inaccurate. To overcome some of these deficiencies, the Food and Drug Administration of the USA (FDA), financed the development and testing of the Computerised On-Line Medical Pharmaceutical Analysis and Surveillance System, (COMPASS).

COMPASS is a large computerised database designed to permit a researcher to enrol and analyze cohorts of patients with specific diseases or those exposed to a drug and to compare them with matched or unmatched control groups (34). The principal advantage of COMPASS is its very large population base, which is over 6,000,000 patients. This allows the study of relatively uncommon illnesses and relatively uncommonly used drugs. Secondly, as COMPASS is population based, this permits the calculation of incidence rates. Third, it includes both inpatient and outpatient diagnoses. Fourth, the data are not subject to recall or interviewer bias. Finally, because the data are collected in an ongoing way as a by-product of an administrative process, it is inexpensive and can address questions of clinical importance very quickly.

An example of the use of COMPASS was when a question was raised over the safety of allopurinol. US Federal Registry reports suggested that the use of allopurinol might be associated with the development of cataracts. Using the large American database, 1,700 takers of allopurinol were identified, together with a similar number of matched controls. No increase in cataracts was found in the group taking allopurinol and the whole study took 20 minutes to perform (35).

In Britain, Prescription Event Monitoring (PEM) has been developed. Prescriptions are priced centrally by a pricing authority. When a prescription is seen by the authority for a drug under enquiry, the details of patient and doctor are passed to the PEM Unit. The doctor is then sent a "green card" and asked to enter details of any medical events the patient might have suffered. In theory, all events related to the prescription of a drug are collected. In practice, many may be missed. Patients may attend Accident and Emergency Departments and, although records of attendance should be sent to the general practitioner, they may not be. Records may not follow patients who move districts, or those who are treated when on holiday outside their usual practice area. Control patients are not usually followed, historical controls being sometimes applied. The system is therefore hypothesis generating, rather than hypothesis testing. Up to 10,000 patients may be followed, but the system still lacks the power to detect rare

events (10).

Australia has the potential to have the world's largest, most comprehensive record linkage systems. A diagnostic code could be added to the Medicare billing slips, which currently include only procedure data, this could be linked with the already available comprehensive Drug Utilisation Data. Drug Utilisation Data in Australia are compiled from the Pharmaceutical Benefits Scheme and pharmacy returns, they are used by the Federal Drug Utilisation Sub Committee to survey changes in prescribing and the various factors which influence that. The privacy legislation in Australia will not at present allow Medicare and drug databases to be joined, although it is possible that in future, cross-linking may be possible using identification numbers that do not allow the individual patient to be traced.

In mild to moderate hypertension, a symptomless condition, and where large numbers of patients must be treated to prevent a low number of serious medical events (36), the benefits of treatment must outweigh the adverse events due to the pharmacological intervention. Drugs used for the treatment of hypertension are used widely and often for many years in a single individual. It is therefore particularly important that accurate and reliable safety and tolerability data are available for such agents. One such hypotensive drug is nifedipine.

Nifedipine

Nifedipine is a dihydropyridine derivative, which is one of a group of compounds that is thought to act by blocking the transmembrane inward movement of calcium (37). It has been used in the treatment of all forms of angina, Raynaud's phenomenon, perniosis, peripheral vascular disease, acute episodes of hypertension and in mild to severe hypertension. Nifedipine may lower mean arterial blood pressure by up to 20% or more and significant reductions ($p<0.001$) in blood pressure occur within 30 minutes of oral administration of the drug (38). Intravenous nifedipine, (1mg to 4mg), produces significant decreases in blood pressure of up to 34% in patients with hypertension, coronary artery disease or hypertrophic obstructive cardiomyopathy (39). Nifedipine produces a greater reduction in blood pressure in those with hypertension than in normotensive individuals (40). The acute administration of sublingual nifedipine has been shown to increase heart rate in cardiac patients and normal volunteers by up to 28% over control values (41). Acute oral administration of nifedipine tablets in doses of 20mg to 60mg in hypertensive individuals has been associated with increases in heart rate between 29% and 38% (42). However, there have been no significant increases in heart rate seen during long term (up to 12 months) administration of nifedipine (43).

Oral nifedipine 30 to 100mg/day has been shown to maintain efficacy in medium term studies in patients with mild to moderate essential hypertension (44). As with single-dose administration, the antihypertensive response is positively correlated with the pre-treatment severity of hypertension and is inversely correlated with plasma renin activity (45). Nifedipine may be particularly beneficial in patients with lower plasma renin activity, such as the elderly (46).

In 1982 a nifedipine tablet was introduced for the treatment of hypertension. Although widely described as a sustained release tablet, it does not have a formal slow release mechanism. Nifedipine tablets are made of film coated, micronised, compressed drug. Solubility of nifedipine is low in this form and thus the drug is more slowly available than in the liquid contents of nifedipine capsules. Therapeutic trials using the tablets have shown that twice daily administration (40mg to 120mg/day) provides 24 hour control of blood pressure (47). Long term, 12 months trials, have shown the antihypertensive properties to be maintained (48).

The incidence of side effects with nifedipine and their duration was not clear, since data were only available from studies with insufficient numbers of patients to give accurate rates. It seemed that most side effects were extensions of the vasodilatory action of nifedipine, the commonest being, headache, flushing, dizziness, gastrointestinal symptoms and oedema of the

lower leg (49). The rates of patients withdrawing from nifedipine treatment were quoted as being between 2% to 20% and it was thought that most side effects appeared within 14 days, were transitory and disappeared with time (50). However, it had also been suggested that more serious side effects such as exacerbations of angina pectoris might occur (51). Side effects increase with dosage, so it was thought that the slower dissolution from oral tablet formulations might minimise those due to peak plasma concentrations (52).

In common with many drugs developed in the late 1970s and early 1980s, many of the original studies with nifedipine are flawed in methodology or low patient numbers. In the latter half of the decade, guidelines for the performance of clinical trials were introduced by the American FDA.

"Good Clinical Practice"

The FDA in America is the oldest regulatory authority in the world and the one most open to public scrutiny. It is very sophisticated in its operation and the most stringent to satisfy. The term "Good Clinical Practice" (GCP) is used to describe the method of performance of a clinical study which will make it acceptable as "providing substantive evidence of effectiveness". The guidelines for GCP were first published in 1977 (53) and have undergone continuous revision and expansion since then.

Clinical trial reports which provide substantive evidence of effectiveness are often collectively referred to as "pivotal data". The definition given in Federal Docket Number 85D-0467 of January 1986, is as follows: "Substantial evidence is defined as evidence consisting of adequate and well controlled investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and reasonably be concluded by such experts that the drug will have the effect it purported or is represented to have under the conditions of use prescribed, recommended or suggested in the proposed labelling".

The elements that make up GCP, as it has evolved to date, are:

1. Protection of the human subject or patient to the highest ethical standard as defined in the declaration of Helsinki Accord; this involves trial approval by an Institutional Review Board or equivalent Ethical Committee if outside of the USA and the informed consent of participants.

2. Adoption through the use of Standard Operating Procedures of a systematic method of checking of all incidents and data records throughout the trial. The principle to be followed is that the monitor employed by the sponsor will check in a specified way on the facilities available at the trial centre, then make regular periodic visits to verify the accuracy of the data records and organise the data trail in such a way that it can be checked and verified either from the records or by means of an audit on-site by an FDA inspector.

3. Full and complete archiving of data from the trial in such a way that all procedures can be shown to have been followed to permit the checking referred to above.

4. Adequate reporting of adverse reactions within specified periods and in specific format and interim reporting on trial progress.

The prospect of carrying out a study to full GCP may seem daunting. However, the standard of medical and ethical care demanded by GCP guidelines, ensures better protection for both patients and doctors. Studies performed to the requirements of GCP are acceptable by the regulatory authorities in both Australia and Britain.

Conclusion

The users of computers in research in 1985 concentrated on entering traditionally collected data into a base unit used for tabulation and analysis. The concept of entering data directly from the consulting rooms of a large number of general practices had neither been attempted nor tested. As research moved back into general practice and the quality of research in general practice consequently improved, together with the need to perform large studies, it was important to develop a fast and economic method of data collection, which largely avoided the need for any paper record with its inherent deficiencies, such as incomplete entries and illegibility.

Nifedipine was in 1989 the second most widely used antihypertensive drug in the world (54) and yet in 1985, seven years after the introduction of the capsules and four years after the introduction of the tablets, there was no accurate measure of the incidence and duration of the side effects of this drug in either formulation. The number of patient records held by the parent company in the nifedipine data-pool was only 400 (55), records from other studies being held separately, on paper, in a form not suitable for combined evaluation.

It was therefore appropriate to test the concept of directly collecting data electronically from a large number of general practices, based on a large

number of patients who suffered from essential hypertension and to test the validity of the data and the method whilst collecting adverse event data on nifedipine and other antihypertensive drugs.

The treatment of mild to moderate hypertension has moved increasingly back into general practice (5), taking with it the need to perform clinical trials with newer anti-hypertensive drugs. These clinical trials have to be performed to the requirements of full GCP. There was thus a need for a clinical trial management system to be developed which would cope with the diversity of general practice and yet still meet the needs of GCP.

This thesis describes the evolution of such a computerised system and its use in a study of nitrendipine, a new dihydropyridine calcium channel blocking drug.

It is recognised that blood pressure lowering drugs may reduce the patient's "quality of Life" (56). The experience of examining the adverse effects of such agents led to a reconsideration of the non-pharmacological treatments of hypertension. As it seemed that doctors may be neglecting the provision of advice about non-pharmacological treatments, a computerised audit programme was developed to evaluate the performance of doctors in this respect.

EVALUATION OF A METHOD OF ELECTRONIC DATA COLLECTION IN GENERAL PRACTICE:
USE IN A POINT PREVALENCE STUDY OF TOLERABILITY OF ANTIHYPERTENSIVE DRUGS, WITH A PROSPECTIVE COHORT SAFETY AND TOLERABILTY STUDY OF NIFEDIPINE 20mg TABLETS IN THE TREATMENT OF MILD TO MODERATE ESSENTIAL HYPERTENSION.

Introduction

The introduction to this thesis described the economic and practical difficulties of performing large studies and the apparent impracticality of ever being able to repeat studies such as the Medical Research Council Study of mild to moderate hypertension (5). However, particularly within the discipline of pharmacoepidemiology, there is a growing need to be able to perform large prospective cohort studies, case-control studies and post-marketing surveillance studies. Although government working parties have recommended the performance of post-marketing surveillance studies (10) the logistics of performing and financing them seem almost insurmountable (57). It was therefore appropriate to test a method of collecting data centrally, taking advantage of the growth of computerisation of general practices and using minimal resources. It was also considered that any method of data collection might distort the data gathered. For example, computers which operate on a binary system prefer to handle data in either a numerical or a YES/NO format rather than free text. It was therefore also considered essential to attempt to test the validity of the data collected by this method before recommending its widespread acceptance and use.

Essential hypertension is a symptomless condition; patients feel well until they are treated. Antihypertensive drugs are less well tolerated than treating physicians appreciate (56). The first clinical part of this investigation was a

point prevalence study of the adverse events reported by patients suffering from essential hypertension who were either currently untreated pharmacologically, or were already taking antihypertensive medication. The second part of this investigation was a cohort study of patients taking nifedipine. Although it was hoped to show that the methodology would be useful in their conduct, these studies did not fall within the definition of post-marketing surveillance.

Although many patients had participated in clinical trials with nifedipine, at the start of this study the pooled adverse event data for nifedipine and consequently its prescribing information (Figure 1), was based on only 400 patients (55). It was considered, therefore, that this information was unlikely to be reliable; for example, the paragraph headed "Side effects" contained the statement "These effects are transient and invariably disappear with continued treatment". There was, therefore, a regulatory requirement to revise the adverse event data in the prescribing information in line with the more stringent regulations that had been put into place since nifedipine had originally been licenced. The suggested number of patients to be observed was to be similar to that in more recent licence applications. For the protection of the large numbers of patients taking nifedipine (54), it was important that the present study provided accurate knowledge for revision of these prescribing guidelines.

Figure 1

Bayer UK Limited
Pharmaceutical Division
Bayer House
Strawberry Hill
Newbury, Berkshire, RG13 1JA

ADALAT® RETARD
ADALAT
ADALAT 5

Presentation *Adalat/Adalat 5:* Orange, soft gelatine capsules containing a yellow viscous liquid. Adalat Capsules over-printed with 'ADALAT' and the Bayer cross contain 10 mg nifedipine. Adalat 5 Capsules over-printed with 'ADALAT 5' and the Bayer cross contain 5 mg nifedipine.

Adalat Retard: Pink-grey lacquered tablets one side marked 1U, the reverse side with the Bayer Cross each containing 20 mg nifedipine.

Uses *Mode of action:* Adalat is a potent calcium antagonist. Its most important effect is to protect the heart against excessive oxygen utilisation during physical activity. There is a reduction in cardiac work and in myocardial oxygen demand. Adalat also causes peripheral vasodilatation and thus reduces peripheral resistance and heart work load. Adalat has no therapeutic antiarrhythmic effect. Since Adalat does not cause a rise in intraocular pressure, it can be used in patients with glaucoma.

Indications: For the treatment and prophylaxis of angina pectoris, for the treatment of hypertension, and for the treatment of Raynaud's phenomena.

Dosage and administration For oral administration, the capsules should be taken with a little fluid during or after meals. The recommended dose is one 10 mg capsule three times daily. If necessary, up to two capsules three times daily may be taken.

If an immediate effect is required, the capsule should be bitten open and the liquid contents allowed to remain in the mouth.

Adalat 5 capsules permit titration of initial dosage in the elderly and those patients on concomitant medication. The recommended dose is one Adalat 5 capsule three times daily.

For the treatment of Raynaud's phenomena the recommended dose is one 10 mg capsule three times a day with subsequent titration of dose according to response, to a maximum of two 10 mg capsules three times a day.

In the treatment of hypertension the recommended dose of Adalat Retard is one 20 mg tablet twice daily swallowed after food with a little fluid. If necessary the dose may be increased to 40 mg twice daily.

Treatment may be continued indefinitely.

Contra-indications, warnings, etc
Contra-indications: Must not be given to women capable of child-bearing.

Warnings and precautions: Adalat is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker, preferably over 8–10 days.

Adalat may be used in combination with beta-blocking drugs and other antihypertensive agents, but the possibility of an additive effect resulting in postural hypotension should be borne in mind. Adalat will not prevent possible rebound effects after cessation of antihypertensive therapy.

Adalat should be used with caution in patients whose cardiac reserve is poor.

Ischaemic pain has been reported in a small proportion of patients within 30 minutes of the introduction of Adalat therapy. Patients experiencing this effect should discontinue Adalat.

The use of Adalat in diabetic patients may require adjustment of their control.

The antihypertensive effect of nifedipine can be potentiated by simultaneous administration with cimetidine. There are no other known incompatibilities.

Side-effects: Adalat is well tolerated. Minor side-effects, usually associated with vasodilatation are mainly headache, flushing and lethargy. Gravitational oedema associated with increased capillary permeability has been reported. These effects are transient and invariably disappear with continued treatment.

Overdosage: Standard measures such as atropine and noradrenaline may be used for resultant bradycardia and hypotension. Intravenous calcium gluconate may be of benefit combined with metaraminol.

Pharmaceutical precautions The capsules and tablets should be protected from strong light and stored in the manufacturer's original container.

Legal category POM.

Package quantities Adalat and Adalat 5 capsules are available in foil strips of 10 in packs of 100. Hospital packs containing 500 Adalat 10 mg capsules are available.

Adalat Retard tablets are also available in foil strips of 10 in packs of 100.

Further information As a specific calcium antagonist, Adalat's main action is to relax arterial smooth muscle both in the coronary and peripheral circulation.

In angina pectoris Adalat capsules relax peripheral arteries so reducing the load of the left ventricle. Additionally Adalat dilates submaximally both clear and atherosclerotic coronary arteries, thus protecting the

Objectives

1. To develop and evaluate a method of clinical trial management that would refute the hypothesis that it was no longer possible to conduct large population studies because of the excessive demands these studies make on financial and other resources.

2. To demonstrate that it was possible to conduct such a study, using this method of management, within such a time that the treatments under evaluation would not be outdated before the completion and reporting of the study.

3. To collect and evaluate the adverse medical events reported by a large population with essential hypertension, comparing those reported in relation to treatment with those reported by untreated hypertensive patients.

4. To collect a large single volume of data on the use of nifedipine in a population with essential hypertension.

Methods

The programme.

Practices with at least four practitioners who were known to have an interest in computing were approached to participate in the study. In 1985, general practice computing in Britain was largely restricted to enthusiasts. These were readily identifiable through such as; the Royal College of General Practitioners User Group, members of the Micros for GPs Scheme, the GPass System in Scotland and other smaller groups. Of the 600 practices approached, 486 agreed to take part, making a total of 1865 participating doctors. These practices are listed in Appendix 1. Any general practice which had a microcomputer and a communications modem was able to access the programme. Processing power within the practice was not necessary.

Development and testing: For each section of the programme, an algorithm was first sketched. For example, for the medication listing, entering a "YES" response against "medication" would lead into a list of classes of medication. A "YES" in a class then led to a list of all available drugs in that class, so that individual drugs could be listed. If only one class was indicated the user was returned to the main programme, if more than one

had been indicated, the user was directed to the individual drugs in each class, until finally being returned to the main programme. Working alongside an experienced computer programmer from the software company, Comedica UK, each of the algorithms was written into programming language. There then followed a testing period when combinations of mock data were entered to test the capacity of the system to follow the algorithms and check the data against the limits which the system should set. In conjunction with the programmer, the programme was then altered and rewritten. When that appeared satisfactory, a final testing period took place using general practitioners who had no previous knowledge of the system, who inevitably exposed additional errors that needed to be corrected. The development and testing period lasted for approximately six months. In parallel with this, the written materials for user training (Appendix 2) were produced.

All data were recorded by on-line transmission to a McDonnell-Douglas Seqoia mini-computer which also held the interactive programme using a data entry network. The data were recorded on a standard ASCII tape in a 1600 bpi unlabelled format. A sample record may be found on the disc accompanying this thesis. File markers are as follows:

: = end of record marker

! = field marker

* = item separator in tables

-9991 = missing value

The file name is MARLEY.TXT and contains 191,747 bytes.

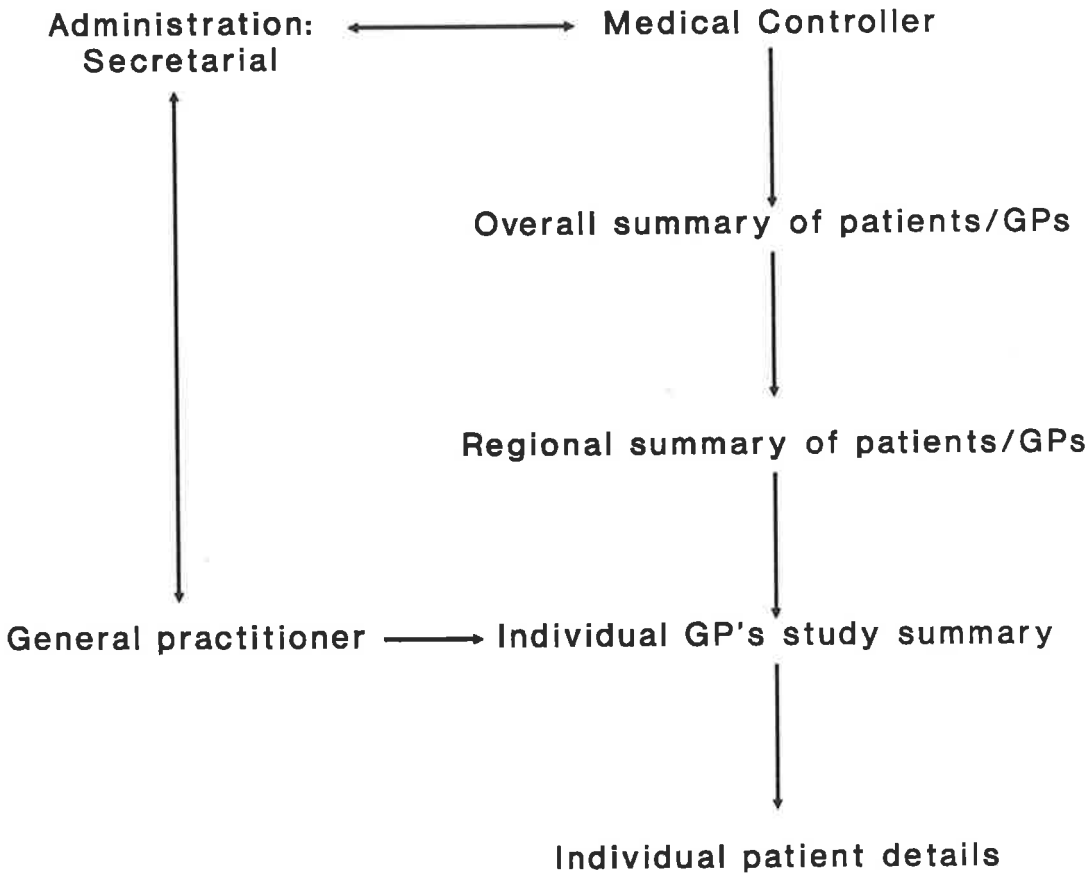
Part samples of the computer data print outs are shown in Appendix 6 (for demography data) and Appendix 7 (for blood pressure data).

The system was available for 24 hours a day with almost no "down time". Anticipated system maintenance periods were notified in advance on a bulletin board automatically presented to each user when logging-on to the system.

A duplicate training programme was available for participants to practise using the system before entering live patient data into the study. Instructions for this are shown in Appendix 2. The training and live systems were protected by different passwords to prevent the inadvertent entry of training data into the live study programme. Each practitioner had a unique password to prevent unauthorised access to the system and the possibility of corrupt data being entered. Each practitioner only had access to their own patient data. This could be displayed as summary tables of study progress or individual patient details. They were also able to view a table of overall study progress. The medical controller (J Marley) was the only person to have access to all the study data. The programme's administrative and hierarchical pathways are shown in Figure 2.

Figure 2

Administration Hierarchical Pathway



Average times taken to use the system were; one minute to log-on, five minutes to enter new patient details and two minutes for subsequent visits. In some practices one doctor performed the data entry for the whole practice, whereas, in others each individual entered his/her own data. Uniformity between the large number of doctors was assisted by the tight control of the protocol exerted by the programme. Checks were made of the data entered by some randomly selected doctors against that entered by others and the study means. In addition, the programme could automatically highlight doctors whose data pattern was unusual.

The use of the programme for data entry meant that it was impossible to skip any of the fields to be completed. At least in theory, there were no missing data. Entry errors were kept to a minimum by the programme checking each value as it was entered, for example, that it lay within a particular range. These checks were applied to all data-entry fields. Examples of their use include;-

1) Blood pressure limits; leading to the automatic rejection of normotensive and severely hypertensive patients whose blood pressures were outside of the inclusion criteria.

2) Weight ranges; leading to the automatic rejection of a keystroke error which might have resulted in a weight of 880kgm being entered instead of 88kgm.

The programme had an "electronic mail" facility, with very limited word-processing power, enabling messages to be sent to and from individual doctors and the medical controller as well as between each other.
After the programme had been designed, it was written for the operating system by Comedica UK Ltd.

Patients.

Patients suffering from mild to moderate essential hypertension with diastolic blood pressures between 95 and 115mmHg were eligible to be studied. They were either newly diagnosed patients or patients already taking antihypertensive pharmacological treatment. Patients were eligible to enter the nifedipine cohort if they were newly diagnosed hypertensives or previously treated but whose treatment was either not tolerated or not adequately controlling their blood pressure.

The study was approved by the Royal Berkshire Hospital Ethical Committee, Reading, Berkshire, UK.

Protocol.

Visit 1: A full medical history was taken, general examination performed and informed consent obtained. Blood pressure was measured on two separate occasions prior to this visit (those data being entered at Visit 1) to confirm the diagnosis of hypertension using the following protocol;

The patient was to sit for five minutes.

The correct sized cuff was to be placed over the brachial artery of the supported arm at the level of the heart.

A mercury sphygmomanometer to be used, with the observer's eye one metre from the mercury column at the same level as the meniscus.

For patients proceeding to treatment with nifedipine, who had been taking other antihypertensive medication, a washout period was required. This was to be one month, except that provision was made that if the patients blood pressure was rising in such a way (confirmed by two readings on separate occasions) that treatment was needed earlier, they could proceed to active treatment sooner.

Adverse medical events experienced in the four weeks prior to entry to the study, by all patients treated or untreated, were recorded at first contact. These data were actually entered into the programme at Visit 1. This enquiry was made by asking for the ten most frequently recorded adverse events related to antihypertensive drug treatment and those collected in response to the question, "Have you felt unwell in any way". These responses were graded subjectively as; 1 = mild, 2 = moderate, 3 = severe and 4 = intolerable.

Statisticians prefer the use of the open question only for adverse events, (J. Curram, Ph D Statistics, personal communication), as least likely to cause bias. However handling large volumes of uncoded and potentially uncodable data is difficult and the use of a questionnaire for the most likely

events reduces the complexity of data entry and analysis. It was important to attempt to test whether this use of a questionnaire collected reliable information, or whether it restricted the gathering of the rare, unusual, but important adverse events.

Nifedipine treatment exclusions:

Patients were excluded from entering treatment with nifedipine if they were;

Pregnant or of child bearing age and not using reliable contraception.

Lactating.

Suffering from significant renal, gastrointestinal or hepatic disease.

Suffered a myocardial infarction within the previous three months.

Taking other antihypertensive medication which could not be safely or ethically withdrawn for the study period.

Over 70 years old.

Suffering from a cardiac arrhythmia.

Known to be intolerant of dihydropyridines.

In those patients taking nifedipine, adverse medical events were recorded in the manner described above at Visit 2 after four weeks, and visit 3 after eight weeks. Blood pressure was also measured at these times.

Tracking and demography: The system allocated each doctor and patient an unchangeable system number. On entering a new patient to the study the

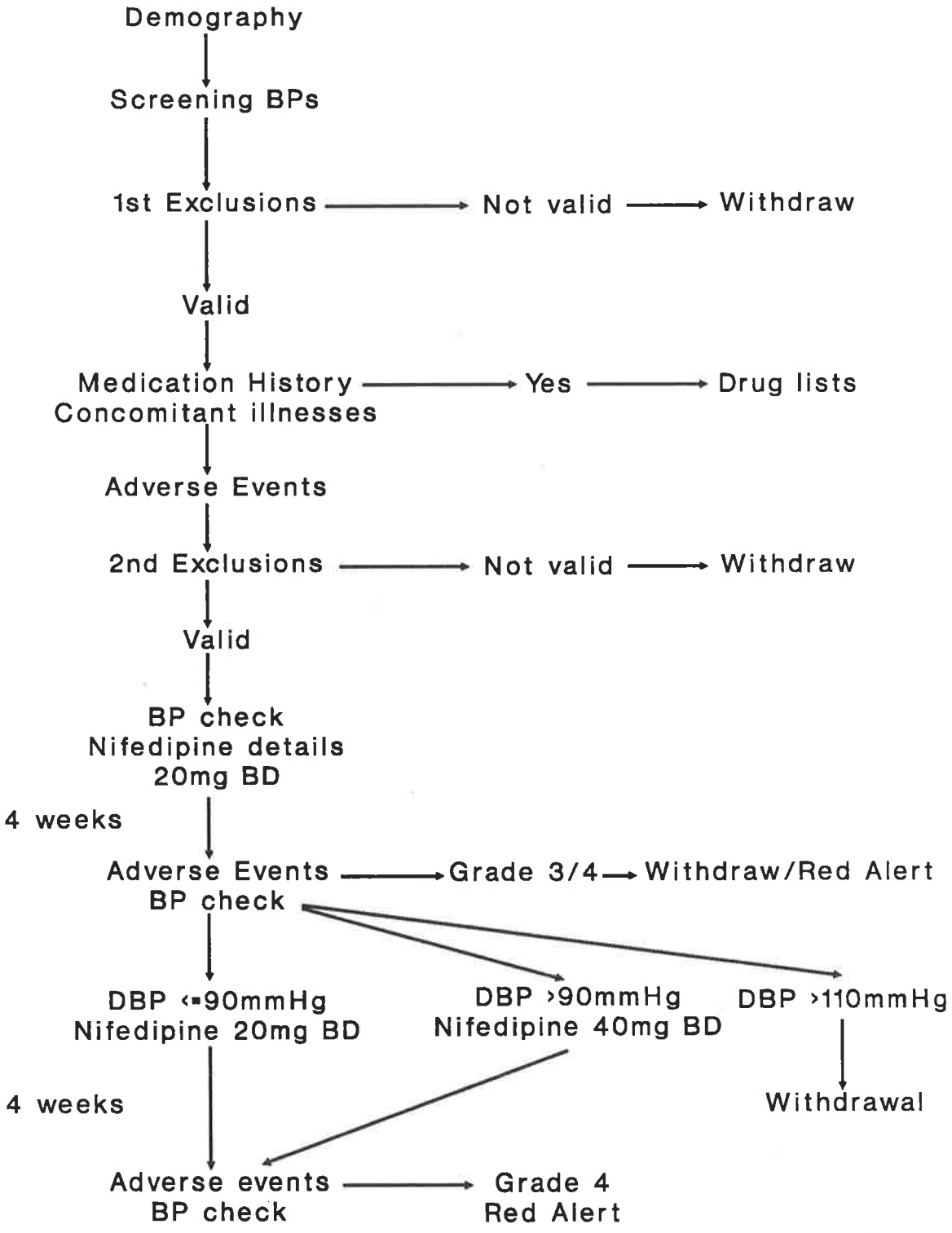
programme asked investigators to allocate their own additional identifier to the patient which would preserve the confidentiality of patient data, but enable them to identify each patient simply for their own use. The investigator was then led through data entry screens collecting demographic details such as; age, sex, height, weight, medical history, hypertension history, systolic and diastolic blood pressures, antihypertensive and other medication.

Details of antihypertensive medication were recorded by doctors entering a YES/NO response in a drug category. For example, on entering YES for "diuretics", they were routed into a screen listing all the currently available drugs in that category, to indicate which specific drug was being taken. Specific enquiry was made for patients taking H2 receptor antagonist drugs and digoxin, since a possible interaction with nifedipine was thought to exist.

Intercurrent illnesses were collected as free text. The investigator was also led through a screen containing the exclusion criteria for the nifedipine taking cohort, contravention of any of these criteria took that patient into an automatic withdrawal route. A flow chart for the programme and the study as a whole, is shown in Figure 3.

Figure 3

Programme Flow Chart



Adverse events: At Visits 2 and 3, the programme asked for adverse event information which at those visits related solely to treatment with nifedipine. These were numerically graded as; 1 = mild, 2 = moderate, 3 = severe and 4 = intolerable.

A response at a severity level of 3 or 4 led the investigator into an automatic withdrawal pathway for that patient. At the discretion of the investigator this could be over-ruled for category 3 events but not for category 4. These events were also automatically displayed to the medical controller of the study, so that any further information necessary could be collected by telephone or mail. These events could also be directly transferred to the electronic adverse event data base of the Committee for the Safety of Medicines. Adverse event recording pathways are shown in Figure 4.

The investigator was also asked to record systolic and diastolic blood pressures, intercurrent illnesses and concomitant medication. The addition of a new antihypertensive drug to a patient in the nifedipine cohort resulted in that patient being automatically withdrawn. The investigator could request patient withdrawal at any time and on indicating this, was led into screens recording the reason for withdrawal. Withdrawal pathways are shown in Figure 5.

Figure 4

Adverse Event Flow Chart

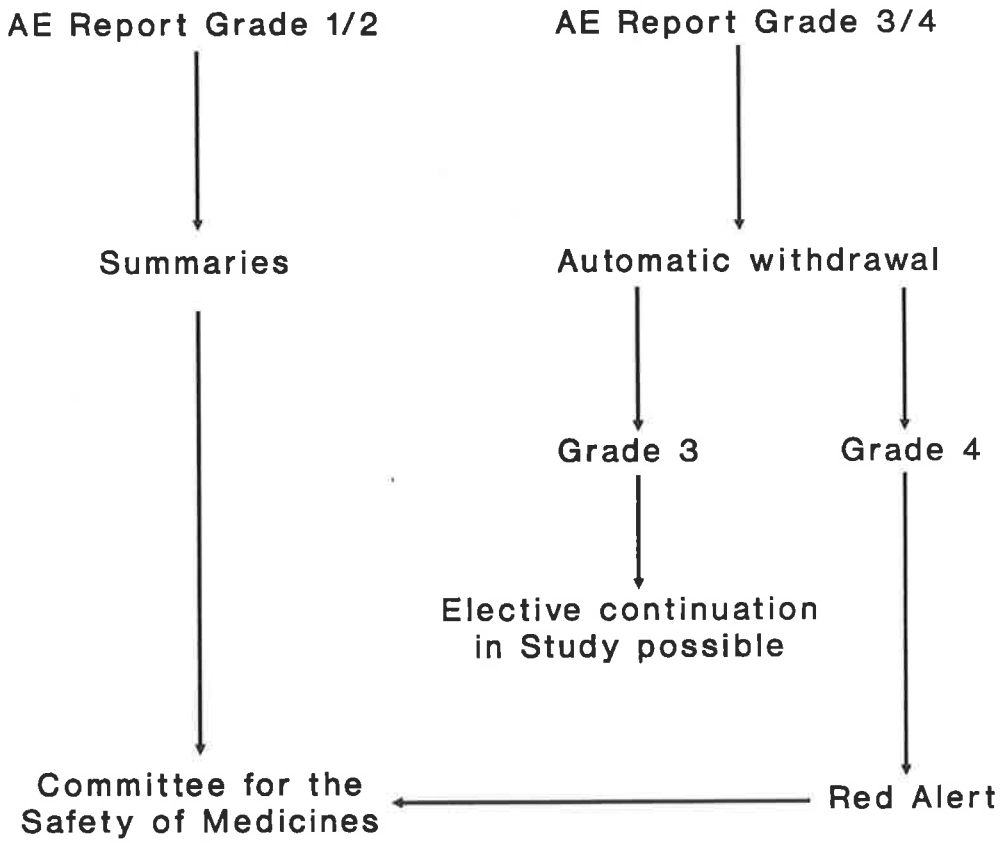
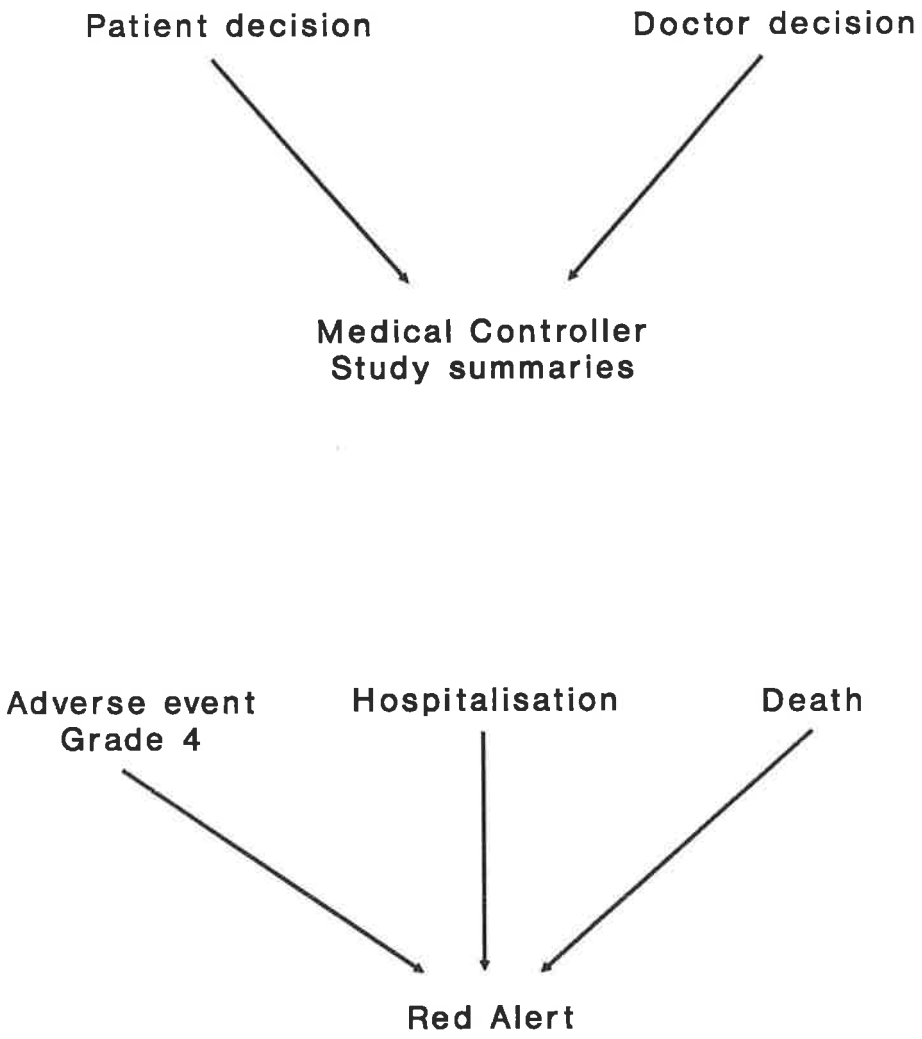


Figure 5

Withdrawal Pathways



Patients overdue for return visits were displayed on the investigator's summary tables enabling action to be taken before the protocol was violated and minimising the number of patients lost to follow-up.

Nifedipine treatment:

Those patients eligible at visit 1 to be treated with nifedipine, started therapy with nifedipine 20mg tablets twice daily. Since this was principally a study of safety and methodology, this treatment was not in any way blind. Those patients whose sitting diastolic blood pressure at visit 2, after 4 weeks treatment, was greater than 90mmHg had their dose of nifedipine tablets increased to 40mg twice daily.

Statistics:

Statistical analysis was performed using SAS (Statistical Analysis System) on an IBM mainframe computer.

The demography and efficacy variables were tested for normality using the Shapiro-Wilk Test. Where data appeared normally distributed, the Student's t-test was used in the statistical analysis. Where the data were categorical, the chi-squared test was used.

Demography (age, sex, weight, height, smoking habit, hypertension whether newly diagnosed, or the number of years since hypertension was diagnosed)

was summarised for all patients at entry, using descriptive statistics; frequency counts or mean/standard deviation.

Efficacy parameters for nifedipine were blood pressures and heart rates. Within group comparisons were performed for; start to week 4, start to week 8 and week 4 to week 8, using Student's paired t-tests.

With such a large sample size most statistical tests were highly significant. No adjustment for repeated testing was made, but a large number of statistical tests were performed.

Results

At visit 1, data were collected for the point prevalence adverse event examination on 3972 patients of whom 2041 were male and 1931 were female. Of these, 2951 were non-smokers. Newly diagnosed and therefore previously untreated hypertensives numbered 2772. Of the remainder who had been previously treated, 346 had been treated with diuretics, 513 with beta-blockers, 180 with diuretics and beta-blockers in combination and 161 with other antihypertensives. These included, 112 taking vasodilators. H2 receptor antagonists were taken by 45 patients and digoxin by six, these numbers were too low to assess any potential interaction.

Full demographic details are shown in Table 2. The untreated and previously treated populations were demographically similar. The cohort who completed eight weeks treatment with nifedipine numbered 2820 patients.

Concurrent diseases listed by sex are shown in Appendix 3. In those patients who were known to be hypertensive and undergoing treatment prior to the study, the mean duration of hypertension was 5.81 years.

Adverse events reported by untreated patients and in previously treated patients related to treatment with groups of antihypertensive drugs are shown

in Table 3. Adverse events collected at visits 2 and 3, together with changes from visit 1, related to treatment by nifedipine, are shown in Tables 4 to 13. It should be noted that the four treatment categories in these tables refer to treatment prior to, but entered at visit 1, the reports at visits 2 and 3 refer to events reported by those patients after four and eight weeks treatment with nifedipine. These tables also show the number of events reported within each age group and according to smoking history. The numbers of patients in each age group at each visit are shown in Table 16.

1560 free text reports were collected in answer to the question "Has your treatment upset you in any way"? These were scanned using word-search facilities for patterns and all were read individually. No discernible pattern emerged from this. All were coded using the "CoStart" Adverse Event Thesaurus of the United States FDA. Free text reports entered as being of severity Grade 3 or 4, are shown in Appendix 4.

TABLE 2

PATIENT DEMOGRAPHY

		MALE	FEMALE	ALL PATIENTS
NUMBER STUDIED:		2041	1931	3972
AGE (YEARS):	MEAN	56.4	58.0	57.2
	SD	9.2	8.4	8.9
WEIGHT (KG):	MEAN	80.8	70.2	75.6
	SD	13.7	13.7	14.7
HEIGHT (M):	MEAN	1.727	1.612	1.671
	SD	0.086	0.069	0.097
SMOKER:	NO	1412	1539	2951
	YES	629	392	1021
SYSTOLIC BLOOD PRESSURE AT ENTRY: (mmHg)	MEAN	172.5	176.8	174.6
	SD	20.3	20.1	20.1
DIASTOLIC BLOOD PRESSURE AT ENTRY: (mmHg)	MEAN	104.2	104.2	104.2
	SD	5.7	5.8	5.8

SD = standard deviation

TABLE 3

PREVALENCE OF ADVERSE EVENTS RELATED TO ANTIHYPERTENSIVE TREATMENT GROUP

TREATMENT	LETHARGY		ANKLE SWELLING		DIZZINESS		HEADACHE		IMPOTENCE	
	n	%	n	%	n	%	n	%	n	%
ANY ANTI-HYPERTENSIVE (N = 1200)	381	31.8	59	4.9	133	11.1	139	11.6	70 (N = 600)	11.6
B-BLOCKER (N = 513)	282	54.9	23	4.5	83	16.2	61	11.9	48 (N = 256)	18.8
DIURETICS (N = 346)	25	7.2	13	3.8	19	5.5	20	5.8	9 (N = 178)	5.2
UNTREATED (N = 2772)	48	1.7	22	0.8	60	2.2	101	3.6	15 (N = 1386)	1.1

TREATMENT	NAUSEA		DYSPNOEA		SKIN FLUSHING		COLD EXTREMITIES		PALPITATIONS	
	n	%	n	%	n	%	n	%	n	%
ANY ANTI-HYPERTENSIVE (N = 1200)	60	5.0	181	15.1	23	1.9	273	22.8	41	3.4
B-BLOCKER (N = 513)	31	6.0	119	23.0	10	1.9	222	43.3	25	4.9
DIURETICS (N = 346)	7	2.0	16	4.6	3	0.9	9	2.6	4	1.2
UNTREATED (N = 2772)	17	0.6	66	2.4	17	0.6	21	0.8	21	0.8

TABLE 4

SIDE EFFECTS PROFILE - NAUSEA

		VISIT 1	VISIT 2	VISIT 3
ALL:		77	99	44
SEX:	Male	30	47	23
	Female	47	52	21
SMOKES:	Yes	17	29	19
	No	60	70	25
AGE:	18-35	-	3	-
	36-50	13	22	10
	51-60	32	33	19
	61+	32	41	15
TREATMENT:	Treated	60	48	21
	Untreated	17	51	23
	Beta Blockers	31	29	9
	Diuretics	7	4	1

TABLE 5

SIDE EFFECTS PROFILE - ANKLE SWELLING

		VISIT 1	VISIT 2	VISIT 3
ALL:		81	249	228
SEX:	Male	22	75	84
	Female	59	174	144
SMOKES:	Yes	18	46	50
	No	63	203	178
AGE:	18-35	2	1	2
	36-50	16	46	42
	51-60	25	93	84
	61+	38	109	100
TREATMENT:	Treated	59	149	123
	Untreated	22	100	105
	Beta Blockers	23	68	58
	Diuretics	13	30	24

TABLE 6

SIDE EFFECTS PROFILE - DYSPNOEA

		VISIT 1	VISIT 2	VISIT 3
ALL:		247	73	50
SEX:	Male	136	31	25
	Female	111	42	25
SMOKES:	Yes	72	20	16
	No	175	53	34
AGE:	18-35	3	1	-
	36-50	44	14	11
	51-60	73	23	17
	61+	127	35	22
TREATMENT:	Treated	181	38	27
	Untreated	66	35	23
	Beta Blockers	119	15	9
	Diuretics	16	8	5

TABLE 7

SIDE EFFECTS PROFILE - IMPOTENCE

		VISIT 1	VISIT 2	VISIT 3
ALL:		85	23	18
SEX:	Male	76	19	15
	Female	9	4	3
SMOKES:	Yes	27	6	6
	No	58	17	12
AGE:	18-35	-	1	-
	36-50	24	8	4
	51-60	31	7	7
	61+	30	7	7
TREATMENT:	Treated	70	14	11
	Untreated	15	9	7
	Beta Blockers	48	4	4
	Diuretics	9	3	2

TABLE 8

SIDE EFFECTS PROFILE - COLD EXTREMITIES

		VISIT 1	VISIT 2	VISIT 3
ALL:		294	33	25
SEX:	Male	144	19	14
	Female	150	14	11
SMOKES:	Yes	85	8	6
	No	209	25	19
AGE:	18-35	4	-	1
	36-50	58	7	3
	51-60	80	13	9
	61+	152	13	12
TREATMENT:	Treated	273	25	13
	Untreated	21	8	12
	Beta Blockers	222	13	5
	Diuretics	9	4	1

TABLE 9

SIDE EFFECTS PROFILE - DIZZINESS

		VISIT 1	VISIT 2	VISIT 3
ALL:		193	145	96
SEX:	Male	72	68	45
	Female	121	77	51
SMOKES:	Yes	49	43	24
	No	144	102	72
AGE:	18-35	1	1	-
	36-50	35	26	14
	51-60	64	65	34
	61+	93	53	48
TREATMENT:	Treated	133	83	42
	Untreated	60	62	54
	Beta Blockers	83	36	19
	Diuretics	19	9	5

TABLE 10

SIDE EFFECTS PROFILE - PALPITATIONS

		VISIT 1	VISIT 2	VISIT 3
ALL:		62	94	51
SEX:	Male	26	53	30
	Female	36	41	21
SMOKES:	Yes	14	25	15
	No	48	69	36
AGE:	18-35	-	4	-
	36-50	14	16	10
	51-60	27	30	23
	61+	21	44	18
TREATMENT:	Treated	41	52	22
	Untreated	21	42	29
	Beta Blockers	25	28	11
	Diuretics	4	3	1

TABLE 11

SIDE EFFECTS PROFILE - LETHARGY

		VISIT 1	VISIT 2	VISIT 3
ALL:		429	146	103
SEX:	Male	208	72	50
	Female	221	74	53
SMOKES:	Yes	118	45	33
	No	311	101	70
AGE:	18-35	11	5	-
	36-50	88	32	21
	51-60	134	50	38
	61+	196	59	44
TREATMENT:	Treated	381	89	62
	Untreated	48	57	41
	Beta Blockers	282	49	27
	Diuretics	25	12	6

TABLE 12

SIDE EFFECTS PROFILE - SKIN FLUSH

		VISIT 1	VISIT 2	VISIT 3
ALL:		40	491	311
SEX:	Male	16	200	135
	Female	24	291	176
SMOKES:	Yes	10	124	81
	No	30	367	230
AGE:	18-35	-	8	6
	36-50	10	103	65
	51-60	14	173	106
	61+	16	207	134
TREATMENT:	Treated	23	256	147
	Untreated	17	235	164
	Beta Blockers	10	124	55
	Diuretics	3	44	30

TABLE 13

SIDE EFFECTS PROFILE - HEADACHE

		VISIT 1	VISIT 2	VISIT 3
ALL:		240	485	244
SEX:	Male	99	224	124
	Female	141	261	120
SMOKES:	Yes	73	142	78
	No	167	343	166
AGE:	18-35	5	10	8
	36-50	58	120	68
	51-60	79	173	73
	61+	98	182	95
TREATMENT:	Treated	139	250	119
	Untreated	101	235	125
	Beta Blockers	61	113	45
	Diuretics	20	38	18

There were three deaths in the course of treatment with nifedipine. Angina commonly accompanied hypertension in patients in the study and a 59 year old male who suffered from both noted increasing angina. This was treated and investigated appropriately but 10 days after withdrawing from the study he suffered a fatal myocardial infarction. A 63 year old male whose blood pressure was well controlled experienced a cerebrovascular accident from which he eventually died. The third death occurred in a woman who as well as suffering from hypertension suffered from pancreatitis, angina pectoris and cardiomyopathy. As well as nifedipine she was also taking propranolol, isosorbide mononitrate and glyceryl trinitrate. She clearly violated the protocol with this therapeutic regimen, since the aim of this part of the study was to collect events related to nifedipine alone. The treating doctor ignored the system prompts and entered incorrect responses to bypass the checks. Careful review of these deaths did not suggest a reason to implicate nifedipine in their cause.

Non-fatal significant adverse events included two cases of moderate left ventricular failure, one of postural hypotension and one of onychogryphosis.

Withdrawals from the study:

561 patients withdrew from treatment with nifedipine due to adverse events,

161 patients violated some aspect of the protocol other than medication,

39 patients did not fully comply with the treatment,

33 patients required alternative treatment of their blood pressure,

36 patients elected to withdraw from the study.

Pharmacodynamics of nifedipine:

Mean blood pressures and heart rates at each visit are shown in Table 14. Changes in blood pressure and heart rate between visits are shown in Table 15.

Mean blood pressures and heart rates are shown in relation to different age groups in Table 16. Changes in systolic blood pressure between visits related to age are shown in Table 17, changes in diastolic blood pressure in Table 18 and in heart rate in Table 19.

Mean blood pressures and heart rates for smokers and non-smokers are shown in Table 20. Changes in blood pressure and heart rate for smokers and non-smokers are shown in Table 21.

Mean blood pressures and heart rates for women and men, together with the numbers of patients increasing their dose of nifedipine to 40mg twice daily, are shown in Table 22.

The changes in blood pressures and heart rates for patients newly diagnosed as hypertensive and those previously treated with any antihypertensive drug are shown in Table 23. Mean blood pressures and heart rates for those

patients previously treated with beta-blockers and diuretics whose treatment was changed to nifedipine, are shown in Table 24. Changes in blood pressures and heart rates between visits in response to nifedipine, for those patients whose previous treatments had been diuretics and beta-blockers, are shown in Tables 25 and 26 respectively.

Means of; weights, heights, systolic blood pressures, diastolic blood pressures and heart rates, broken down by sex, age and smoking habit, are shown in Table 27 for patients whose hypertension was newly diagnosed.

Means of; weights, heights, systolic blood pressures, diastolic blood pressures and heart rates, broken down by sex, age and smoking habit, together with years of hypertension, are shown in Table 28 for patients whose hypertension was not newly diagnosed. Table 29 shows mean weights for all patients in each age group.

Scatter plots for diastolic blood pressures against body mass index, for treated and untreated patients, to show correlation, are shown in Figures 6a and 6b. In these plots; A = 1 count, B = 2 counts, C = 3 counts, etc.

Lists of numbers of patients at each value for body mass index, against diastolic blood pressures, together with diastolic blood pressure against body mass index statistical calculations, are shown in Appendix 8.

TABLE 14

MEAN BLOOD PRESSURE & HEART RATE
ALL PATIENTS
(MM HG/BPM)

		VISIT 1	VISIT 2	VISIT 3
SYSTOLIC BP	N	3972.0	3332.0	2820.0
	MEAN	174.6	154.8	150.5
	SD	20.1	19.8	17.9
DIASTOLIC BP	N	3972.0	3324.0	2820.0
	MEAN	104.2	90.6	87.4
	SD	5.8	14.6	9.3
HEART RATE	N	3972.0	3320.0	2818.0
	MEAN	78.6	79.2	78.7
	SD	8.9	9.4	9.0

No. of patients increasing dose to 40mg at VISIT 2: 1115.
No. of patients with BP>160/90 at VISIT 3: 921.

TABLE 15

CHANGES IN BLOOD PRESSURE (MM HG) AND HEART RATE (BPM) - ALL PATIENTS

		SYSTOLIC BP	DIASTOLIC BP	HEART RATE
VISIT 1-2	MEAN DIF	-19.9*	-13.6*	-0.7*
	SD DIF	19.8	14.6	8.9
VISIT 1-3	MEAN DIF	-24.3*	-16.8*	-0.2
	SD DIF	20.2	9.9	9.1
VISIT 2-3	MEAN DIF	-4.0	-2.4*	-0.3
	SD DIF	14.6	9.9	6.9

* ($p <= 0.001$)

TABLE 16

MEAN BLOOD PRESSURE AND HEART RATE BY AGE

	AGE	SYSTOLIC BP (MM HG)			DIASTOLIC BP (MM HG)			HEART RATE (BPM)		
	YRS	N	MEAN	SD	N	MEAN	SD	N	MEAN	SD
VISIT 1	18-35	64	157.7	16.3	64	101.2	5.3	64	78.9	8.1
	36-50	827	167.2	17.9	827	104.2	5.8	827	78.2	8.9
	51-60	1411	172.7	19.0	1411	104.3	5.7	1411	78.4	8.7
	61+	1670	180.4	20.4	1670	104.3	5.8	1670	78.8	9.2
VISIT 2	18-35	51	148.2	14.2	51	91.3	9.6	51	80.6	11.3
	36-50	651	150.2	17.4	650	91.7	10.8	648	78.8	9.5
	51-60	1190	153.7	19.7	1186	91.7	20.3	1184	79.1	9.5
	61+	1235	153.5	18.8	1235	86.6	9.3	1284	78.9	9.1
VISIT 3	18-35	42	143.1	16.6	42	89.0	8.9	42	81.9	10.6
	36-50	550	146.3	16.5	550	88.4	9.8	550	78.1	8.5
	51-60	993	149.4	16.8	993	87.9	9.1	992	78.8	9.1
	61+	1235	153.5	18.8	1235	86.6	9.3	1284	78.9	9.1

	18-35	36-50	51-60	61+
No of patients increasing dose to 40mg at Visit 2:	19	254	423	416
No of patients with BP>160/90 at Visit 3:	12	173	311	445

TABLE 17

CHANGE IN SYSTOLIC BLOOD PRESSURE BY AGE
(mmHg/yrs)

		18-35	36-50	51-60	61+
VISIT 1-2	MEAN DIF	-11.6*	-17.0*	-18.8*	-22.4*
	SD DIF	14.0	18.0	19.5	20.7
VISIT 1-3	MEAN DIF	-15.8*	-21.0*	-22.7*	-27.3*
	SD DIF	18.1	19.1	19.0	21.2
VISIT 2-3	MEAN DIF	-3.5*	-3.7*	-3.6*	-4.5*
	SD DIF	11.3	13.3	14.1	15.6

* ($p <= 0.001$)

TABLE 18

CHANGE IN DIASTOLIC BLOOD PRESSURE BY AGE MM HG/YRS

		18-35	36-50	51-60	61+
VISIT 1-2	MEAN DIF	-10.6*	-12.6*	-12.6*	-15.0*
	SD DIF	9.7	10.8	20.8	10.0
VISIT 1-3	MEAN DIF	-12.5*	-16.0*	-16.3*	-17.7*
	SD DIF	9.3	10.2	9.7	9.9
VISIT 2-3	MEAN DIF	-1.4	-2.7*	-2.5*	-2.3*
	SD DIF	7.8	10.1	9.8	9.9

* ($p <= 0.001$)

TABLE 19

CHANGE IN HEART RATE BY AGE
(BPM/YRS)

			18-35	36-50	51-60	61+
VISIT 1-2	MEAN	DIF	1.9	0.0	0.9*	0.8
	SD	DIF	10.3	8.4	9.2	8.9
VISIT 1-3	MEAN	DIF	3.0	-0.9	0.5	0.3
	SD	DIF	10.5	9.1	8.9	9.2
VISIT 2-3	MEAN	DIF	1.1	-0.5	-0.2	-0.3
	SD	DIF	7.5	7.5	7.2	6.4

* ($p <= 0.001$)

TABLE 20

MEAN BLOOD PRESSURE AND HEART RATE
(mmHg/bpm)
FOR SMOKERS AND NON SMOKERS

		VISIT 1		VISIT 2		VISIT 3	
		YES	NO	YES	NO	YES	NO
SYSTOLIC BP	N	1021.0	2951.0	873.0	2459.0	754.0	2066.0
MM HG	MEAN	173.6	174.9	154.6	154.9	149.4	150.9
	SD	19.4	20.4	19.1	20.0	18.6	17.6
DIASTOLIC BP	N	1021.0	2951.0	873.0	2451.0	754.0	2066.0
MM HG	MEAN	104.2	104.2	90.8	90.6	87.8	87.3
	SD	5.8	5.7	10.6	15.8	9.3	9.4
HEART RATE	N	1021.0	2951.0	871.0	2449.0	753.0	2065.0
BPM	MEAN	79.5	78.3	79.9	79.0	79.5	78.5
	SD	9.1	8.9	9.2	9.5	8.6	9.1

	SMOKER	
	YES	NO
No of patients increasing dose to 40mg at visit 2:	314	801
No of patients with BP>160/90 at visit 3:	249	692

TABLE 21

CHANGE IN BLOOD PRESSURE (MM HG) & HEART RATE (BPM) AS RELATED TO SMOKING HABIT

			SYSTOLIC BP YES	SYSTOLIC BP NO	DIASTOLIC BP YES	DIASTOLIC BP NO	HEART RATE BP YES	HEART RATE BP NO
VISIT 1-2	MEAN	DIF	-20.2*	-18.8*	-13.6*	-13.4*	0.8*	0.5
	SD	DIF	20.1	18.8	15.9	10.1	9.3	7.9
VISIT 1-3	MEAN	DIF	-24.5*	-23.6*	-17.1*	-16.3*	0.2*	0.0
	SD	DIF	20.3	19.8	10.1	9.5	9.2	8.8
VISIT 2-3	MEAN	DIF	-3.9*	-4.2*	-2.5*	-2.1*	-0.2*	-0.3*
	SD	DIF	14.6	14.6	10.2	9.1	7.1	6.5

* ($p <= 0.001$)

TABLE 22

MEAN BLOOD PRESSURE (MM HG) & HEART RATE (BPM) BY SEX

		VISIT 1		VISIT 2		VISIT 3	
		FEMALE	MALE	FEMALE	MALE	FEMALE	MALE
SYSTOLIC BP MM HG	N	1931.0	2041.0	1589.0	1743.0	1321.0	1499.0
	MEAN	176.8	172.5	156.6	153.2	151.6	149.5
	SD	20.1	20.0	20.1	19.3	17.5	17.8
DIASTOLIC BP	N	1931.0	2043.0	1585.0	1739.0	1321.0	1499.0
	MEAN	104.2	104.2	90.3	90.9	87.2	87.6
	SD	5.8	5.7	10.1	17.8	9.0	9.6
HEART RATE	N	1931.0	2041.0	1584.0	1736.0	1321.0	1497.0
	MEAN	78.9	78.3	79.6	78.9	79.0	78.5
	SD	8.8	9.1	10.0	8.9	9.6	8.5

No. of patients increasing dose to 40mg at visit 2	Female:	500
	Male:	615
No. of patients with BP>160/90 at visit 3	Female:	445
	Male:	496

TABLE 23

CHANGE IN BLOOD PRESSURE (MM HG) & HEART RATE (BPM) - FOR PREVIOUSLY TREATED & UNTREATED PATIENTS

			SYSTOLIC BP UNTR	SYSTOLIC BP TR	DIASTOLIC BP UNTR	DIASTOLIC BP TR	HEART RATE BP UNTR	HEART RATE BP TR
VISIT 1-2	MEAN	DIF	(21.0)*	(18.7)*	(13.9)*	(13.2)*	(0.1)	1.5*
	SD	DIF	19.1	20.3	17.8	10.9	8.1	9.7
VISIT 1-3	MEAN	DIF	(25.7)*	(22.9)*	(17.5)*	(16.1)*	(0.6)	0.9*
	SD	DIF	19.9	20.3	10.1	9.7	8.1	10.1
VISIT 2-3	MEAN	DIF	(4.4)*	(3.6)*	(2.7)*	(2.2)*	(0.2)	(0.3)
	SD	DIF	14.1	15.1	9.3	10.3	6.7	7.1

* ($p <= 0.001$)

TABLE 24

MEAN BLOOD PRESSURE AND HEART RATE
(mmHg/bpm)
IN PATIENTS PREVIOUSLY TREATED WITH BETA BLOCKERS & DIURETICS

		VISIT 1		VISIT 2		VISIT 3	
		BETA BLOCKER	DIUR	BETA BLOCKER	DIUR	BETA BLOCKER	DIUR
SYSTOLIC BP	N	857.0	346.0	718.0	283.0	589.0	250.0
MM HG	MEAN	173.3	172.7	155.4	155.2	151.8	151.5
	SD	21.4	17.7	21.2	20.5	19.8	17.2
DIASTOLIC BP	N	857.0	346.0	715.0	282.0	589.0	250.0
MM HG	MEAN	103.4	103.1	90.4	90.2	87.7	87.3
	SD	5.9	5.3	10.4	9.1	9.0	8.1
HEART RATE	N	857.0	346.0	714.0	282.0	589.0	250.0
BPM	MEAN	77.1	79.0	79.2	78.6	79.3	77.9
	SD	9.4	8.0	9.4	9.5	8.9	8.9

	BETA BLOCKER	DIUR
No of patients increasing dose to 40mg at visit 2:	225	97
No of patients with BP>160/90 at visit 3:	194	84

TABLE 25

CHANGE IN BLOOD PRESSURE (MM HG) AND HEART RATE (BPM) - PATIENT PREVIOUSLY TREATED WITH DIURETIC

		SYSTOLIC BP	DIASTOLIC BP	HEART RATE
VISIT 1-2	MEAN DIF	-17.8*	-13.0*	-0.3
	SD DIF	20.3	9.3	8.3
VISIT 1-3	MEAN DIF	-21.5*	-15.8*	-0.9
	SD DIF	18.7	8.7	7.6
VISIT 2-3	MEAN DIF	-3.7*	-2.3*	-0.3
	SD DIF	12.2	8.1	6.0

* ($p <= 0.001$)

TABLE 26

CHANGE IN BLOOD PRESSURE (MM HG) AND HEART RATE (BPM) - PATIENT PREVIOUSLY TREATED WITH A BETA BLOCKER

		SYSTOLIC BP	DIASTOLIC BP	HEART RATE
VISIT 1-2	MEAN DIF	-17.9*	-13.1*	-3.0*
	SD DIF	20.9	10.2	10.8
VISIT 1-3	MEAN DIF	-21.5*	-15.8*	-2.3*
	SD DIF	21.2	9.7	11.4
VISIT 2-3	MEAN DIF	-3.1*	-2.3*	-0.0
	SD DIF	15.7	8.5	7.5

* ($p <= 0.001$)

TABLE 27

NEWLY DIAGNOSED HYPERTENSION: RELATIONSHIP BETWEEN BLOOD PRESSURES (mmHg), PULSE RATE(bpm) SEX, SMOKING HABIT AND AGE

SEX	SMOKER	AGE	MEAN WEIGHT	MEAN HEIGHT	MEAN SBP	MEAN DBP	MEAN HR
FEMALE	NO	18-35	81.83	156.17	163.33	103.83	78.50
		36-50	73.47	162.47	171.88	104.84	77.98
		51-60	70.85	161.37	176.75	104.66	79.40
		61+	68.93	160.39	183.18	105.04	79.73
SUBTOTAL FEMALE NON-SMOKER			70.58	161.09	178.60	104.86	79.28
FEMALE	YES	18-35	74.00	162.20	157.00	105.00	80.00
		35-50	65.12	162.41	170.09	104.33	80.19
		51-60	67.55	162.00	177.52	104.52	80.27
		61+	65.91	159.44	180.67	105.91	80.06
SUBTOTAL FEMALE SMOKER			66.47	161.30	175.84	104.92	80.17
MALE	NO	18-35	91.00	176.14	161.29	100.50	81.36
		35-50	81.50	171.27	164.84	104.61	77.42
		51-60	82.65	172.76	171.38	104.80	78.85
		61+	78.03	171.71	180.00	104.83	78.45
SUBTOTAL MALE NON-SMOKER			80.79	172.06	172.79	104.68	78.39
MALE	YES	18-35	81.00	172.87	155.00	100.12	78.87
		35-50	81.98	174.40	166.90	105.01	80.43
		51-60	80.56	173.23	172.45	104.60	81.48
		61+	78.72	171.79	181.77	103.97	81.25
SUBTOTAL MALE SMOKER			80.37	173.08	173.52	104.40	80.98
TOTAL			75.55	167.16	175.33	104.72	79.33

TABLE 28

PATIENTS ALREADY UNDER TREATMENT FOR HYPERTENSION - BLOOD PRESSURES, SEX, SMOKING HABITS AND AGE GROUPS AND DURATION OF HYPERTENSION (YEARS)

SEX	SMOKER	AGE	MEAN WEIGHT	MEAN HEIGHT	MEAN SBP	MEAN DBP	MEAN HR	YRS WITH HYPER
FEMALE	NO	18-35	73.86	160.14	161.14	100.14	80.29	2.70
		36-50	74.48	161.25	167.57	103.23	79.07	5.06
		51-60	72.40	161.83	174.12	103.95	77.58	6.14
		61+	68.12	161.01	180.32	104.09	78.34	6.32
SUBTOTAL FEMALE NON-SMOKER			70.61	161.32	176.07	103.88	78.21	6.03
FEMALE	YES	18-35	60.00	157.25	146.25	101.25	79.00	8.39
		35-50	65.96	160.21	169.32	103.14	76.57	4.50
		51-60	72.81	162.10	171.86	103.60	78.06	6.15
		61+	70.31	160.46	179.73	103.52	79.16	6.68
SUBTOTAL FEMALE SMOKER			70.46	161.01	174.41	103.45	78.35	6.16
MALE	NO	18-35	90.17	176.75	152.08	101.50	78.92	2.69
		35-50	85.20	173.93	166.14	103.89	77.04	4.45
		51-60	82.25	174.01	168.39	103.79	76.88	5.29
		61+	77.14	171.17	179.64	103.37	77.09	7.25
SUBTOTAL MALE NON-SMOKER			80.86	172.86	172.34	103.60	77.04	5.93
MALE	YES	18-35	91.12	171.75	155.62	102.00	82.37	2.93
		35-50	85.04	175.31	165.75	103.87	78.16	3.17
		51-60	81.23	173.82	172.60	104.37	77.24	5.40
		61+	78.90	171.59	174.25	103.58	78.35	5.01
SUBTOTAL MALE SMOKER			81.39	173.19	171.30	103.88	78.03	4.69
TOTAL			75.74	167.04	173.92	103.74	77.79	5.81

TABLE 29

MEAN WEIGHT (Kgm) FOR ALL PATIENTS BY AGE (Years)

AGE	MEAN WEIGHT
18-35	80.37
36-50	76.59
51-60	76.29
61+	73.25
ALL AGES	76.62

Figure 6a

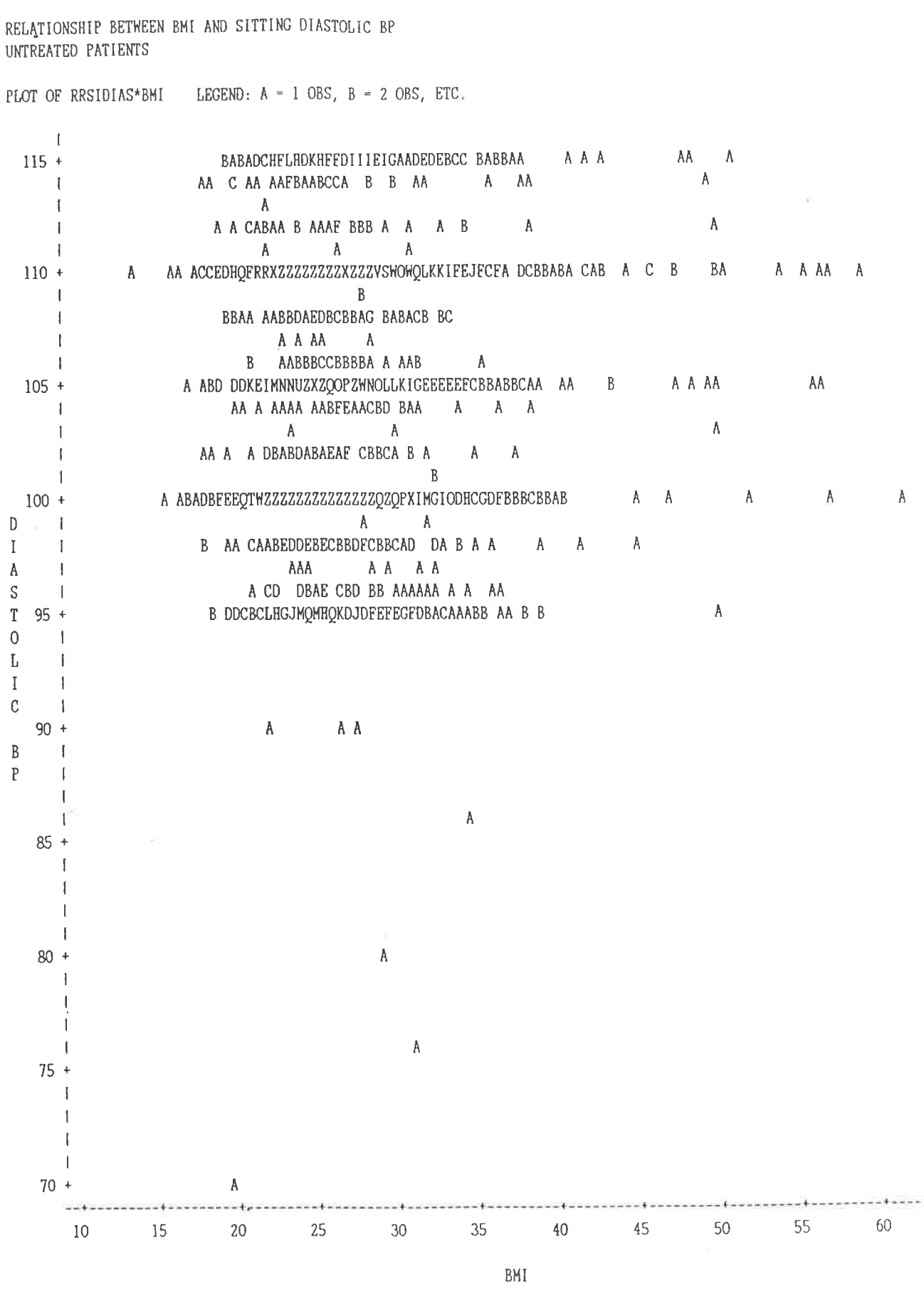
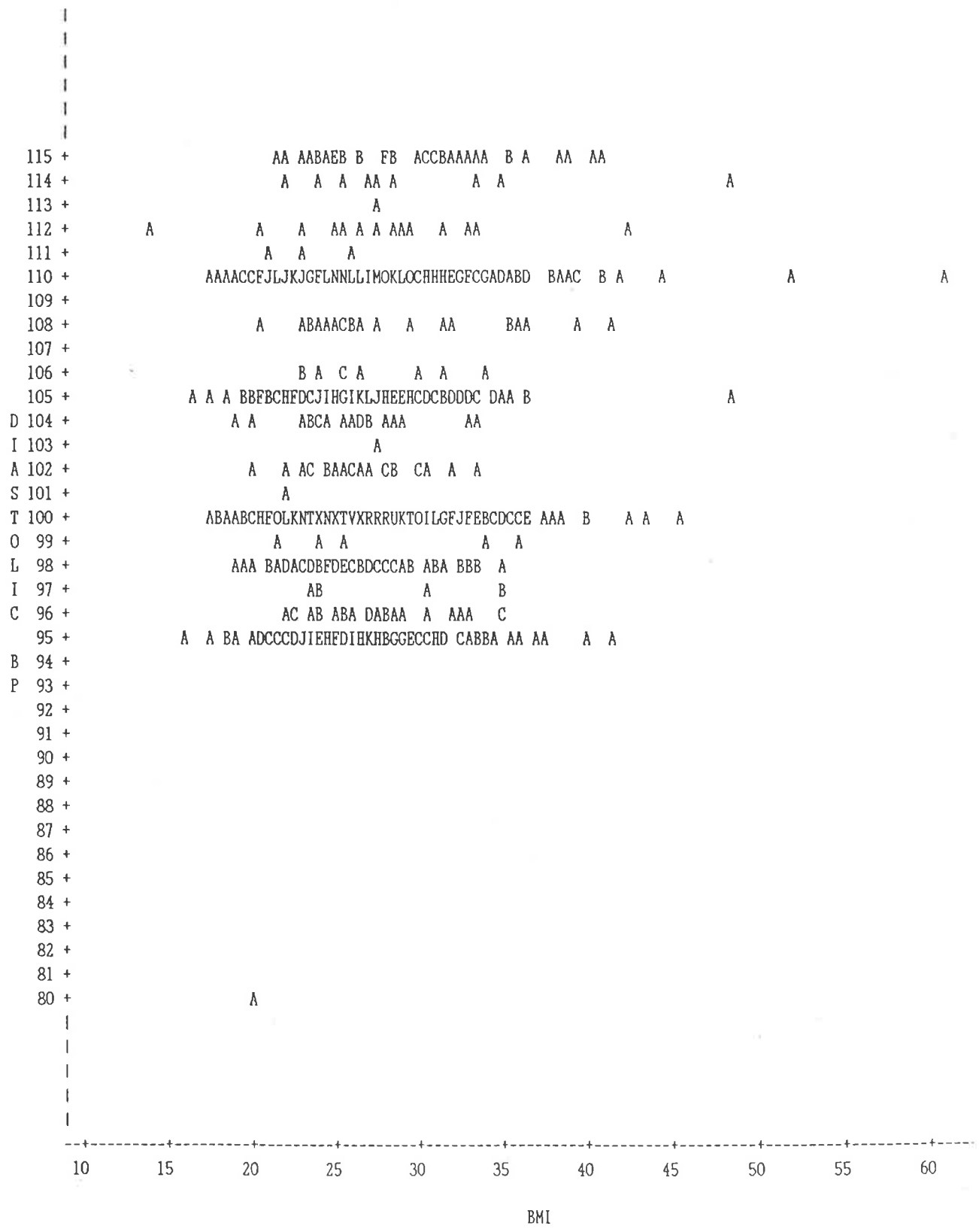

RELATIONSHIP BETWEEN BMI AND SITTING DIASTOLIC BP
UNTREATED PATIENTS
PLOT OF RRSIDIAS*BMI LEGEND: A = 1 OBS, B = 2 OBS, ETC.
DIASTOLIC BP
BMI
NOTE: 313 OBS HIDDEN

Figure 6b

RELATIONSHIP BETWEEN BMI AND SITTING DIASTOLIC BP
TREATED PATIENTS

PLOT OF RRSIDIAS*BMI LEGEND: A = 1 OBS, B = 2 OBS, ETC.



Discussion

The programme:

The amount of patient data collected by this study amounted to 11 megabytes, approximately equivalent to 90 editions of the Journal of the Royal Society of Medicine, in which the first results were published. To have collected this amount of data from 486 different locations over a large geographical area using paper records, had it been possible, would almost certainly have taken longer than the sixteen month period of this study. It would certainly have required more resources than the two secretaries who constituted the only additional study personnel.

A period of "data cleaning" for missing and illegible entries would have been necessary and transcription errors might have occurred. The computerised system not only enabled the data to be collected quickly, it had many additional advantages, such as, the provision of date prompts for patient recall and aids for the prevention of unsafe practice.

It is important, particularly for safety studies, that the outcome is known in all or as many patients as possible. In this study only 322 (0.1%) patients were lost to follow up. Computers were used in an unstructured way in a captopril assessment (58). In that study, in which the safety of captopril was said to have been established, no attempt was made to validate the data

collected; of the 13,295 patients entered, 8000 were lost to follow up most of whom were only seen once, at the first visit, their fate being unknown (59).

Inevitably, problems peculiar to this method of data collection were experienced. At the time this study was planned and commenced, because of limitations in the size of memory available on microcomputers, it was not possible to run the programme and collect data other than on a central minicomputer. The data were therefore transmitted "on-line" and line-breaks were a constant source of frustration. The communication system monitored the amount of telephone line noise, because this noise could be interpreted by the system as stray characters and thus corrupt the data. If the noise reached a critical level the system would automatically disconnect. It proved impossible to transmit data from some practices in Northern Ireland because of interference, presumably from the military electronic surveillance used in those areas. The system only saved data when all the details for a visit had been entered, so that if a line break occurred when most, but not all the data for that visit had been entered, the data were lost and it was necessary to log-on once again and re-enter the information. Future systems should save each page of data as soon as that page is complete, so that in the event of disconnection little data are lost and need to be re-entered.

Such has been the development in microcomputers that by the time this study was completed it was possible to obtain reasonably priced systems with sufficient memory to hold both programme and data. One such machine would have been capable of running the whole study, rather than having to use a minicomputer. Many general practices now have these machines for routine computing. It would now be possible to provide each practice with a programme, written, for example, as a "run-time version" in DBase4, which would prevent having to have the programme at a remote location. Data could still be collected centrally by either sending discs by mail, or by periodically transmitting the entire disc contents electronically, a process which takes only a few minutes.

Less than two thirds of the doctors used the training programme at all. Consequently, many of the problems and irritations that were experienced arose because of lack of familiarity with the system and failure to read the instructions provided.

Data entry errors were too difficult to correct and some unpredicted, original solutions to this arose. One investigator corrected her mistake by "killing" the patient, temporarily increasing the number of study deaths to four and demonstrating how this method of data collection might distort the results of as study. Fortunately, this sort of false entry will always be detected, since it is necessary to check and obtain full details of serious events from

original case records.

The messaging system lacked sufficient word-processing power to be really useful and again the difficulty of correcting typographical errors meant that time was wasted in retyping. Some doctors abandoned the messaging system and resorted to telephone or mail.

Data validation:

There is no easy way of validating the adverse event data collected. In spontaneous reporting of adverse events to either the CSM or the drug's Manufacturer the number of patients taking the drug is not known so there is no denominator against which to set the number of reports. Nifedipine has not been subject to Prescription Event Monitoring (11), the only system in which the number of patients taking a drug is known. It was therefore decided to define a pattern of adverse events expressing the number of events in a particular category as a percentage of the total number of known events. These percentages are shown in Table 30. Patterns so produced from four sources were compared; spontaneous reports to the CSM, spontaneous reports to the Manufacturer, a previous paper based study of 3242 nifedipine takers (60) and this study, Figure 7. The standard, as least likely to be biased, must be assumed to be the pattern of CSM reports. The closest similarity with that pattern is seen with the pattern from this study, suggesting that this method has collected reliable adverse event data.

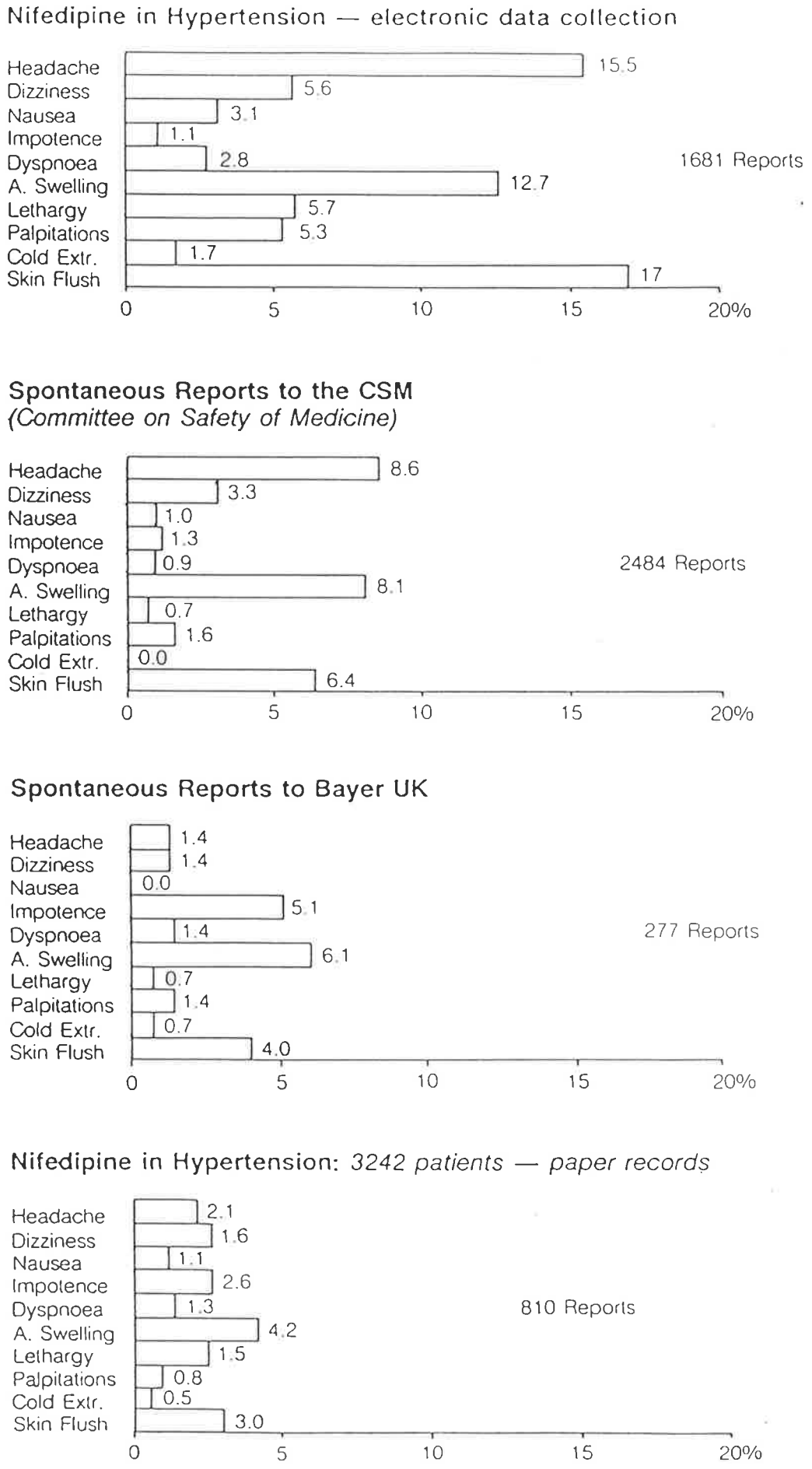
TABLE 30

ADVERSE EVENT FREQUENCY AS A PERCENTAGE OF TOTAL NUMBER OF REPORTS

	CSM REPORTS	PAPER-BASED STUDY	SPONTANEOUS REPORTS	THIS STUDY
NO OF REPORTS	2484	810	277	1681
HEADACHE	8.6	2.1	1.4	15.5
DIZZINESS	3.3	1.6	1.4	5.6
NAUSEA	1.0	1.1	0.0	3.1
IMPOTENCE	1.3	2.6	5.1	1.1
DYSPNOEA	0.9	1.3	1.4	2.8
ANKLE SWELLING	8.1	4.2	6.1	12.7
LETHARGY	0.7	1.5	0.7	5.7
PALPITATIONS	1.6	0.8	1.4	3.3
COLD EXTRIMITIES	0.0	0.5	0.7	1.7
SKIN FLUSHING	6.4	3.0	4.0	17.0

Figure 7

Specific reports expressed as a percentage of the total number of reports; this study and three other sources



Computing:

In the UK in 1987 the two main suppliers of computers to general practice, VAMP Health and AAH Meditel, offered computers to practices at low cost in return for access to aggregated patient data. These could be sold to interested parties, pharmaceutical companies being the most obvious customers (61). Databases covering 1500 general practices and 3,000,000 patients were envisaged which could be used to examine prescribing habits, preventive care, management and post-prescription events. All but the first were outside the contractual obligations.

The early hopes for large data bases have not been fulfilled (62) and VAMP's financial difficulties have brought the whole viability of these schemes into question (63). The main problem has been incomplete data recording and only one practice in three has achieved an acceptable standard. Jick and colleagues demonstrated that a group of practices whose standard of data collection was good could be used to collect adverse reactions to non-steroidal drugs (64). This group of doctors may also have been more careful prescribers so that the data collected may not be truly representative. The standard of data entry was validated by comparing diagnoses in consultant's letters with those entered in the computers. Although these large databases have not proved successful, Jick et al have shown that specific questions can be answered if recording is good.

The large North American and Canadian databases have proved useful, but the standard of data held within them is poor, there are many missing or incorrect entries and studies conducted through them usually involve laborious checking of original paper records (A Morgan, Professor of Epidemiology, Harvard University, USA, personal communication, August 1991).

The type of programme developed and described in this Thesis, which controls the quality of data and does not allow missing entries, is still likely to be the most successful approach to the management of large population studies.

Antihypertensive drugs:

Point prevalence of adverse events of antihypertensive drugs:
It can be seen from Table 3 that, as might be expected, the group of hypertensive patients who were not receiving any treatment reported the lowest number of adverse events in each category. Dizziness is a commonly reported symptom to doctors and, in hypertensives, who as a group are thought to be more prone to postural hypotension, a greater percentage than the 2.2% reporting this symptom might have been expected.

In addition, the percentage reporting lethargy, 1.7%, was below expectation. The untreated hypertensive men (1386) reported an impotence rate of 1.1%.

The poor tolerability of beta-blockers was striking, even allowing for the fact that those suffering from adverse events might be over-represented in this population. If such a bias were present, it would apply equally to those treated with diuretics and to the group treated with other anti-hypertensives. The tolerability of treatment in both of these groups was markedly better than in those treated with beta-blockade. Over half of the group taking a beta-blocker reported feeling lethargic, one fifth of the men reported impotence, a quarter reported shortness of breath and almost half reported having cold extremities.

In contrast, diuretics were comparatively well tolerated with the highest percentage reported, 7.2%, being for lethargy. Impotence was reported at a rate five times greater than in the untreated group, but at a third of the frequency experienced in the group treated with beta-blockers. Ankle swelling was four times more common than in the untreated group, but it may be that diuretics were particularly chosen to treat hypertensives who had pre-existing ankle oedema. Dizziness was two and a half times more common than in the untreated group, but only one third of the rate of the beta-blocker treated group. Dyspnoea was twice as common as in the untreated group, but again, may reflect a choice of use of diuretics for those

already suffering from this.

Safety and tolerability of nifedipine:

There were three deaths during the study period. These are described in the results section and none of these were thought to be related to treatment with nifedipine. Five hundred and sixty one patients (14% of total) were unable to tolerate treatment with nifedipine. Grade 4, intolerable adverse events, were reported on only 121 occasions. The discrepancy between the number of events graded as severe and the number of patients stopping treatment with nifedipine, may have arisen through patients withdrawing after having suffered several mild events rather than one severe event.

A considerable increase in skin flushing, as a result of the vasodilatory action of the drug, occurred. Sixteen patients reported intolerable flushing and 55 reported severe flushing during the first four weeks of treatment. Mild flushing persisted with continuing treatment, whereas reports of other grades reduced with time. Only 0.6% of patients found the flushing intolerable and apart from those in this group, treatment may be continued in the expectation that for most patients, the flushing may become tolerated.

The reports of headache followed a similar pattern. Thirty four patients reported an intolerable headache during the first four weeks of treatment,

but the percentage reporting headache reduced with continuing treatment. Thus it is again possible to recommend continuing treatment unless the headache is intolerable, anticipating that it will reduce in intensity with time.

Ankle oedema did not follow this pattern. The oedema which develops with nifedipine treatment does not seem to be mediated by sodium and water retention but is thought to be related to a change in capillary haemodynamics with increased filtration of fluid, particularly on standing (65). This oedema is not sensitive to either diuretics or salt restriction (66). Fifteen people developed intolerable ankle swelling during the first four weeks of treatment and a further five in the next four weeks. The percentage of patients reporting mild ankle swelling, 3.7% after four weeks, increased to 4.4% after a further four weeks treatment. Reports of other grades of severity remained constant. Ankle swelling therefore does not reduce with time and neither diuretics nor sodium restriction will reduce it (66). If a patient finds that the ankle swelling is unacceptable treatment should be stopped and an antihypertensive other than a dihydropyridine should be substituted. As a result of this observation the world-wide prescribing information for nifedipine has been changed (Figure 8).

The original prescribing information (Figure 1) indicated to physicians that side effects were invariably transient and disappeared with continued treatment, this study demonstrated that this was not so and the consequently

revised prescribing information (Figure 8) does not contain this statement. As a result of the observations in this study and given the widespread use of nifedipine, many patients worldwide may have been prevented from distress through the inappropriate continuation of their nifedipine treatment.

Reports of dyspnoea were reduced in all groups following treatment with nifedipine; in those whose treatment had been changed to nifedipine as well as those who had not been previously treated. It would be expected that changing treatment from a beta-blocker to a dihydropyridine would reduce reports of dyspnoea, but the reduction in reports in the group who had not been previously treated and whose first treatment was nifedipine, suggests an independent bronchodilating effect. Nifedipine has been shown to have mild bronchodilatory properties, although not useful enough to be considered an independent treatment for obstructive airways disease (67). This effect is however useful for hypertensives who have obstructive airways disease.

Reports of impotence were also reduced with nifedipine treatment. As before, the most striking reduction in reports was seen in the group whose treatment was changed from beta-blockade. The reduction in reports in the group whose first treatment was nifedipine, again suggests a small but potentially useful treatment effect and is consistent with previous reports of priapism caused by nifedipine (68). Table 7, (Side effects profile - impotence), contains some reports of apparent female impotence. These

Figure 8

Bayer UK Limited
Pharmaceutical Business Group
Bayer House
Strawberry Hill
Newbury, Berkshire, RG13 1JA

ADALAT®
ADALAT® 5

Presentation *Adalat capsules:* Orange, soft gelatin ovoid capsules containing a yellow viscous fluid. Each capsule is overprinted with "ADALAT" and the Bayer cross and contains 10 mg nifedipine.

Adalat 5 capsules: Orange, soft gelatin ovoid capsules containing a yellow viscous fluid. Each capsule is overprinted with "ADALAT 5" and the Bayer cross and contains 5 mg nifedipine.

Uses

Mode of action: As a specific and potent calcium antagonist, the main action of Adalat is to relax arterial smooth muscle both in the coronary and peripheral circulation.

In angina pectoris, Adalat capsules relax peripheral arteries so reducing the load on the left ventricle. Additionally, Adalat dilates submaximally both clear and pre-stenotic, stenotic and post-stenotic coronary arteries, thus protecting the heart against coronary artery spasm and improving perfusion to the ischaemic myocardium.

Adalat capsules reduce the frequency of painful attacks and ischaemic ECG changes, irrespective of the relative contribution from coronary artery spasm or atherosclerosis.

Adalat causes a reduction in blood pressure such that the percentage lowering is directly related to its initial height. In normotensive individuals, Adalat has little or no effect on blood pressure.

Indications: For the treatment and prophylaxis of angina pectoris, and the treatment of Raynaud's phenomenon and all grades of hypertension.

Dosage and administration: For oral administration, the capsules should be taken with a little fluid during or after food. The recommended dose is one 10 mg capsule three times daily with subsequent titration of dosage according to response. The dosage may be adjusted within the range 5 mg three times daily to 20 mg three times daily.

If an immediate anti-anginal effect is required, the capsule should be bitten open and the liquid contents held in the mouth.

Adalat 5 capsules permit titration of initial dosage in the elderly and those patients on concomitant medication. The recommended dose is one Adalat 5 capsule three times daily.

Patients with hepatic dysfunction should commence therapy at 5 mg three times daily with careful monitoring. Patients with renal impairment should not require adjustment of dosage.

There are no recommendations for use in children.

Treatment may be continued indefinitely.

Contra-indications, warnings, etc

Contra-indications: Adalat should not be administered to patients with known hypersensitivity to nifedipine or to women capable of child-bearing. Adalat should not be used in cardiogenic shock.

Warnings and precautions: Adalat may be used in combination with beta-blocking drugs and other antihypertensive agents but the possibility of an additive effect resulting in postural hypotension should be borne in mind. Adalat will not prevent possible rebound effects after cessation of other antihypertensive therapy.

Adalat should be used with caution in patients whose cardiac reserve is poor.

Caution should be exercised in patients with severe hypotension.

Ischaemic pain has been reported in a small proportion of patients within 30 to 60 minutes of the introduction of Adalat therapy. Although a 'steal' effect has not been demonstrated, patients experiencing this effect should discontinue Adalat.

The use of Adalat in diabetic patients may require adjustment of their control.

The antihypertensive effect of Adalat may be potentiated by simultaneous administration of cimetidine. When used in combination with nifedipine, serum quinidine levels have been shown to be suppressed regardless of dosage of quinidine.

No information is available on the use of Adalat during lactation.

Side-effects: Most side-effects are consequences of the vasodilator effects of nifedipine and include headache, dizziness and flushing. Gravitational oedema, not associated with heart failure or weight gain, has also been reported.

Other less commonly reported side-effects include, rash, nausea, lethargy and increased frequency of micturition.

There are reports of gingival hyperplasia which may regress on withdrawal of therapy.

Rare cases of hypersensitivity-type jaundice have been reported.

Overdosage: Reports of overdosage are limited and symptoms are not necessarily dose-related. Severe hypotension, bradycardia and unconsciousness have been observed.

Gastric lavage and charcoal instillation have been employed. Intravenous calcium gluconate or calcium chloride appear most helpful, with intravenous atropine for bradycardia. Metaraminol has been beneficially

were volunteered reports of female failure of orgasm. Female sexual function also depends on erectile tissue and dysfunction may be more common with anti-hypertensive drug treatment than has been assumed. Female dysfunction is less visible than male impotence and enquiry about it has not been a part of either routine clinical management of hypertension or of clinical trials.

For all adverse events, the group of patients who had been previously treated for hypertension and whose treatment had been changed to nifedipine, were more likely to report adverse events from nifedipine than those hypertensives who were newly diagnosed. There appears to be a proportion of hypertensive patients whose ability to tolerate the unwanted effects of any antihypertensive drug is less than that of others.

Efficacy of nifedipine:

There was no control group thus the assessment of efficacy in this type of study must be debatable (69). It could, however, be argued that the changes in blood pressure in such a large population are likely to be representative of what would happen in clinical practice. This is borne out by comparison with data from a double blind study of nifedipine and atenolol alone and in combination (70). That study showed that each agent alone reduced the diastolic blood pressure of 60-70% of patients to below 95mmHg, a similar fall to that seen in this study. In addition, mean entry

blood pressure in the nifedipine treated group in that study was 175.8/104.9mmHg compared with 174.6/104.2mmHg in this study, suggesting that the studied populations were similar.

With such a large sample size, most statistical tests are likely to be highly significant, so these should be interpreted in the light of their clinical relevance.

The criterion which was set for control of sitting diastolic blood pressure by nifedipine (ie 90mmHg or below after one months treatment) might now be considered to be too strict (J Ledingham personal communication). However, this was achieved after four weeks treatment in 66.5% of patients. Had a criterion for control been set at 95mmHg or below after four weeks of treatment, 79% of patients would have achieved this. Thus, 12.5% of patients may have had their dose of nifedipine unnecessarily doubled to 40mg twice daily, with a consequent decrease in tolerability.

Acute administration of dihydropyridine calcium antagonists causes an acute rise in heart rate which has been thought to persist for up to a year (40). However, the rise in mean heart rate after four weeks treatment with nifedipine was 0.7 beats per minute (bpm), which although statistically significant, is not clinically noticeable. After a further four weeks treatment, the mean heart rate was within 0.2 bpm of the starting mean heart rate.

The acute tachycardia caused by nifedipine, therefore, disappears within four weeks of starting treatment in the population as a whole. The tachycardia is a reflex response to the peripheral vasodilatory action of the drug. Table 19 shows the changes in heart rate within the different age groups in the study. The youngest group (18 to 35 years) had a sustained rise of 3 beats per minute throughout the study, presumably reflecting their more compliant, less arteriosclerotic peripheral vasculature, while a similar rise was not recorded in the older groups. These changes in pulse rate should be viewed with caution since the changes are small and the standard deviations relatively large, (eg, 3.0 SD 10.5 BPM in the 18 to 35 years age group), the distributions of pulse rates were normal but comparatively flat.

The majority of the population were aged 51 years or older. Nifedipine has been thought to be more effective in the older population, who have lower plasma renin activity (46) but it also has an effect directly proportional to the pre-treatment elevation of blood pressure (45). In this study the fall in blood pressure was greatest in the elderly, 27.3/17.7mmHg in the 61 years and older group compared with 15.8/12.5mmHg in the group aged 18 to 35 years. However, the older group had a pre-treatment blood pressure of 180.4/104.3mmHg compared with 157.7/101.2mmHg in the younger group. Thus the greater fall in blood pressures in the older group is probably related to the initial blood pressure rather than to age. The increase in mean heart rate in the younger group of 3.0 bpm was greater than the mean

increase in the older group of 0.3 bpm. This may reflect the greater compliance of peripheral arteries and greater capacity for peripheral vasodilatation in the younger age group.

Throughout the study women had slightly higher mean systolic blood pressures than men, 176.8mmHg compared with 172.5mmHg at the start of treatment and 151.6mmHg compared with 149.5mmHg after eight weeks of therapy. There was no difference in diastolic blood pressures. The fall in mean systolic blood pressure was greater in women but this reflects the higher starting blood pressure rather than a greater effect of nifedipine in women.

Smokers are known to require higher doses of other antihypertensive drugs such as beta-blockers and diuretics (71). It was consequently important to compare the effect on blood pressure, of nifedipine, in smokers and non-smokers to test if this would also be found to be the case with this drug. Similar falls in mean blood pressures were seen in both groups, 24.5/17.1mmHg in smokers compared with 23.6/16.3mmHg in non-smokers. Accordingly, nifedipine appears to be equally effective in smokers and non-smokers in lowering blood pressure. It might have been anticipated that a difference would be seen in pulse rate between the groups. Smokers might have been expected to have more atherosclerotic, less compliant peripheral arteries, so that vasodilatation and reflex tachycardia would have been less,

but in fact, there was no difference seen in pulse rate after four weeks treatment.

Changes in blood pressures and heart rates in newly diagnosed and those whose treatment had been changed to nifedipine, were very similar, 19.9/10.1mmHg compared with 20.3/9.7mmHg, respectively. Mean blood pressures and heart rates were similar in the groups whose treatment had been changed from beta-blockers or diuretics to nifedipine, 173.3/103.4mmHg compared with 172.7/103.1mmHg at entry and 151.8/87.7mmHg compared with 151.5/87.3mmHg after eight weeks treatment. Previous treatment for hypertension does not make subsequent treatment more difficult.

Body mass index (BMI), weight and blood pressure.

Body weight and blood pressure have been shown to be linked, with hypertension being twice as prevalent in the young obese than in controls (72). A 12Kgm weight loss caused a fall in blood pressure of 7/4mmHg (73) and it has been calculated that a downward shift in the population blood pressure distribution of 2 to 3mmHg would have an effect on cardiovascular disease equivalent to treating all patients with a diastolic blood pressure greater than 105mmHg or more (74).

Prospective clinical studies in severely obese patients have shown a correlation between change in weight and blood pressure in patients treated with diet or a bariatric (eg, stomach stapling) operation (75). Weight reducing diets are widely considered to be effective treatments for moderate hypertension in obese subjects (76,77). The mechanism behind the close relationship between body weight and blood pressure is unclear (78). The relation between intra-arterial pressure and relative weight demonstrates that the correlation is not solely a cuff-measurement artefact (79). In a study of 2530 patients a significant correlation was shown between weight gain and systolic and diastolic blood pressures (80). It has been suggested that the relationship between blood pressure and weight change is due to shared environmental causal factors such as, sodium intake in food, sodium retention (dependent on degree of insulinaemia) or both (78).

BMI is measured as weight(kgm) divided by height(m) squared. Severe obesity may be defined as a BMI greater than or equal to 30 Kgm/M^2 (81). In spite of the large volume of literature on weight and blood pressure, there are few published data concerning the relationship between BMI and hypertension. One recent study in severely obese hypertensives, showed that hypertension was more prevalent in subjects with an unchanged BMI as that index increased over the range studied (82); at any BMI studied, hypertension was more prevalent in subjects who had increased to this index and less in those who had decreased to it, than in those who had stayed the

same weight.

In the present study, the mean weight of the youngest age group, ie those aged 18 to 35 years, was greater than the mean weight for the study population as a whole, (80.37 kgm compared with 76.62kgm). It seems that, at least in this age group, weight was a factor in the aetiology of their hypertension. The higher mean body weight in this age group might be related to alcohol intake, itself a possible factor in the development of their hypertension. Information volunteered on alcohol consumption is unreliable (83). However, it was an omission not to have attempted to collect it. Public health campaigns aimed at reducing alcohol consumption should draw the association between alcohol and hypertension to public notice and might, therefore, potentially reduce the prevalence of hypertension, particularly in this age group.

Non-smokers in the younger age groups were markedly heavier than smokers. Newly diagnosed female non-smokers aged 18 to 35 years, had a mean weight of 81.83kgm compared with 74.00 in the smokers. The same applied for men in this group with male non-smokers having a mean weight of 91.00kgm compared with 81.00 for smokers. Similar differences were seen in the group who were known to have hypertension. In this group the mean weight of female non-smokers aged 18 to 35 years was 73.86kgm compared with 60.00kgm for female smokers; however, male non-smokers

in this age range had a mean weight of 90.17kgm compared with 91.12kgm for male smokers. It is known that young women, in particular, may smoke as an aid to slimming, since smoking reduces appetite and increases metabolic rate. In addition, there is an average 8kgm weight gain on giving up smoking (84). The overweight men in the currently treated group, who also smoked, would seem to be at greater risk and although they may represent a particularly recalcitrant group, efforts obviously need to be made to identify and correct the adverse factors in their lifestyle.

In this study, Mean diastolic blood pressure was 104.2(SD 5.8)mmHg and mean BMI was 27.1 (SD 4.9)kgm/m^2. They had a very weak positive correlation; r = 0.076, p = 0.0001. An increase in BMI of 1 Kgm/m^2 was associated with a rise in diastolic blood pressure of approximately 0.09mmHg. The relation between BMI and diastolic blood pressure in this study was at best, weak. These findings are puzzling given those of another BMI study (82). The two may not be incompatible in that the other study was in patients who were severely obese, whereas the present evaluation was in patients with a full range of BMIs and further, the previous study suggested that a change in blood pressure was associated with a change in BMI. It may be that although in the present study no relationship was shown between BMI and diastolic blood pressure, a change in BMI is necessary to alter blood pressure, rather than an absolute value. It may also be that obesity shares causal factors with arterial hypertension, rather than

leading to the disease (82).

Conclusions

This study has successfully refuted the hypothesis that it is no longer possible to conduct studies of the size of the "MRC Study of Mild to Moderate Hypertension", because of the large demands they make on financial and other resources. It has also demonstrated that it is possible to establish and complete a large study before the investigated treatments become outdated.

Conducting a large study in general practice, involving thousands of patients, is feasible using a programme such as described here. The only personnel required were one medical practitioner and three clerical staff. The data collected by this structured method appears to be reliable and the method does not appear to have caused any particular data distortion. The problems described may be overcome by taking advantage of the developments that have taken place within micro-computers. Hypotheses may be more reliably and efficiently tested using this trial management system, than by attempting to utilise unstructured, pooled general practice data or, the large American data-bases.

The collection of point prevalence reported adverse medical events in patients with hypertension, showed a large excess of reports in those patients who were receiving antihypertensive drug treatment when compared

with those who were not. In particular, even allowing for the possible over-representation of event reporters at this point, beta-blocking drugs appear to be particularly badly tolerated. In contrast, diuretics seem to be better tolerated.

This Study is the largest single nifedipine data-set in existence, greater by a factor of ten than any other.

Adverse events reported by the nifedipine taking group produced the anticipated pattern of vasodilatory flushing and headache typical of dihydropyridine calcium channel blocking drugs. The finding that the ankle oedema produced by nifedipine did not reduce with time and if present and not tolerated, should lead to cessation of treatment, resulted in the changing of the world wide prescribing information for this drug, protecting patients further. The study showed that nifedipine might be particularly useful for patients with hypertension and obstructive airways disease or impotence.

The falls in blood pressure noted with nifedipine treatment were typical of those produced in other earlier studies. The rise in pulse rate previously noted with acute administration of nifedipine had settled after one month of treatment. The large sample size, with the computerisation of the data, enabled group comparisons to be made. Nifedipine appeared equally effective in younger and older patients, in smokers, in both sexes and in

those who had previously been treated with other antihypertensive medication.

Younger hypertensive patients were heavier than the older ones and it seems likely that obesity was a factor in the aetiology of their hypertension. However, surprisingly, there was only the weakest of correlations between body mass index and diastolic blood pressure seen throughout the whole study population. The relationship between body mass index and diastolic blood pressure requires further investigation.

Addendum

Nifedipine and motion sickness.

Not all unexpected effects of drugs are disadvantageous. At the same time as conducting the study reported here, I was also conducting at the Cardiology Clinic of St Peter's Hospital, Chertsey, UK, a study of the treatment of essential hypertension by atenolol alone or in combination with nifedipine. As a result of a chance observation, I was able to report the alleviation of motion sickness by nifedipine (85).

A 39 year old man had experienced severe motion sickness throughout his life. He was able to travel by air but suffered frequent vomiting in cars, buses or ships. His occupation entailed frequent trips by cross-channel ferry, on which he usually vomited, to France. He also suffered from hypertension and agreed to take part in the double blind clinical trial of treatment with atenolol alone or in combination with nifedipine, for essential hypertension.

The patient was randomised to receive;

1. 50mg of atenolol daily for one month
2. 50mg of atenolol plus 20mg of nifedipine daily for three months

then,

3. 50mg of atenolol daily.

During the treatment phase in which he was receiving nifedipine, he spontaneously commented that his travel sickness had totally resolved, that at last he had "got his sea-legs and grown out of it". He had not taken his usual anti-emetics during the study having assumed that they might interact with the trial medication. He had not noticed any reduction in symptoms whilst taking atenolol alone during the first month and, reported a return of symptoms when he was randomised back to atenolol in the last stage. When the code was broken, his relief of motion sickness was found to coincide with the period in which he took nifedipine.

After this observation, twelve volunteers from the staff of St Peter's Hospital, who were to spend their summer holiday sailing in small yachts, were recruited to take 10mg of nifedipine, in an open evaluation of its potential to prevent motion sickness. All reported past experience of motion sickness at the start of a sailing holiday. Exposed to a variety of uncontrolled motion stimuli, seven reported an absence of the usual vomiting, three reported a reduction and two, no effect. All reported some flushing and headache.

Drugs available for the treatment of motion sickness are; antihistamines, phenothiazines or atropine derivatives. These can cause drowsiness or blurred vision which can be dangerous in vehicle drivers. Cinnarazine is

indicated for the treatment of motion sickness and has calcium antagonistic properties (86). It appears to exert a significant depressant effect on the vestibular nuclei, possibly by antagonising the stimulated influx of calcium ions from the endolymph into the vestibular sensory cells (87). Cinnarazine can cause drowsiness, possibly due to its anti-histamine activity (88). Dihydropyridine calcium antagonists are potent blockers of calcium flux, neurotransmitter release and calcium-dependent biochemical responses in the brain (89). It is therefore possible that nifedipine reduces motion sickness by antagonising the influx of calcium ions into vestibular cells. An effective drug for motion sickness that does not impair mental function or reactions would be valuable. The observation described here is currently being tested by the British Navy in a double blind placebo controlled study.

A COMPUTERISED MULTICENTRE TRIAL MANAGEMENT SYSTEM

Introduction

Multicentre studies are difficult to organise and conduct. Problems include; achieving consistency in performance between different centres and obtaining ethical committee approval from different committees without uniform requirements. Multicentre trials are often necessary in Phase II studies of diseases such as; asthma, diabetes and hypertension. These studies are often of long duration, unlike the short term drug administration that may be all that is needed in an antibiotic study. There may be several months between patient visits and patients are commonly lost by violating the protocol through forgetting a visit, there being no prompt to the doctor to signal that a particular patient is overdue to return.

In studies involving dose titration, it may be necessary to provide each centre with drugs for all the possible dose combinations, considerably increasing the costs of the study through wastage.

Phase II studies are often designated as "pivotal" for licensing applications to the American FDA. This means that the study will have to be conducted to the full requirements of "Good Clinical Practice" (GCP), necessitating organised data trails, standard operating procedures and systematic checking methods. There are strict requirements under GCP for the reporting of adverse events to the FDA within minimum time periods. Failure to adhere

to these may mean the suspension or cancellation of an entire new drug investigational programme. Although investigators are made aware at the start of a study of these requirements, over a period of time they may be forgotten and consequently not adhered to.

Physicians often perceive themselves to be working in isolation, often with little idea as to how the other centres are performing. They may never receive the results of a study in which they have participated, leading to the suspicion that unfavourable results are being withheld (90,91).

There was then, a need to develop a multicentre trial management system which might;

i. Enable patient visits to be tracked, providing reminders when patients were due and, indicating overdue patients in sufficient time for them to be contacted to prevent their being lost as protocol violators.

ii. Enable adverse events to be noted in time to meet the requirements of the American FDA.

iii. Improve the standards and uniformity of data entry.

iv. Provide feedback about their own and overall study progress to investigators.

v. Reduce the need to supply drugs in all dose combinations to each centre for dose-titration studies.

vi. Speed recruitment and reduce the length of the study.

Methods

It was decided to develop and test a computerised trial management system for use in a multicentre study of nitrendipine. Nitrendipine is a new dihydropyridine calcium antagonist which was thought to have a possible twenty-four hour duration of action. This study was designed to compare once and twice daily treatment regimen, measuring blood pressure at 24 or 12 hour trough levels. After a placebo run-in phase patients were randomised in a double blind fashion to one of the two regimen. Patients who were classified as non-responders after four or eight weeks of treatment had their dose of nitrendipine doubled for a further four weeks, whereas those who had responded continued their treatment unaltered for a similar time period. The study took place in twelve locations, divided between hospital clinics and general practices and aimed to recruit 200 patients.

This study, had it demonstrated that nitrendipine was as effective when given once daily as twice daily, would have been part of a worldwide regulatory submission. It had, therefore, to be conducted to the highest possible standards. The study contained several dose-titration steps for which large quantities of drugs to cover each possibility would normally have been sent to each centre. It was to be a long study, so that there was

a real chance that patients would be lost through missed appointments as the study progressed.

A full description and report of the study may be found in Appendix 5.

Programme:

The programmes to manipulate the data were written in the SAS (Statistical Analysis System) language and run on an IBM mainframe computer. The design objective was not to computerise or gather directly the medical data from the study, but rather to computerise the administrative aspects, particularly patient scheduling and drug supply.

The programme was used to keep track of how many patients were being recruited at each centre. It predicted when each patient's next visit was due and raised an overdue flag if they did not attend on that day. The study protocol allowed a one week "window" for the visit so that the warning enabled the patient to be recalled before becoming a protocol violator. Responses at weeks four and eight were entered and these were used to direct the dosage and sending of drug supplies for the next part of the study.

The programme was developed in a way similar to that described for the programme used in Chapter 2. Algorithms were sketched to cover all parts

of the programme, one for each separate area. For example; patient visits, adverse event reporting and trial supply ordering. Working alongside the programmer (D. Lal), the algorithms were written in SAS for the mainframe computer. The progamme was tested, "de-bugged" and rewritten using pseudo trial data. Extensive testing at this stage meant that almost no adjustment to the programme was necessary when the trial proper was in progress. This process of development, writing and testing occupied approximately two months.

Data collection:

A nominee at each centre was contacted by telephone during the same half day each week. At each contact information was sought about; the date of entry of new patients, patients passing weeks four and eight and their responses to treatment, patients completing the study, patients withdrawing from the study and the reason for withdrawal and any significant adverse events particularly those requiring reporting to the FDA. Database variables are listed in Table 31.

Data manipulation:

The entered data were used to produce a number of lists, described in Table 32. These lists could be printed on a collective basis or on a centre by centre and investigator by investigator basis. The data could also be sorted and displayed graphically, for example as pie charts or histograms. Sorting

TABLE 31

DATABASE VARIABLES

Patient Name
Patient Initials
Centre Name
Investigator Name
Placebo Phase Entry Date
Active Treatment Date
Withdrawal Date
Drug Supply Date
Trial Completion Date
Response at Week 4
Response at Week 8
ADR Flag
Days Into Trial

TABLE 32

DATA MANIPULATION

1. Lists of patients who were late in coming forwards for their Week 4 examinations.
2. Lists of patients who were late in coming forwards for their Week 8 examinations.
3. Responders and non-responders at Week 4.
4. Responders and non-responders at Week 8.
5. Lists of new patients recruited.
6. Patient overview - all known data per patient per centre.
7. Trial stage; an n-way table in which the n dimension was a list of centres and the other dimension was the number of patients in each of the following stages: placebo; day 1 to 28; day 29 to 56; day 57 to 84; day 85 plus (ie, finished patients).
8. Chronology table - numbers of patients recruited since the commencement of the project.
9. Recruitment distribution, centre by centre.
10. Overview of withdrawals.
11. Drug supply history.

and tabulating the data allowed a comparison of recruitment rates at each centre as well as recruitment patterns. Performance could be compared between centres and between an individual centre and the centres as a whole.

Use of collected information:

The purpose of collecting the information was to improve trial management and to reduce time and cost; therefore, the information was used principally for the following purposes;

i. Overall study recruitment was constantly monitored against the target recruitment rate. Each month a news bulletin was sent to each participating centre. The bulletin gave information about the overall study progress and a breakdown of recruitment by each centre. The centres were identified in the bulletin by centre-code only, so that although they could compare their own performance with that of other centres, they could not readily identify other centres which might be performing poorly. The bulletin also provided each centre with an overview of its own performance, listing all currently known data about each patient at that centre. This was an essential check to confirm the validity of the data collected at each weekly telephone report, checking as well, for entry and transcription errors.

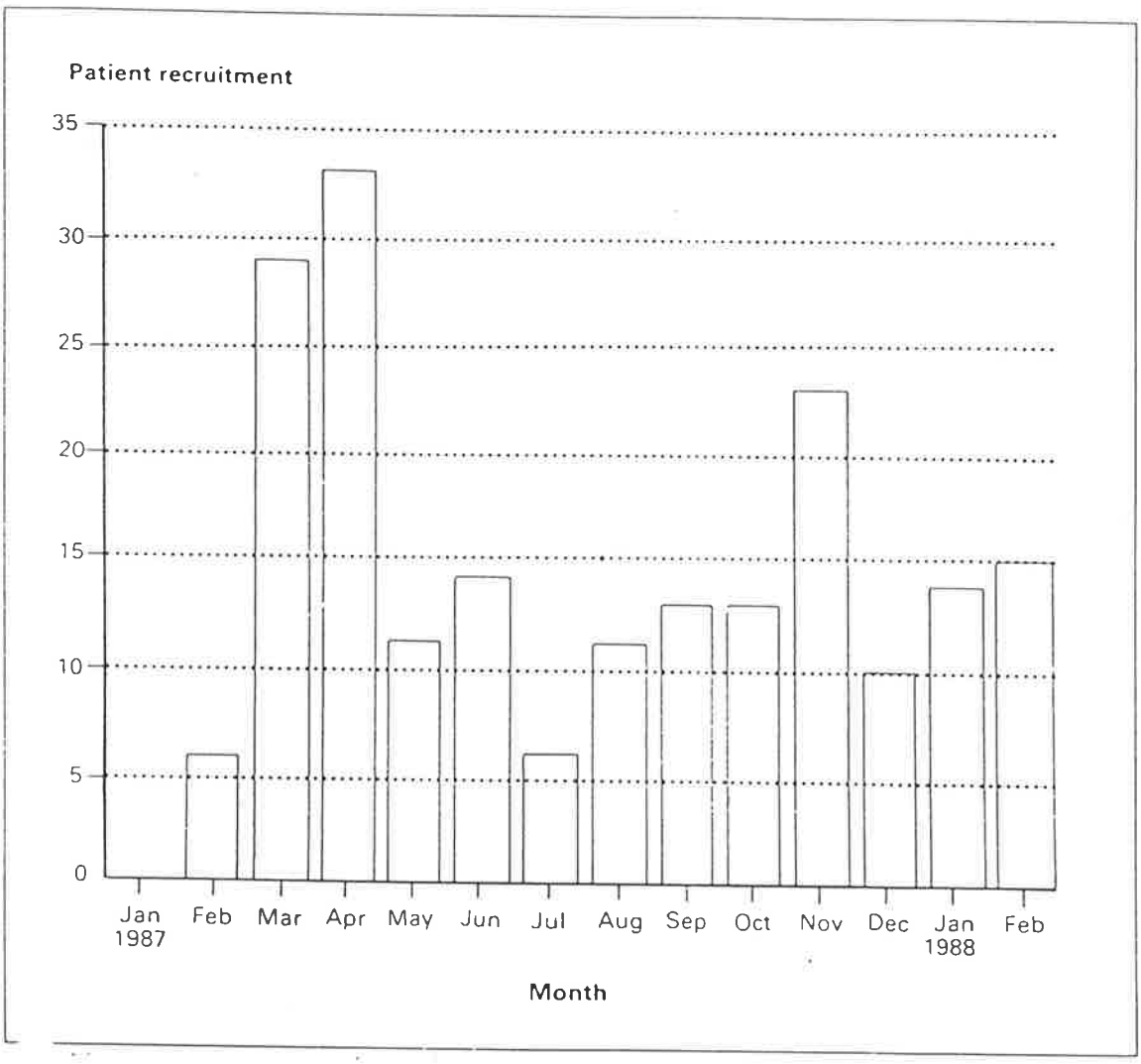
ii. The clinical trials pharmacy was notified of individual patient responses in the later stages of the trial so that the appropriate doses of trial medication could be dispensed and sent to the participating centre.

iii. By providing a constant check of actual recruitment against an ideal or predicted value, it was possible to arrange meetings of the investigators for times when recruitment was falling below that which was desired. These meetings were then used to discuss problems with the trial and any perceived barriers to recruitment.

Results

The sample size calculation for the study required that 200 patients be recruited in order to meet the levels of power and significance set (see Appendix 5). It was hoped to recruit this number of patients within a nine month period which ended in November 1987. Recruitment started well and was initially better than that predicted. However, it became apparent that in May and June it was falling well below that hoped for. In addition, four centres had not recruited any patients. This information was made apparent to investigators in the June news bulletin and was used to plan a July investigators meeting. The improvement in recruitment after this meeting is shown in Figure 9. The final recruitment target was not altered but the

Figure 9



Monthly Recruitment of Patients

recruitment period was extended by three months based on the mean recruitment line drawn from the data gathered this far. The final recruitment figure was reached by this date. Seven months before the trial was completed it was possible to predict accurately when that finishing date would be, enabling the statisticians to make advance arrangements for the statistical analysis of the study.

All significant adverse events which occurred in the course of the study were known, at the latest, within six days of their occurrence.

The information passed to the clinical trial pharmacy, with appropriate dispensing, resulted in a saving of approximately one fifth of the cost of trial medication.

Patients may have elected to withdraw from the study, but the overdue patient warning system prevented the loss of patients through forgotten appointments.

Discussion

Use of this trial management system aided recruitment, improved the collection of important safety data and reduced costs. Patients were successfully tracked and not lost from the study through missed

appointments. Centres were successfully provided with individual dosage packs for particular patients as a result of dose titration, saving the expense of packing and supplying drugs for all eventualities. The system described, with little modification, may be used for the management of all multicentre clinical trials, of any size or complexity.

This system demonstrated the value of good communication in the conduct of studies. Investigators were keen to know how their centre's performance compared with that of others and looked forward to the meetings and monthly news bulletins. More information (rather than less) was always requested. The peer pressure provided by the bulletins and meetings improved motivation so that recruitment finished within three months of the original target date.

The study was conducted in both hospital and general practice. General practitioners work in greater isolation than hospital physicians and the meetings and bulletins provided useful opportunities for the postgraduate education of both. Hospital physicians were able to impart useful knowledge of the disease area, general practitioners were able to educate the physicians on the quality and capability of general practice research and the trial supervisors were able to provide instruction in research methodology.

Far from being simply an expensive use of time and resources, the communication and management system described here should be an essential part of any multicentre study.

IS THE NON-PHARMACOLOGICAL TREATMENT OF HYPERTENSION NEGLECTED?

Introduction

Essential hypertension is a symptomless condition and patients feel well, at least until they are treated (56). Simply telling a patient on one occasion that their blood pressure is elevated leads to more time lost from work, a deterioration in family relationships and a greater amount of neurotic illness (92).

The study described in an earlier part of this Thesis confirmed that antihypertensive drugs, particularly beta-blockers, may not be well tolerated. This, together with the knowledge that the majority of patients whose treatment related adverse events were surveyed in that study, were taking only one drug for treatment of their hypertension, led to the question being posed;- "Was the non-pharmacological treatment of hypertension being neglected?"

Non-pharmacological treatment of hypertension:

Blood pressure may be reduced through alterations in diet and activity. Before prescribing what might well be life-long drug treatment for hypertension, the following measures whose effectiveness is proven should be considered.

Weight loss:

Hypertension is twice as prevalent in the young obese and 50% more prevalent in the older obese individuals than in normal weight controls (72). A weight loss of 12kgm, which should be achievable in most overweight hypertensives, through an appropriate behavioral change programme, causes a fall in blood pressure of 7/4mmHg, equivalent to treatment with one drug in mild to moderate hypertension (73). Metoprolol, a beta-blocker, given in a dose of 100mg twice daily was compared with weight loss. Weight loss led to a fall in diastolic blood pressure significantly greater than that seen with metoprolol, without the adverse effects on plasma lipids and lipoproteins associated with drugs such as metoprolol (93).

Sodium restriction:

Citations of the benefits of salt restriction go back to the ancient Greeks. In patients with hypertension a significant reduction in blood pressure has been shown through consuming a low sodium diet (94). Sodium restriction has been shown to be as effective as treatment with hydrochlorothiazide (95).

In three recent publications, meta-analyses of trials of sodium reduction have been performed. The first used data on average blood pressure and sodium consumption for different communities to predict an individual's change in blood pressure for a given change in sodium intake, given his or her age

and initial blood pressure (96). The second showed that these estimates from comparisons between different communities can, contrary to previous opinion, be readily reconciled with data relating to findings from people in single communities after allowing for the effect of bias (97). The estimates of individual changes in blood pressure resulting from a given change in sodium intake were confirmed by showing that they accurately predicted the blood pressure reductions achieved in trials of salt reduction (98).

The foregoing three papers taken together, show conclusively that salt reduction lowers blood pressure and provide quantitative estimates of the size of this effect. Moderate dietary salt reduction (by 50 mmol of sodium (3 gm of salt) each day) in people over 50 years lowers systolic blood pressure by about 5mmHg on average and by 7 mmHg or 8 mmHg in those with high blood pressure. Such a reduction in salt intake by a whole Western population is estimated to reduce the incidence of stroke by 22% and ischaemic heart disease by 16%, a larger effect than could be achieved by treating high blood pressure with drugs in a population. With a reduction in the amount of salt added by manufacturers to processed food, however, the average reduction in blood pressure could be twice as great and this would in turn reduce mortality from stroke by an estimated 39% and from ischaemic heart disease by 30%. In a population the size of Britain, this would be equivalent to preventing 65,000 deaths a year (99).

Alcohol consumption:

Alcohol consumption increases blood pressure, the threshold for this effect is not clear but the effect tends to disappear when the consumption is stopped. A survey of patients on admission to hospital showed that 51.5% whose mean daily alcohol consumption exceeded 80gm, had hypertension (100).

Meat reduction:

It was assumed that blood pressure fell when meat consumption was reduced because the reduction in consumption was associated with weight loss and a lowered sodium intake. However, a lacto-ovovegetarian diet fed to volunteers for six weeks was associated with a significant fall in diastolic blood pressure (101). This fall was independent of changes in sodium, potassium or weight. A further study which also corrected for weight changes showed that a vegetarian diet lowered blood pressure; hypertension recurred at the end of the period of dietary restriction (102).

Smoking:

Chronic smoking does not cause a prolonged rise in blood pressure, but smokers have a higher frequency of accelerated phase hypertension and subarachnoid haemorrhage. In addition, the metabolism of antihypertensive drugs is influenced and smokers require higher doses than non-smokers (71).

Exercise:

Exercise has beneficial effects in reducing cardiovascular sequelae although it does not cause a prolonged lowering of blood pressure. Catecholamine levels are reduced and endorphin levels increased by exercise, effects which are beneficial in improving well-being.

Relaxation techniques:

Blind controlled trials are difficult to construct; however, a randomised controlled trial of yoga and biofeedback demonstrated a highly significant reduction in blood pressure with treatment (103). It has also been demonstrated that behaviour modification has the additional benefits of reducing serum cholesterol (104), plasma renin activity and plasma aldosterone (105).

Treating hypertension through changes in diet and activity is more physiological, cheaper and should be the first line of management.

Patients often wish to take more responsibility for their own treatment, so regaining a measure of autonomy and aiding compliance with treatment (106). For non-pharmacological treatment of hypertension, it was thought that they might be denied this opportunity through lack of provision of suitable advice. The present study was performed to assess whether general practitioners and hospital physicians gave their patients advice about non-

pharmacological treatment of hypertension and as far as possible, whether this advice was followed.

Methods

A questionnaire was administered, in the form of a structured interview, to patients who were attending the Department of Cardiology, St Peter's Hospital, Chertsey, Surrey, UK, as either outpatients or inpatients over a six month period from February to July 1989. It was originally hoped that all the junior resident medical staff would participate in the Study. However, this was not to be possible, so that the author and one of the resident staff (Dr N. Davis) covered all the patients. Because of this, it was possible to use a structured interview rather than a self-administered questionnaire. This had the advantages of reducing the inter-assessor variability and providing the opportunity to gauge the reliability of the patients response. A sample record sheet is included in Appendix 10.

Patients included in the study were suffering from essential hypertension, with a pre-treatment systolic blood pressure equal to, or greater than 170mmHg and a pre-treatment diastolic blood pressure equal to, or greater than 100mmHg. Patients were all referred from general practice and had all been seen at least once before in the hospital prior to inclusion in the study. Thus, all patients had previously had the opportunity to receive advice about

non-pharmacological treatment of their hypertension from both hospital and general practitioners.

Fifty three questions sought to establish whether the patient recalled receiving advice from hospital or general practice about;-

Weight reduction

Reducing alcohol consumption

Lowering salt intake

Stopping smoking

Yoga

Progressive muscular relaxation

Biofeedback

Increasing exercise

Reducing meat consumption

For some patients it had been noted in the general practitioner's letters or in the hospital notes that advice had been given and where possible this was recorded in association with the patient's questionnaire.

For some patients, compliance with the advice had also been recorded, for example, a record of weight in the notes. Where possible this was also linked with the patient's questionnaire. In particular, patients could be scored from clinical and recorded observations for past and present weight

loss and smoking status. Interviewers were invited to make a judgement, if appropriate, of the probability that the patient was denying being given the advice when, in fact, it might have been given. Patients were also asked if they knew that they were suffering from hypertension.

Approval for the study was given by the Ethical Committee of St Peter's Hospital, Chertsey.

Statistics:

The data were entered into and analyzed by, the programme Dbase 3+, using an Amstrad PC1640 micro-computer. The structure of the database is included in Appendix 10. The full dataset may be found on the floppy disc at the back of the thesis, in a file;- LIFESPH.DBF.

Descriptive statistics were used and analysis was by cross-tabulation and frequency counts. Formal tests of significance were not appropriate.

Results

Sixty nine patients completed the study. Fifty of the patients were or had been overweight. Fifty were smokers or ex-smokers. It was not practical within this study to attempt to confirm smoking status by measurements

such as that of salivary cotinine. Lifelong non-smokers were not included in the denominator for counts of provision of advice to stop smoking, neither were those who had never been overweight included in the denominator for the provision of advice to lose weight.

The results of the questionnaire are shown in Table 33.

This Table also records the numbers of patients responding positively to the advice given by general practitioners, hospital physicians or both.

All patients knew that they were suffering from hypertension.

It was possible from the completed questionnaires to audit the performance of individual practitioners in providing advice to patients. A pointer to the validity of the data collected and the honesty of the patient's answers, was that the performance of individual practitioners was consistent. The study collected information about advice previously given, so that practitioners did not have the opportunity to modify or improve their performance at the time of the study.

TABLE 33

ADVICE RECALLED FROM GENERAL AND HOSPITAL PRACTICE WITH COMPLIANCE OF THOSE ADVISED

	GENERAL PRACTICE	HOSPITAL	NEITHER	ADVICE FOLLOWED
WEIGHT REDUCTION	31/50	27/50	11/50	23/39
ALCOHOL INTAKE	20/69	18/69	44/69	21/25
SMOKING	22/50	18/50	23/50	20/27
MEAT REDUCTION	11/69	8/69	54/69	12/15
YOGA	1/69	2/69	66/69	3/3
PROG MUSCLE RELAX	2/69	2/69	65/69	3/4
BIOFEEDBACK	0/69	1/69	68/69	0/1
SALT INTAKE	25/69	10/69	39/69	28/30
EXERCISE	16/69	14/69	46/69	22/23

Discussion

Antihypertensive drug treatment may not be well tolerated (56); it is also expensive. In the United States of America the cost of antihypertensive drug treatment in 1987 was 2.5 billion US Dollars (107). In the United Kingdom, in the same year, the net ingredient cost of antihypertensive drugs (not including packaging), drugs dispensed by dispensing doctors, hospitals and community health services, was £100.6 million (108). In Australia, in 1988, the cost of antihypertensive drugs to the Australian Pharmaceutical Benefits Scheme was $180 million (109), (the total National cost would include drugs prescribed outside of the scheme, but these costs are not compiled or available).

More than 50% of patients with essential hypertension are treated with one drug alone (107). Both weight loss (93) and sodium restriction (95) have been shown to be more effective than treatment with one drug alone. As has been stated, a small downward shift in blood pressure distribution of 2-3 mmHg, would have an effect on cardiovascular disease equal to treating all patients with a diastolic blood pressure of 105mmHg or more (74). This shift might be accomplished by downward shifts in the population in weight, sodium intake or alcohol consumption. The potential therefore exists to reduce the cost of antihypertensive drug treatment by half, if doctors were to give suitable advice, accompanied by appropriate behavioral management

plans and patients were to be able to make the necessary changes.

Seventy percent of the hypertensive patients in this study were, or had been, overweight. One quarter of these could not recall being given advice, from either hospital or general practice, to lose weight, or having lost weight, not allow their weight to increase. Of the patients advised, 62% of the advice was given in general practice and 54% in hospital; 78% of the overweight population received advice from one or both sources.

Of greater concern is the number of smokers who could not recall being advised to stop smoking. Fifty of the patients should have received advice to stop, but only 44% were advised by general practitioners and only 36% received advice in hospital. Forty six percent did not receive advice from either. Patients who have hypertension and smoke are at particular risk and the MRC Trial of the treatment of mild to moderate hypertension (6), showed that the only effective intervention for hypertensive smokers, was to stop them smoking. It may be that the dangers of smoking are so widely known, that it is assumed that either patients know them already, or, they will have been previously advised.

Two thirds of the hospital notes did not contain documentation of the patients alcohol intake and alcohol was not referred to in any of the communications from general practitioners. The amount of advice given to

reduce alcohol consumption from both sources was similar, being 26% in hospital and 28% in general practice. No advice was recalled by 64% of the patients.

Low sodium diets have been discussed for many years and because of its low capacity for harm, a trial of such a diet in cardiovascular disease has been widely advocated (94,95). It was therefore surprising to find that only 36% of patients recalled being advised to lower their sodium intake by general practitioners and only 14% in hospital. Fifty six percent could not recall being advised by either. Again, past blood pressure awareness campaigns, which have often advised salt reduction, may have led to the assumption that patients must know that they should reduce their salt intake.

It was less surprising to find that 78% had not been advised by either source to reduce their meat consumption, since the studies (101,102) on this may be less widely known. Of those who were advised, 16% received this advice in general practice and 12% in hospital. Although this difference is small and may well be meaningless, it might have been expected that for a less well known non-pharmacological treatment, the greater percentage of advice would have been given in hospital.

Increasing exercise was recommended to 23% of patients in general practice and 20% in hospital, while 66% received no recommendation for this at all. There have also been, and still are, many public campaigns commending the value of exercise and practitioners may assume that patients are aware of its value and do not need further advice.

It was little surprising to find that almost no advice was given for yoga and relaxation techniques. Practitioners were unaware of the works of Patel (103,104,105) and sceptical of their value. Some of the study doctors felt that these techniques "were not proper medicine" and that patients would not take them, or the advising doctor, seriously. However, four of the patients had independently made arrangements to attend psychologists to learn these techniques for themselves. The place of environmental stresses in the aetiology of essential hypertension is unclear but amongst patients there is a popular belief that stress is an important factor.

As the study progressed it was apparent that patients obviously consulted other health care or alternative practitioners, for example, psychologists and acupuncturists. Therefore, all patients should have been asked about other practitioners of whatever type that they had consulted in relation to their blood pressure. It became clear that patients frequently consulted other "practitioners", but the data collected were not sufficient to be able to provide accurate numbers.

Measurement of patient compliance is difficult and usually inaccurate, even in the carefully controlled setting of a clinical trial (110,111). Within quite severe limitations of accuracy, compliance with the advice where it had been given and recalled, appeared to be good.

It was thought that it might be easier for patients to deny having been given advice, than admit to having not been able to follow it, but patients appeared to be surprisingly honest and willing to admit that they had not managed to comply with their doctor's recommendations. There was a loose correlation between weight loss recorded in the notes with advice noted as having been given to lose weight, which did not appear to be present in those where no such advice was recorded. Two thirds of those recalling advice to lose weight had lost weight and three quarters of those recalling advice to reduce their alcohol intake claimed to have done so. Two thirds of the smokers had stopped smoking.

Almost all of the patients recalling advice to reduce their salt intake and increase exercise appeared to have done so. This may be a reflection of the prominence given to these measures in public health hypertension campaigns over the years, so that patients were already aware and accepted their validity.

The very few patients who were given advice about relaxation techniques appeared to have followed it. Patients sought these techniques for themselves and were more interested in and accepting of them than their physicians. Consideration should therefore be given to making them a more routine part of the management of hypertension.

Deficient provision of advice may occur because;

i. It takes a longer time than prescribing a drug.

ii. It may be thought to be ineffective.

iii. It may be assumed that the patient has already, or will receive advice from another doctor.

iv. It may be assumed that the patient is incapable of changing their behaviour.

Many patients wish to take greater responsibility for the management of their illnesses and may be denied this opportunity through lack of appropriate advice (106). Changing behaviour is not easy and the most difficult challenge is not the induction of change, but the maintenance of the new behaviour (112).

While many patients wish to try non-pharmacological treatments for their hypertension either before taking, or to reduce the dose of such drug treatment as may be necessary, other patients will not wish to try and will

find it easier to maintain their existing life-style, whilst controlling their blood pressure with drugs.

Conclusion

There appear to be shortcomings in both hospital and general practice in the provision of lifestyle advice to those patients suffering from hypertension, even though such advice when given seems to be heeded.

Greater provision of advice has the potential to increase patient autonomy and thus aid treatment compliance. It may enable lower doses of antihypertensive drugs to be used or, in the treatment of mild hypertension, avoid the necessity for these drugs to be used at all. The adverse effects of pharmacological treatment might thus be reduced or avoided, with a consequent improvement in the patient's quality of life.

If only a small percentage of the patients currently treated with one antihypertensive drug only were able to be treated non-pharmacologically, large savings would be made in the costs of providing drugs. This would enable diminishing financial resources to be used in other health care areas.

THESIS: SUMMARY AND CONCLUSIONS

In 1966, Richard Asher wrote in the Middlesex Hospital Journal:-

"Intracranial computers. Efficient but enigmatic in action, how do they compare with their extracranial counterparts? Are transistors superior to synapses? There is no doubt that electric computers will be increasingly used in most branches of medicine: they can store a greater number of data and with greater accuracy than the human brain. To what extent will machines supersede brains? This is a matter about which people feel strong emotions. The allure of the technical and transistorised and the appeal of the elaborate and the esoteric, combined with the prestige value of computers, assures their popularity with one kind of person. The fact that computers are not equipped with souls damns them in the eyes of another.

I have never regarded the possession of a soul as being of equal importance to that of a stethoscope and ophthalmoscope in medical work, but despite that I regard the present vogue for computers with cautious scepticism. I imagine that computers will be used to store information derived from countless clinical records and to detect significant associations between the various items. Highly important associations may exist for many years before they are noticed.

Human brains have the advantage over mechanical ones that the conclusions derived from the data provided are selected and scrutinised below the level of consciousness and those that are obviously valueless are screened off

before reaching serious consideration. The material you collect to think over is just as important as the way you think over it. Both human and mechanical brains are dependent on the data fed into them (113)."

Twenty five years later, with computers commonly accepted in most branches of medicine, it remains just as important to evaluate carefully their use and reliability. Collecting large amounts of unstructured data because there is a computer in which to store it, may result in an expensive and valueless exercise (63). Correct, directional use, may enable complex tasks to be performed which might otherwise never be possible.

The first study in this Thesis has demonstrated that studies of the size and nature of the Medical Research Council Study of mild to moderate hypertension (6), far from being impossible to repeat, may be undertaken using this methodology which is not only faster, but requires minimal resources in comparison with the original study. It would have been inconceivable to those planning and executing the MRC Study, that a study involving thousands of patients and hundreds of doctors could have been carried out by one doctor and three clerical assistants, within a relatively short space of time. Yet, such has been the development of computing, that this was possible only a few years after the MRC Study was performed. In this study recruitment proceeded rapidly and was only limited by reaching the preset patient limit.

This Study has demonstrated that this methodology is capable of gathering reliable, useful data and facilitating original observation. The speed of development of memory size and computing power that has taken place at the micro-computer level, together with the growth in the number of practices having computers, means that the potential exists to perform large studies with multiple copies of interactive programmes placed on these machines, using even fewer central resources. Placing programmes on the local computers, using periodic central collection by down-loading onto disc or through telephone data-link, would avoid the single largest source of frustration in this Study, line-breaks during data entry. This frustration was compounded by the system only "saving" data when all details of each visit had been entered, so that several pages of data entry might be lost and have to be re-entered following a line-break. Data should be automatically saved at least as often as at the completion of entry of each page. Such has been the interest in the methodology of this study, that it has been presented in three continents and the data collected, presented in a fourth.

This system, if used in the way described, is useful only for hypothesis generation. It could be used differently for hypothesis testing using case-control methodology. It is not suitable for studies undertaken within the guidelines of GCP. Those studies require extensive documentation and site visiting. When planning this Study it was envisaged that paper records

would be unnecessary. This turned out not to be so. There were the described difficulties in data entry and as well, records may need to be checked to enable source-data verification to take place. Unfortunately fraud in medical research is not uncommon. It is no easier to fabricate data using a computer than on paper, but the scale of this type of study makes checking and detection of fraud more difficult. Performing source-data verification on a 20% sample of the patients in this Study might have involved 600 site visits. Such a task might negate some of the advantages of using this methodology. Patient compliance checking by the chief investigator is not possible when that investigator is a computer link away. Checking may be performed by the treating doctor, but is no better than the patients memory or honesty since even the most complex checking systems developed can be defeated. Compliance is still universally checked by returned tablet counting, a practice shown to be worthless (110,111).

The system requires most common adverse events to be entered in response to direct questions. The need to enter rare or unusual events in plain text might lead to their being ignored. No study is ever likely to have the power to detect all rare adverse events, since the number of patients to be followed is almost unlimited (10). Important less rare events will be detected in smaller hypothesis generating studies and, since product licence applications contain low numbers of carefully selected, mostly male patients, which are unrepresentative of the whole population of potential users of the

drug, the performance of these studies remains essential. Spontaneous reporting of adverse events will always remain of prime importance, but under reporting is a major problem (33). Being involved in studies such as described in this Thesis must at least increase awareness of the need to report. Low frequency adverse events may still be missed. In spite of using word-search facilities, the majority of free text event reports still required laborious individual reading, interpretation and hand coding.

There is a lack of long term outcome data for the newer antihypertensive drugs, such as calcium antagonists and ACE inhibitors. The observation period obviously cannot be shortened but often, as in the MRC Study (6), there are long, labour intensive recruitment periods. Delays such as these can be overcome using the methodology of Chapter 2, with considerable financial savings.

The importance of adequate pilot testing of all study procedures is crucial. This testing period is often seen as delaying the business of getting on with the study. The majority of doctors in this Study did not appear to consider using the training programme or, to see much value in reading any of the instructions. They did not complain that the written material was inadequate, although in retrospect, it should have been clearer and more detailed. Although a great deal of the programme was intuitive to those with some knowledge of computing, much frustration would have been

avoided by a little attention to the guidelines. Using the messaging part of the programme to ask for help, rather than referring to the written instructions, served to highlight the inadequate word-processing power of the programme. For the future, the answer to these difficulties would appear to be to provide "on-screen" help, as well as greater word-processing power for messages. Frequently case-record forms, particularly in multicentre studies, are designed almost as an after-thought and not tested. Consequently they need constant revision and amendment while the study is in progress. At best this is frustrating and at worst, may mean that important data are not recorded and the study fails.

Ninety-five percent of new drugs are prescribed by only 5% of doctors; the patients of these doctors are at considerable risk (57). These doctors are easily identified and they and their patients constitute a group that it would be particularly important to follow.

New drugs are often prescribed to inappropriate groups of patients. For example, the HMG Co-A reductase inhibitor simvastatin was recently introduced in Australia. Preliminary data show that the largest single group to which the drug is being prescribed is elderly women (Federal Drug Utilisation Sub Committee, personal communication, February 1992).

The size of large data bases, particularly those such as COMPASS in North America, may give impressions of infallibility. However, in reality, records may be incomplete and may not include all data, such as for example, "over the counter" self medications. In reviewing data from them it is important to consider the following: why the data were collected - data collected primarily for accounting may be clinically unreliable; what the data have been used for before - does that use appear reliable; do the data require credulity to be acceptable.

In 1977 the standards of data required by regulatory authorities were far below that expected today. Nifedipine was introduced in that year, initially for the treatment of angina. After the indication for hypertension was added, it soon became the second most widely used cardiovascular drug in the world. The pooled data on which assessment of tolerability and the prescribing information was based, was that collected from 400 patients. The licence submissions contained many more patient data, but these were held on paper in single, uncompilable study reports. Prescribing information, once in place, is rarely changed and may remain unreviewed for many years, unless some serious problem comes to the notice of the authorities (R Mann, Secretary, Committee on the Safety of Medicines, London 1987, personal communication). This study is the biggest single collection of data on nifedipine in existence, it constitutes the only large reference source on the use of nifedipine in a hypertensive population. This

study caused the prescribing information for nifedipine to be changed, which, if physicians read the information, will save many patients from unnecessarily experiencing adverse effects of the drug. It is never likely to be repeated, or superseded.

Present day development of new drugs is expensive, the average cost being $320,000,000, it is also long, the typical development time being 16 years. The patent life of many drugs expires before they are marketed. Regulatory authorities demand ever higher standards from clinical trials. In contrast, it is possible to introduce a new surgical operation without evaluation, ethical committee approval or regulatory submission. Disasters with new drugs still happen and therefore, the development process is likely to become ever longer and more expensive. There is an urgent need to develop management systems to make clinical trials more efficient and contain costs.

The second study has described a computerised management system for conducting high quality multicentre clinical trials economically, with minimal patient loss and to the standard of US "Good Clinical Practice". Since its first publication it has already been used in other studies, such as a year long study of miglitol, an alpha-glucosidase inhibitor in Type II diabetes. There has been further development of the programme following the author's move to the University of Adelaide. The programme is commercially available from the author at the Department of Community

Medicine and may be tailored to the needs of individual studies. It is currently in use in the management of a year long study of terbenafine in toenail onychomycosis, conducted to US-GCP, and is to be used in studies in schizophrenia, psoriasis and hypertension.

The third study had its origins in the tolerability data gathered on antihypertensive drugs in the first study. The results of this study suggest that the provision of lifestyle advice to patients suffering from hypertension appears to be deficient. The Study depended on patient recall of information, so was open to the obvious bias that patients might deny being given advice that they did not wish to follow. On the whole, patients appeared very honest and would candidly admit when advice had been given that they were unable to follow.

The Study did not start out as a method of auditing the performance of individual doctors, but it became apparent that some doctors were particularly deficient in providing advice to patients. The observed consistency amongst patients of these doctors tended to lend credibility to the honesty of responses of their patients. Of real concern was the lack of enquiry about and recording of alcohol use amongst patients by both hospital and general practitioners. The wider community consequences of alcohol abuse are well known and doctors need to be more active in their prevention than they appear to be. The attitude of some of the doctors

studied to Patel's well conducted work on hypertension and relaxation (103,104,105) was disappointing. These Studies were carefully designed and conducted and overcame many of the technical difficulties of defining controls for an obvious intervention. Scepticism and honest evaluation by the doctors of these less usual studies would have been appropriate, their simple dismissal was not.

No country in the world, however wealthy, can afford to deliver all that is possible in medicine to all of its population on demand; rationing is essential and choices have to be made (114). It is important that medical technology, together with tactical expertise in curative medicine, is not allowed to distract from the essential need to provide good preventative advice to patients, which is constantly reinforced. In the 1950s around 70% of the Australian adult population smoked, it is now around 29%. Consider, if this change had not taken place, what the demand today might be for coronary artery surgery and, the financial impossibility of meeting it. Effective prevention may be the only hope for the economic survival of any system of medicine. It will save, as this study suggests, scarce health care resources for use in other areas.

New technology should only be used in medicine if it results in improved, or more patient care. The patient should not be allowed to become secondary to the equipment or the technique. Twenty five years ago Asher

placed the importance of the human factor in context:- "I wanted to use in a lecture a cartoon I recollected seeing in Punch some 30 or 40 years previously. I sent a brief description to the Punch editorial office and asked if there was any chance of their finding it. They sent it back to me by return. As they must have published well over 50,000 cartoons during my life-time I was much impressed, and I wrote to thank them, saying what an elaborate system of classifications and indexes and cross references they must have to achieve such a feat. They wrote back to say that all they had was one elderly lady with a rather good memory."

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APPENDIX 2

Training programme

Introduction

The purpose of this guide is to enable you to become familiar and conversant with the study program. It has been compiled on a step by step basis and checklists have been included to clarify possible problem areas that you may encounter.

The setting up of the equipment and how to connect into the service should have been successfully completed.

This guide assumes you can connect into the service.

The sections to be covered will be:

- Connecting to the study program
- Complete a patient visit assessment
- Withdraw a patient from the study
- Look up doctor study progress
- Look up patient details
- Send and view a message
- Amend own password

Special Consideration

The training program requires entry of the prefix ZZ. If you do not enter ZZ and you are accepted into the program it means you have selected the live service option.

Connecting to the Study Program

Following the successful entry of and f3 you will be required to enter your user number and password. Both must be entered correctly and you have only TWO attempts to get it right.

Action	Comment
Enter your user number and press Return	The program will display a dash to indicate a character as been recorded. If in doubt key ** and re-enter the number
Enter your password and press Return	If successful the next screen will welcome you and indicate when you last used the service If unsuccessful you will have a second attempt to reenter both the user number and password
Key 1 Return or Key 2 Return	The next screen will be the sign on

Study Program Sign On

Study Live Service

You will have entered 1 Return from the previous screen. The top left hand corner of the screen will display
Co Medica Systems.

The Medical Controller will have allocated to you an identity and system number, and a personal password. You will have THREE attempts to enter the identity or system number, and password correctly. Successful entry will take you to your Welcome Main Index.

Should you be unsuccessful, the program will request re-entry of both, the identity or system number, and password. Three unsuccessful attempts and you will be disconnected from the program and requested to contact the Medical department at Bayer, Newbury.

Study Training Program

You will have entered 2 Return from the previous screen. The top left hand corner of the screen will display
Training

When you wish to enter the training program your identity or system number must be prefixed by ZZ eg: ZZ identity or ZZ100. The personal password remains the same.

All information entered under "ZZ" will be for training only to enable you to become familiar with the program.

You will have THREE attempts to enter the ZZ identity or ZZ system number, and personal password.

Complete a patient visit assessment

The steps involved will be

- Patient selection and acceptance into the study
- Visit 1 details
- Visit 2 details
- Visit 3 details

Please follow and complete the demonstration sequence.

Patient selection and acceptance into the study

Action	Comments
From the Welcome Main Index - Key 1 and Press Return	Next screen "patient details"
- Enter these details Patient doctor identity = ABCD1 Sex = W Change to M or F	L23 message - check sex status
Age = 20 to 69	Enter 71 or over and L23 message Withdrawal patient - too old
Weight on kg = 45 to 110	For numbers 100, enter number and press Return
Height in cm = 150 to 250 Smoker = N Recently stopped = N Hypertension newly diag=N Years/Months first diag=Enter Return and 6 to 12 Medical history = N	Enter Y = Yes or N = No If Y=Yes details will be required
Key 1 to continue = 1	Next screen will be Pre-entry details
Pre-entry details consists seven(7) mandatory questions to be answered as Y=Yes N=No	All answers must be correct for patient selection
Questions will be on two screens	One incorrect response may be corrected; two or more will withdraw the patient automatically
- Enter these details	
Q1 = N Q2 = N Q3 = Y	L23 message "check category 3 or withdraw patient"
Q3 = change Y to N Q4 = N Key 1 to continue = 1 or Return	1 displayed by the system. Press 1 or Return to move on. Next screen will be question 5 - 7

Action	Comments
- Enter these details Q5 = N Q6 = N Q7 = Y Key 1 to continue = 1 or Return	Next screen will be "Pre-entry to study" At this stage patient selected but not accepted into study. This will be dependent upon blood pressure.
- Enter these details Date first readings = 010785 SBP = 150 DBP = 110 HR = 95	Note patient identity and the number generated by the system for this patient
Date second recording = 160785 SBP = 145 DBP = 110 HR = 95	
Key 1 to confirm = 1 or Return	Patient will be accepted into study

Visit 1 details

There will be four (4) sections to be completed

- Concomitant disease
- Concomitant medication
- Pre-study side effects noted
- Treatment details

Concomitant medication will be a summary screen linked to seven (7) more detailed screens. Access and sequence will be dependent on the selection if any from this screen.

Action	Comments
Visit 1 details	The screen will be "Concomitant-Disease"
- Enter these details	
Date of visit = todays date unless changed	Last visit will be date of 2nd recording Change todays date to match 2nd recording date if a 3rd recording for todays date is not required.
Q1 Angina = Return Number of months = Return	No data required
Q2 Myocardial Infarction = Y Number of months = 2	L23 message "Withdraw Patient MI' Withdrawal/exclusion criteria
Change 2 to 3 or more Q3 = Return	If Y is entered L23 message will be displayed
Q4 = Return Q5 = Return Q6 = Return	
Key 1 to continue = 1 or Return	Next screen will be "Concomitant Medication"
Concomitant Medication	When Y is entered against a category group the program will route to that screen details. If no Y entries have been made the program will sequence to the next screen "Pre study side-effects noted"
- Enter these details	
Diuretic = Return	
B-blockers = Y	
Combination = Return	
Other anti-hypers = Return	
Hypoglycaemic agents = Return	
H2 antagonists = Y	
Other = Return and Return	Press return to move the cursor onto the next line

Action	Comments
Key 1 to continue = 1 or return	B-blockers and H2 antagonists have been selected. The program will sequence via these screens
B-blockers - enter these details	
- Select two listed drug by entry of Y in the field - Press Return to move onto the next field	Program will only allow two drugs to be identified
- Patient withdrawal = Y	In this instance the next screen will be H2 antagonists
H2 antagonists - enter these details	
- Select 0, 1 or 2 drugs by entry of Y in the field required	
Key 1 to continue = 1 or Return	Next screen will be "Medication Reaction"

Action	Comments
Medication Reaction - enter these details	Press return to move onto the ne: field or enter number (1-4) to indicate the intensity of the identified side effect
- Select two side-effects and enter (1-4)	Note this screen is for pre-study treatment information.
- Other Press Return and Return	
- Key 1 to continue = 1 or Return	Next screen will be "Treatment Details V1"
Treatment Details V1 = enter these details	
- Visit 1 recordings	
Displayed SBP = Return Displayed DBP = Return Displayed HR = Return	SBP, DBP, HR will only be require if the second recording date is not the same as todays date as entered in Concomitant disease. If these recordings are required the screen fields will be blank; if not the program will redispla the entered details. These details may be changed and accepted as a third recording = Visit 1 details. Press Return, Return, Return to skip over these fields.
Tablet given to patient = 56	Note date of next visit
Key 1 confirm record = 1	Only at this point will visit 1 details for this patient be confirmed and the records updated. Information has been checked and validated in the sequence but not confirmed until this decision command.
Alternative decision Key 0 to cancel	If the visit 1 details are cancelled, you will have to re-enter the details. Select option 2 and enter the patient system number from the Welcome Main Index

Visit 2 Details

To enter visit 2 details for a patient, select option 2 and enter the system number for the patient (01-99) in the Welcome Main Index. The system will automatically identify the correct visit for the patient, display the first screen and indicate the visit status (in this case visit 2).

Three sections require completion
- Symptom details
- Treatment medication reaction
- Visit 2 treatment details

Action	Comments
Symptom details - enter these details. Todays date = 310785 SBP = 140 DBP = 100 HR = 90	Not more than 35 days forward of last visit date, or the patient will be withdrawn by the program at the end of the visit 2 record
Concomitant Medication change = N	If Y is entered, the program will route to Concomitant Medication summary and the doctor can enter the changes. If Y has been entered in error, 0 cancel/index will return the doctor to this screen and redisplay the details
Key 1 to continue = 1	Next screen will be "Treatment Medication Reaction" Key 0 will cancel the visit record and it will have to be re-entered.
Treatment Medication Reaction - enter these details	
- Select one side-effect and enter a 1 or 2 for intensity - Select one side effect and enter a 3 or 4 for intensity	You will be routed to the system withdrawal alert for this patient because a severe (3) or intolerable (4) side effect has been noted.
- Enter 7 in "System Withdrawn Alert" screen to return to Medication Reaction to amend the date	If you enter 1, the patient will be withdrawn If you key 8, the information will be recorded, but the patient <u>will not</u> be withdrawn. The next screen will be "Visit 2 Treatment details.

Action	Comments
Change the entered 3 or 4 to 1 or 2 or press space bar to delete the entry from the field	
Press Return until cursor is in option box, and enter 1 or press Return if 1 is displayed.	Next screen will be "Visit 2 Treatment Details".
Visit 2 Treatment Details - enter these details	
- Tablets returned - None so press Return	
	Note change in dosage from 20 to 40 mg bd, because the DBP recording was greater than 95mm Hg.
- Tablets given to patient = 120	
- New signs = Y	
- Details enter Patient reported several nose bleeds - press Return to finish	
- Key 1 to confirm = 1	Visit 2 details will now be confirmed and records updated. You will be returned to the Welcome Main Index.

Visit 3 Details

To enter visit 3 details for a patient select option 2 and enter the system number for the patient (01-99) in the Welcome Main Index. The system will automatically identify the correct visit for the patient, display the first screen and indicate the visit status (in this case visit 3).

Three sections require completion similar to visit 2.

- Symptom details
- Treatment medication reaction
- Visit 3 Treatment details

The program will follow the Concomitant Medication reaction sequence if activated.

Action	Comments
Visit 3 symptom details - enter these details	
- Todays date = 300885 SBP = 120 DBP = 95 HR = 85	
Concomitant medication changed = N	
Key 1 to continue = 1	Next screen will be "Treatment medication reaction"
Treatment Medication Reaction - enter these details	
- Press Return until the cursor is in the option entry field	No side effects to report
- Key 1 to continue = 1 or Return	
Visit 3 Treatment Details - enter these details	
- Tablets returned by patient = 6 and press Return	2 character entry field. 10 or more will move the cursor onto the next field.
- Patient continue treatment = Y	If N=No is entered, details will be required.
- Press Return and Return to move onto New signs? - New signs? = N	
- Press Return and Return to move onto patient assessment - Assessment? = 1	
- Key 1 to confirm = 1	Visit 3 details will be confirmed and the records updated The assessment for the patient has now been completed

Practical Exercise

Now that you have successfully completed your first patient assessment please complete the following task.

- Select for study acceptance 5 more patients
- Two patients will be completed assessments
- One patient will be visit 1 record completed
- Two patients will be accepted but visit 1 details still to be entered

Withdraw a Patient from the Study

The doctor may withdraw a patient directly by either selecting the option and entering the patient system number in the Welcome Main Index, or confirming the withdrawal of a patient as a result of the system withdrawal alert.

Patient Withdrawal by the Doctor

Action	Comment
Select your patient with visit 2 completed and from the Welcome Main Index	
- Enter 3 and the patient system number	Next screen will be Withdrawal Reasons
- Select your decision number (1-7)	
- Key 1 continue = 1	Next screen options Decision No 1 goto Withdraw Side Effects 2,3,4 goto Patient Withdraw - 1 5,6,7 goto Patient Withdrawal - 2
If decision number 1	
- Identify side-effect and enter numeric grade (1-4). Press Return to move onto next field	
- Enter 7 to amend withdrawn	Next screen will be Withdrawal Reasons
If decision number 2, 3, 4 enter the following	
For 2 Press Return until the cursor is in the SBP field	Screen will be Patient Withdrawal 1 Note display of reason
- Enter SBP = 160 DBP = 120	Withdrawal criteria
- Enter 7 to amend withdrawal	Next screen will be Withdraw Reasons
If 3 - select reason (1-5)	If 4 or 5 entered you will need to add details in comment area.
- Press Return for SBP and DBP	Note display of reason
- Key 7 amend = 7	Next screen will be Withdrawal Reasons

Action	Comment
If 4 - select reason (1-5)	Note display of reason
- Press Return for SBP and DBP	
- Key 7 amend = 7	Next screen will be Withdrawal Reasons
- If 5, 6, or 7 enter comment	Note display of reason
- Key 7 amend = 7	Next screen will be Withdraw Reason
Now Select withdrawal reason, complete the sequence, but this time Key 1 confirm patient withdrawal	Next screen will be Welcome Main Index
System withdraw alert has been demonstrated in the patient assessment sequence when triggered. The doctor will either confirm the alert ie the entered details as displayed, select amend and be returned to the previous screen to correct the entry, or in the case of side effects only may cancel the side effect withdraw and continue with the patient in the study	
	The program will trigger the withdrawal alert for - Protocol violation - Blood pressure - Side effects

Look Up Doctor Study Progress

The doctor may look up own study progress at anytime.
Select option 4 and Press Return from the Welcome Main Index.

The Screen will display the following details

- Doctor name
- Total patients setup by the doctor
- Total patient assessments completed
- Total patients withdrawn
- Individual patient status by patient system number (01-99)

From this screen the doctor is able to look up patient record details by entering the patient number into the option field. Alternatively the doctor may select option 5 and enter the patient system number from the Welcome Main Index.

Look Up Patient Details

The doctor may look up individual patient details in the following way.

- Patient Assessment Summary
- Patient History details
- Patient visit record by visit

Patient Assessment Summary: This screen will summarised selected information from the visit details by visit. The text information will be in an abbreviated form. Eight (8) abbreviations will be listed ie

BP = Blood pressure as SBP/DBP
HR = Heart rate
mg = Tablet dosage
Tg = Tablets given
Tr = Tablets returned
SP = Side effects noted pre study
SE = Side effects noted in study
W Code = Withdrawal + code

Patient History Details: This screen will display the patient details as entered for the initial selection of the patient.

Patient Visit Record: The patient visit record consists of five (5) possible screen displays. The sequence is made up from the following screens.

- Concomitant disease
- Treatment details
- Medication during last 28 days
- Side-effects noted
- Withdrawal details

The doctor will be reminded there is another screen to view for the patient visit by the prompt "key # more details".

Exercise to do

Please complete this exercise as it will identify alternative routing decisions that may be taken from various screens.

Start at the Welcome Main Index

Action	Comment
- Key 4 and press Return	Next screen will be "study progress" Route options - Enter patient number and goto to details - Return main index
- Select patient 1 = 1 and press Return	Next screen will be "Patient Summary for patient 1 Route options - Select visit record = (1, 2 or 3) - Patient history = 4 - Next patient summary = 5 - Return study progress = 9 - Return main index = 0
- Select patient history = Key 4	Next screen will be Patient History Route options - Select visit record = (1, 2 or 3) - Next patient = 5 - Patient summary = 6 - Study progress = 9 - Return main index = 0
- Select visit 1 record = Key 1	Next screen will be visit 1 record Concomitant disease as recorded Route options - Select new visit record = (1,2 or 3 - Patient history = 4 - Next patient = 5 - Patient summary = 6 - Study progress = 9 - Return main index = 0 - Next screen details for visit 1 = Return
- Select visit 2 record = Key 2	Next screen will be visit 2 record Treatment details as recorded. Some displays will be blank because they relate to visit 3 entry details. Route options - Select new visit record = (1,2 or 3 - Patient history = 4 - Next patient = 5 - Patient summary = 6 - Study progress = 9 - Return main index = 0 - Next screen details for visit 2 record = Return

Action	Comments
- Select next screen details = press Return	Next screen will be side effects note in last 28 days Route options - As described above expect "Next screen details" should not appear because patient 1 was a completed assessment.
- Select next patient = Key 5	Next screen will be "Patient Summary for next patient in sequence by system number.
- Select study progress = Key 9	Next screen will be "Study Progress"
- Return Welcome Main Index = Key 0 and Return	Next screen will be "Welcome Main Index" You have returned to this index by each summary level above the displayed screen. Obviously the alternative route options on the screen will speed up the process. In order to view all the patient details in the visit record sequence you will have to create a patient which you subsequently withdraw.

Additional Exercise

Create another patient and select and accept into the study

- Record visit 1 details entering a record entry for each screen
- Record visit 2 details including change in medication - use routes 5,6,7 or Other.
- Then withdraw patient and confirm

Now select patient details from the Welcome Main Index and look up visit 2 record details.

Send and View a Message

The program is designed to enable the doctor to send messages to and receive messages from the medical controller. A doctor may send as many messages as is desired and can receive up to three (3) maximum at any one time.

Send a Message

To send a message select option 6 and press Return from the Welcome Main Index. The program will automatically display the send message screen and create certain entries i.e.

- To : Medical Controller
- From: Doctor name
- Date: Todays date
- Time: Time when message screen was requested.

The doctor will be required to enter the following

- Message subject
- Message text
- Confirm or cancel the message

Action	Comments
You have selected the send message option. The cursor will be on the subject entry line.	
- Type in subject text. Should the text not complete the line press Return to move the cursor onto the next line.	All messages will be displayed in upper (capitals) case, irrespective o entry
- Type in message text.	Six (6) lines are available for message entry. Each line is indicat by a yellow bracket sign.
- When you have completed the message press Return until the cursor is displayed in the option field.	
- Confirm message = Key 1	Next screen will be Welcome Main Ind
	In the event that the program will not allow you to send a message and comment is displayed on line 23, thi means the medical controller new message area is full. Until these messages have been viewed, the program will continue to prevent access to the send a message option.

Receive a Message

Should a message have been sent by the medical controller to a doctor, an alert will be displayed in the Welcome Main Index screen. The doctor will select option 7 and press Return from this screen to view the message. The program will display the message and details as to when it was sent.

The only option route decision from this screen is "Key 1 to erase message and continue". If there is only one new message to view, the program will return to the Welcome Main Index. When two or three messages are waiting to be viewed, the program will automatically display the next message. "Key 1 to erase message" will either return to the Welcome Main Index or display the next message. For the third new message the doctor will be returned to the Welcome Main Index.

Amend your Own Password

To amend your own password select option 8 and press Return. The next screen will display selected details and a single entry field for the new password text. The details displayed on the screen will be your:

- System user number identity
- Surname identity
- Initials
- "Old Password" = Existing password

To change your password simply enter in the new details and press Return to not move onto the confirm or cancel field if required.

"Key 1 confirm" will create the new password and it becomes effective immediately!

"Key 0 cancel" will leave the old password unchanged.

APPENDIX 3

Concurrent diseases by age and sex

CONCURRENT DISEASES BY SEX

TABLE OF DISEASE BY SEX

DISEASE	SEX		
FREQUENCY	MALE	FEMALE	TOTAL
NONE	1522	1547	3069
OBESITY	42	45	87
DIABETES MELLITU	27	16	43
ARTERIOSKLEROSE	1	0	1
ANAEMIE	0	2	2
HEMIPARESE	1	0	1
EMPHYSEM	0	1	1
RAYNAUD-SYNDROM	1	2	3
HYPERLIPIDAEMIE	0	1	1
MIGRAENE	1	1	2
DEPRESSION	2	6	8
BRONCHITIS	0	2	2
ULCUS DUODENI	6	1	7
MYOKARDINFARKT	87	30	117
ANGINA PECTORIS	175	107	282
GICHT	9	1	10
ASTHMA	6	3	9
DYSPEPSIE	1	0	1
RHINITIS ALLERGI	2	0	2
DIABETISCHE NEUR	1	0	1
CERVICAL SPONDYL	3	4	7
REAKTIVE DEPRESS	0	1	1
Z.N.CHOLECYSTEKT	0	1	1
TOTAL	2302	2149	4451

(CONTINUED)

CONCURRENT DISEASES BY SEX

TABLE OF DISEASE BY SEX

DISEASE / SEX	MALE	FEMALE	TOTAL
FREQUENCY			
NONE	1522	1547	3069
OBESITY	42	45	87
DIABETES MELLITU	27	16	43
ARTERIOSKLEROSE	1	0	1
ANAEMIE	0	2	2
HEMIPARESE	1	0	1
EMPHYSEM	0	1	1
RAYNAUD-SYNDROM	1	2	3
HYPERLIPIDAEMIE	0	1	1
MIGRAENE	1	1	2
DEPRESSION	2	6	8
BRONCHITIS	0	2	2
ULCUS DUODENI	6	1	7
MYOKARDINFARKT	87	30	117
ANGINA PECTORIS	175	107	282
GICHT	9	1	10
ASTHMA	6	3	9
DYSPEPSIE	1	0	1
RHINITIS ALLERGI	2	0	2
DIABETISCHE NEUR	1	0	1
CERVICAL SPONDYL	3	4	7
REAKTIVE DEPRESS	0	1	1
Z.N.CHOLECYSTEKT	0	1	1
TOTAL	2302	2149	4451

(CONTINUED)

CONCURRENT DISEASES BY SEX

TABLE OF DISEASE BY SEX

DISEASE	SEX		
FREQUENCY	MALE	FEMALE	TOTAL
UEBERGEWICHT	6	6	12
INSOMNIA - SCHLA	1	0	1
ISCHEMIC HEART D	0	1	1
BRONCHITIS,CHRON	1	3	4
THYREOTOXIKOSE	1	0	1
ANGSTZUSTAENDE	10	10	20
KOPFSCHMERZEN	2	1	3
DIZZINESS	0	6	6
TIREDNESS - MUED	0	1	1
ERKAELTUNG	1	0	1
TIA	0	1	1
HIATUSHERNIE	3	3	6
OSTEOARTROSIS	0	2	2
PSORIASIS	0	5	5
DIABETES,INSULIN	1	0	1
SINUSITIS	0	1	1
MENIERE	0	1	1
CLAUDICATIO INTE	0	2	2
DIABETES,NICHT I	6	2	8
PERIPHERAL VASCU	60	38	98
Z.N.MYOKARDINFAR	2	0	2
PERIPHERE DURCHB	0	1	1
VERTIGO	0	1	1
TOTAL	2302	2149	4451

(CONTINUED)

CONCURRENT DISEASES BY SEX

TABLE OF DISEASE BY SEX

DISEASE / FREQUENCY	MALE	FEMALE	TOTAL
Z.N.CEREBRO-VASC	1	1	2
RHEUMATOIDE ARTH	3	2	5
TINNITUS	0	1	1
EKZEM	2	1	3
DIABETES	2	0	2
SCHLAFLOSIGKEIT	0	1	1
LOW BACK PAIN	2	0	2
ATEMWEGSINFEKTIO	1	0	1
INGUINALE HERNIE	3	0	3
ARTERIOSCLEROTIC	1	0	1
ARTHRITIS	6	3	9
ARTHRITIS KNEE A	1	0	1
ARTHRITIS OF NEC	2	0	2
ARTHRITIS KNEES	1	2	3
ARTHRITIS DUE TO	1	0	1
ARTHRITIS SHOULD	0	1	1
ARTHRITIS OF HIP	1	1	2
ARTHRITIS OF KNE	1	0	1
ARTHRITIS OF SPI	2	1	3
OSTEOARTHRITIS	14	14	28
EMERY	0	1	1
EPISTAXIS	1	1	2
GALL BLADDER DIS	0	1	1
TOTAL	2302	2149	4451

(CONTINUED)

CONCURRENT DISEASES BY SEX

TABLE OF DISEASE BY SEX

DISEASE	SEX		
FREQUENCY	MALE	FEMALE	TOTAL
NECK FIBROSIS	0	1	1
SILVER WIRING IN	0	1	1
ABDO/PERINEAL RE	0	1	1
ABSENT PULSES FR	0	1	1
RETINOPATHY GRAD	5	1	6
TRIPAL VESSEL IN	0	1	1
ACNE ROSACEA	0	1	1
ALLERGIC MINUITI	1	0	1
AMPUTATED LITTLE	1	0	1
ANKLE OEDEMA	1	4	5
SILENT MI (STILL	0	1	1
CHEST INFECTIONS	0	1	1
ANT.PROLAPSE,BIL	0	1	1
NEUROSIS	0	2	2
AORTIC BIFURCATI	1	0	1
ARCUR DENTIS	0	1	1
ARTH NECK	0	1	1
ATRIAL FIBRILLAT	1	0	1
AV NIPPING	0	1	1
B/K AMPUTATION O	2	1	3
BACK STIFFNESS	0	1	1
BACKACHE	1	0	1
BASAL CREPITATIO	0	1	1
TOTAL	2302	2149	4451

(CONTINUED)

CONCURRENT DISEASES BY SEX

TABLE OF DISEASE BY SEX

DISEASE / SEX	MALE	FEMALE	TOTAL
FREQUENCY			
BILATERAL CATARA	1	1	2
BILATERAL BLEPHE	1	0	1
BIRD FANCIERS LU	1	0	1
BRONCHOSPASM	1	0	1
CEREBRO-VASCULAR	4	0	4
CARDIOMEGALIE	0	1	1
CATARRH	1	0	1
CATARACT EXTRACT	1	0	1
CHEST SOMETIMES	1	0	1
CHEST-RHONCHI	1	0	1
CHILBLAINS	0	2	2
CHRONIC ACTIVE H	1	0	1
CHRONIC PROSTATI	1	0	1
CHRONIC PSORIASI	0	1	1
CHRONIC VENOUS I	0	1	1
COLD AND PULSELE	0	1	1
COLD FEET	0	1	1
COLD HANDS AND F	1	0	1
CONTROLLED ATRIA	0	1	1
DEAFNESS	2	1	3
DEGENERATIVE ART	1	0	1
DERMATITIS HANDS	1	0	1
DISCHARGE FROM E	0	1	1
TOTAL	2302	2149	4451

(CONTINUED)

CONCURRENT DISEASES BY SEX

TABLE OF DISEASE BY SEX

DISEASE SEX

FREQUENCY	MALE	FEMALE	TOTAL
DIVERTICULITIS	0	1	1
DUPYTRANS CONTRA	1	0	1
DVT LEG (DEEP VE	1	0	1
DYSPNOEA	0	1	1
DYSPNOEA ON EXER	1	0	1
LETHARGY	0	2	2
CLAUDICATION	1	0	1
UTI (E.COLI)	1	0	1
RETINAL CHANGES	0	2	2
RETINOPATHY	2	0	2
SPONDYLOSIS	1	0	1
LEFT VENTRICULAR	1	0	1
ENLARGED PROSTAT	1	0	1
ENLARGED FIBROID	0	1	1
EPILEPSY	3	0	3
EPISODES OF DOUB	0	1	1
EPITHELIOMA RIGH	1	0	1
ERYTHROEDEMA PSO	0	1	1
EV OF OLD CVA	1	0	1
MCV 102 MCH 33.6	1	0	1
FE DEV ANAEMA AS	0	1	1
FIT	1	1	2
FIT LOL	1	0	1
TOTAL	2302	2149	4451

(CONTINUED)

CONCURRENT DISEASES BY SEX

TABLE OF DISEASE BY SEX

DISEASE / SEX	MALE	FEMALE	TOTAL
FREQUENCY			
FLUSHED APPEARAN	0	1	1
FUNDI GRADE 1	0	1	1
GENERAL FATIGUE	1	0	1
GIDDYNESS	1	0	1
GOUT IN TOE	2	0	2
HYPERTENSIVE RET	1	5	6
RETINOPATHY GRA	1	2	3
COLD HANDS	0	1	1
HAYFEVER	1	0	1
RVF	0	1	1
HIGH COLOUR TENS	1	0	1
HYPERACIDITY	1	0	1
THYROID NODULE	0	1	1
HYSTERECTOMY	0	2	2
PROTEINURIA	0	1	1
IMPOTENCE	1	0	1
INDIGESTION	1	0	1
INDUSTRIALLY IND	1	0	1
INTENTIONAL TREM	1	0	1
INTERMITTENT BRO	1	0	1
IRON DEFICIENCY	0	1	1
IRRITABLE BOWEL	0	1	1
LABYRINTHITIS VI	0	1	1
TOTAL	2302	2149	4451

(CONTINUED)

CONCURRENT DISEASES BY SEX

TABLE OF DISEASE BY SEX

DISEASE / SEX	MALE	FEMALE	TOTAL
FREQUENCY			
CRAMPS IN LEGS	1	0	1
THYROID GOITRE	0	1	1
BELLS PALSY	0	1	1
LIGHT STRUCTURE	0	1	1
LIPODERMATOSCLER	1	0	1
VENOUS STASIS UL	1	0	1
LIPOMAS ON ABDO	1	0	1
LOST SENSE OF TA	0	1	1
LOWER RESPIRATOR	1	0	1
LUMBAR AND CERVI	0	1	1
LUMBAR ARTHRITIS	0	1	1
OSTEOARTHRITIS L	3	2	5
LUMBAR BACK PAIN	0	1	1
MARKED V.B.I.	0	1	1
MASTECTOMY	0	3	3
MASTECTOMY FOR C	0	1	1
OSTEOARTHRITIS H	4	5	9
MENIERES DISEASE	0	1	1
MENOPAUSAL FLUSH	0	1	1
PALPITATIONS	0	1	1
AIRWAYS OBSTRUCT	0	1	1
DERMATITIS	1	0	1
INNOCENT SYSTOLI	1	0	1
TOTAL	2302	2149	4451

(CONTINUED)

CONCURRENT DISEASES BY SEX

TABLE OF DISEASE BY SEX

DISEASE / SEX FREQUENCY	MALE	FEMALE	TOTAL
RESIDUAL WEAKNES	0	1	1
SOA	0	1	1
UPPER RESPIRATOR	1	1	2
WEAKNESS OF HAND	0	1	1
WEAKNESS RT SIDE	0	1	1
CHRONIC OBSTRUCT	0	1	1
BENIGN PROSTASTI	1	0	1
MINIMAL SIGNS OF	0	1	1
DRY SKIN CONDITI	0	1	1
MITRAL REGURGITA	1	0	1
MITRAL SYSTOLIC	0	1	1
RHEUMATOID OSTEO	0	1	1
MYXOEDEMA	0	2	2
NASAL POLYPS	1	0	1
NAUSEA	0	1	1
NERVOUS TENSION	0	1	1
OBSTRUCTIVE AIRW	124	89	213
NIGHT CRAMPS	0	1	1
HIP REPLACEMENT	1	0	1
OSTEOARTHRITIS K	4	6	10
Z.N.BASALZELL-CA	1	0	1
NOCTURIA	1	0	1
ENLARGED PROSTRA	2	0	2
TOTAL	2302	2149	4451

(CONTINUED)

CONCURRENT DISEASES BY SEX

TABLE OF DISEASE BY SEX

DISEASE	SEX		
FREQUENCY	MALE	FEMALE	TOTAL
ISCHAEMIC ECG	1	0	1
OSTEOARTHRITIS S	4	2	6
OSTEOARTHRITIS W	0	1	1
VAGINITIS, ATROP	0	1	1
CONJUNCTIVITIS	1	0	1
LEG INJURIES	1	0	1
EXERTIONAL S/O/B	1	0	1
VARICOSE VEINS	2	5	7
ACNE	0	1	1
ECTOPIC BEATS, O	0	1	1
ACCOUSTIC NEUROM	0	1	1
DEFICIENT CIRCUL	0	1	1
OSTEOARTHROSIS S	0	1	1
OVARIAN CYST.	0	1	1
EYES A.V NIPPING	1	0	1
PACEMAKER	1	0	1
PAIN IN BACK	0	1	1
PAIN UNDER RIBS	1	0	1
PAIN IN KNEE	1	0	1
PALE LEFT DISC	1	0	1
URINE TRACE PROT	1	0	1
PANSYSTOLIC MURM	0	1	1
A/V NIPPING	0	1	1
TOTAL	2302	2149	4451

(CONTINUED)

CONCURRENT DISEASES BY SEX

TABLE OF DISEASE BY SEX

DISEASE / SEX	MALE	FEMALE	TOTAL
FREQUENCY			
TRANSIENT VISUAL	0	1	1
Z.N.PNEUMONECTOM	1	0	1
SEHSTOERUNG (EIN	0	1	1
PARTIAL THICKNES	1	0	1
Z.N.DIABETES	1	0	1
Z.N.DUCTUS ARTER	0	1	1
ARTHRITIS FINGER	0	1	1
PEAK FLOW 220 LI	0	1	1
PEFR=170	0	1	1
PEPTIC ULCER	2	0	2
PERNICIOUS ANAEM	1	0	1
PERSISTANT COUGH	0	1	1
PLETHORIC	1	0	1
POLIO LEG	0	1	1
POOR PULSES POPL	1	0	1
ALCOHOL ABUSE	1	0	1
PROCIDENTIA	0	1	1
PROSTATIC SYMPTO	1	0	1
PROSTATISM	1	0	1
DUPUYTRENS CONTR	1	0	1
PROSTETIC AORTIC	0	1	1
PRURITIS ANI	1	0	1
Z.N.R I H REPAIR	1	0	1
TOTAL	2302	2149	4451

(CONTINUED)

CONCURRENT DISEASES BY SEX

TABLE OF DISEASE BY SEX

DISEASE	SEX		
FREQUENCY	MALE	FEMALE	TOTAL
UNDERWEIGHT	0	1	1
RAISED FASTING L	0	1	1
CHOLESTEROL 8.0	1	0	1
RAISED URIC ACID	1	0	1
CHEST INFECTION	2	0	2
REFLUX OESOPHAGI	1	1	2
PARAPLEGIA	0	1	1
SLURRING SPEECH	1	0	1
RETINAL VEIN OCC	0	1	1
RETINITIS PIGMEN	0	1	1
CATARACTS	0	1	1
RHONCHI	0	1	1
CAROTID BRUIT	1	0	1
HEMIPLEGIA	0	1	1
ROTATOR CUFF SYN	1	0	1
CARPAL TUNNEL	1	0	1
MONOPERISIS	1	0	1
S O B EXERTION	1	0	1
SCATTERED RHONCH	1	0	1
SCATTERED CREPS	1	0	1
SCIATICA	0	2	2
HEARTBURN,WATERB	0	1	1
SHINGLES	0	1	1
TOTAL	2302	2149	4451

(CONTINUED)

CONCURRENT DISEASES BY SEX

TABLE OF DISEASE BY SEX

DISEASE / SEX FREQUENCY	MALE	FEMALE	TOTAL
SHORT TERM MEMOR	1	0	1
HYSTERECTOMY SCA	0	1	1
SIGNS OF CVA	1	0	1
SIGNS OF CHRON.O	1	0	1
SILVER WIRING	0	1	1
SKIN KERATOSIS	0	1	1
VALSALVA NEGATIV	0	1	1
TACHYCARDIA	1	0	1
WHEEZE	2	3	5
SMOKERS COUGH	0	1	1
SPASTIC QUADRAPA	0	1	1
SPRAINED BACK MU	0	1	1
SPRAINED WRIST	1	0	1
STIFF NECK	0	1	1
SWOLLEN KNEE	0	1	1
SYSTOLIC MURMUR	2	1	3
TENDERNESS IN LO	0	1	1
TENNIS ELBOW	1	0	1
THYROIDIC	0	1	1
THYROTOXIC	0	1	1
TRANSIENT CEREBR	1	0	1
TREMOR,UPPER LIM	1	0	1
COLITIS, ULCERAT	0	1	1
TOTAL	2302	2149	4451

(CONTINUED)

CONCURRENT DISEASES BY SEX

TABLE OF DISEASE BY SEX

DISEASE	SEX		
FREQUENCY	MALE	FEMALE	TOTAL
UMBILICAL HERNIA	1	0	1
URINE, BLOOD ONE	1	0	1
VARICOSE ECZEMA	1	1	2
VARICOSE ULCER L	0	1	1
VARICOSE VEINS E	0	1	1
POOR VISION	1	0	1
SPLIT NAILS	0	1	1
WEAK DIAST.PRESS	0	1	1
WEAK GRIP HAND	1	0	1
ISCHEMIC CHANGES	0	1	1
NOT OTHER SPECIF	1	0	1
ATR	0	1	1
ITCHY SKIN	0	1	1
IMPAIRED BLOOD F	0	1	1
TOTAL	2302	2149	4451

CONCURRENT DISEASES BY AGE

TABLE OF DISEASE BY AGEYEAR

DISEASE AGEYEAR

FREQUENCY	- 35	36 - 50	51 - 64	65 -	TOTAL
NONE	67	686	1627	689	3069
OBESITY	6	28	45	8	87
DIABETES MELLITU	0	7	26	10	43
ARTERIOSKLEROSE	0	0	0	1	1
ANAEMIE	1	0	0	1	2
HEMIPARESE	0	0	1	0	1
EMPHYSEM	0	0	0	1	1
RAYNAUD-SYNDROM	0	3	0	0	3
HYPERLIPIDAEMIE	0	0	0	1	1
MIGRAENE	0	1	1	0	2
DEPRESSION	0	1	3	4	8
BRONCHITIS	0	0	2	0	2
ULCUS DUODENI	0	1	5	1	7
MYOKARDINFARKT	1	13	74	29	117
ANGINA PECTORIS	2	25	153	102	282
GICHT	0	3	3	4	10
ASTHMA	0	2	4	3	9
DYSPEPSIE	0	1	0	0	1
RHINITIS ALLERGI	0	2	0	0	2
DIABETISCHE NEUR	0	0	0	1	1
CERVICAL SPONDYL	0	1	4	2	7
REAKTIVE DEPRESS	0	0	1	0	1
Z.N.CHOLECYSTEKT	0	0	1	0	1
TOTAL	85	901	2388	1077	4451

(CONTINUED)

CONCURRENT DISEASES BY AGE

TABLE OF DISEASE BY AGEYEAR

DISEASE / AGEYEAR	- 35	36 - 50	51 - 64	65 -	TOTAL
FREQUENCY					
UEBERGEWICHT	0	4	7	1	12
INSOMNIA - SCHLA	0	1	0	0	1
ISCHEMIC HEART D	0	0	1	0	1
BRONCHITIS,CHRON	0	0	1	3	4
THYREOTOXIKOSE	0	0	1	0	1
ANGSTZUSTAENDE	0	6	10	4	20
KOPFSCHMERZEN	0	1	1	1	3
DIZZINESS	0	0	3	3	6
TIREDNESS - MUED	0	0	0	1	1
ERKAELTUNG	0	0	1	0	1
TIA	0	0	1	0	1
HIATUSHERNIE	0	1	3	2	6
OSTEOARTROSIS	0	0	1	1	2
PSORIASIS	0	0	5	0	5
DIABETES,INSULIN	0	0	1	0	1
SINUSITIS	0	0	1	0	1
MENIERE	0	1	0	0	1
CLAUDICATIO INTE	0	0	0	2	2
DIABETES,NICHT I	0	2	5	1	8
PERIPHERAL VASCU	0	10	58	30	98
Z.N.MYOKARDINFAR	0	0	2	0	2
PERIPHERE DURCHB	0	1	0	0	1
VERTIGO	0	0	1	0	1
TOTAL	85	901	2388	1077	4451

(CONTINUED)

CONCURRENT DISEASES BY AGE

TABLE OF DISEASE BY AGEYEAR

DISEASE AGEYEAR

FREQUENCY	- 35	36 - 50	51 - 64	65 -	TOTAL
Z.N.CEREBRO-VASC	0	0	0	2	2
RHEUMATOIDE ARTH	0	1	3	1	5
TINNITUS	0	0	1	0	1
EKZEM	0	1	0	2	3
DIABETES	0	0	1	1	2
SCHLAFLOSIGKEIT	0	0	1	0	1
LOW BACK PAIN	0	0	2	0	2
ATEMWEGSINFEKTIO	0	1	0	0	1
INGUINALE HERNIE	0	1	2	0	3
ARTERIOSCLEROTIC	0	0	1	0	1
ARTHRITIS	0	1	8	0	9
ARTHRITIS KNEE A	0	0	1	0	1
ARTHRITIS OF NEC	0	0	2	0	2
ARTHRITIS KNEES	0	0	2	1	3
ARTHRITIS DUE TO	0	0	1	0	1
ARTHRITIS SHOULD	0	0	1	0	1
ARTHRITIS OF HIP	0	0	0	2	2
ARTHRITIS OF KNE	0	0	1	0	1
ARTHRITIS OF SPI	0	0	3	0	3
OSTEOARTHRITIS	0	2	18	8	28
EMERY	1	0	0	0	1
EPISTAXIS	0	0	2	0	2
GALL BLADDER DIS	0	0	0	1	1
TOTAL	85	901	2388	1077	4451

(CONTINUED)

CONCURRENT DISEASES BY AGE

TABLE OF DISEASE BY AGEYEAR

DISEASE AGEYEAR

FREQUENCY	- 35	36 - 50	51 - 64	65 -	TOTAL
NECK FIBROSIS	0	0	1	0	1
SILVER WIRING IN	0	0	1	0	1
ABDO/PERINEAL RE	0	0	0	1	1
ABSENT PULSES FR	0	0	1	0	1
RETINOPATHY GRAD	0	1	4	1	6
TRIPAL VESSEL IN	0	0	1	0	1
ACNE ROSACEA	0	0	0	1	1
ALLERGIC MINUITI	0	0	1	0	1
AMPUTATED LITTLE	0	1	0	0	1
ANKLE OEDEMA	0	1	2	2	5
SILENT MI (STILL	0	0	0	1	1
CHEST INFECTIONS	0	1	0	0	1
ANT.PROLAPSE,BIL	0	0	1	0	1
NEUROSIS	0	1	1	0	2
AORTIC BIFURCATI	0	0	0	1	1
ARCUR DENTIS	0	0	1	0	1
ARTH NECK	0	0	1	0	1
ATRIAL FIBRILLAT	0	0	0	1	1
AV NIPPING	0	0	1	0	1
B/K AMPUTATION O	0	1	0	2	3
BACK STIFFNESS	0	0	1	0	1
BACKACHE	0	0	1	0	1
BASAL CREPITATIO	0	0	1	0	1
TOTAL	85	901	2388	1077	4451

(CONTINUED)

CONCURRENT DISEASES BY AGE

TABLE OF DISEASE BY AGEYEAR

DISEASE AGEYEAR

FREQUENCY	- 35	36 - 50	51 - 64	65 -	TOTAL
BILATERAL CATARA	0	0	1	1	2
BILATERAL BLEPHE	0	0	0	1	1
BIRD FANCIERS LU	0	0	1	0	1
BRONCHOSPASM	0	1	0	0	1
CEREBRO-VASCULAR	0	0	2	2	4
CARDIOMEGALIE	0	0	1	0	1
CATARRH	0	0	1	0	1
CATARACT EXTRACT	0	0	0	1	1
CHEST SOMETIMES	0	0	0	1	1
CHEST-RHONCHI	0	0	1	0	1
CHILBLAINS	0	0	1	1	2
CHRONIC ACTIVE H	0	0	1	0	1
CHRONIC PROSTATI	0	0	1	0	1
CHRONIC PSORIASI	0	0	1	0	1
CHRONIC VENOUS I	0	0	1	0	1
COLD AND PULSELE	0	0	1	0	1
COLD FEET	0	0	0	1	1
COLD HANDS AND F	0	1	0	0	1
CONTROLLED ATRIA	0	0	0	1	1
DEAFNESS	0	0	1	2	3
DEGENERATIVE ART	0	1	0	0	1
DERMATITIS HANDS	0	0	0	1	1
DISCHARGE FROM E	0	0	1	0	1
TOTAL	85	901	2388	1077	4451

(CONTINUED)

CONCURRENT DISEASES BY AGE

TABLE OF DISEASE BY AGEYEAR

DISEASE AGEYEAR

FREQUENCY	- 35	36 - 50	51 - 64	65 -	TOTAL
DIVERTICULITIS	0	0	1	0	1
DUPYTRANS CONTRA	0	0	1	0	1
DVT LEG (DEEP VE	0	0	1	0	1
DYSPNOEA	0	1	0	0	1
DYSPNOEA ON EXER	0	0	1	0	1
LETHARGY	0	2	0	0	2
CLAUDICATION	0	0	1	0	1
UTI (E.COLI)	0	0	1	0	1
RETINAL CHANGES	0	0	1	1	2
RETINOPATHY	0	0	0	2	2
SPONDYLOSIS	0	0	1	0	1
LEFT VENTRICULAR	0	0	0	1	1
ENLARGED PROSTAT	0	0	1	0	1
ENLARGED FIBROID	0	1	0	0	1
EPILEPSY	1	1	0	1	3
EPISODES OF DOUB	0	0	0	1	1
EPITHELIOMA RIGH	0	0	0	1	1
ERYTHROEDEMA PSO	0	0	1	0	1
EV OF OLD CVA	0	0	0	1	1
MCV 102 MCH 33.6	0	0	0	1	1
FE DEV ANAEMA AS	0	1	0	0	1
FIT	0	1	1	0	2
FIT LOL	0	1	0	0	1
TOTAL	85	901	2388	1077	4451

(CONTINUED)

CONCURRENT DISEASES BY AGE

TABLE OF DISEASE BY AGEYEAR

DISEASE / AGEYEAR FREQUENCY	- 35	36 - 50	51 - 64	65 -	TOTAL
FLUSHED APPEARAN	0	1	0	0	1
FUNDI GRADE 1	0	0	1	0	1
GENERAL FATIGUE	0	0	1	0	1
GIDDYNESS	0	0	0	1	1
GOUT IN TOE	0	0	2	0	2
HYPERTENSIVE RET	1	1	4	0	6
RETINOPATHY GRA	1	0	1	1	3
COLD HANDS	0	0	1	0	1
HAYFEVER	0	0	1	0	1
RVF	0	0	0	1	1
HIGH COLOUR TENS	0	1	0	0	1
HYPERACIDITY	0	1	0	0	1
THYROID NODULE	0	0	1	0	1
HYSTERECTOMY	0	2	0	0	2
PROTEINURIA	0	1	0	0	1
IMPOTENCE	0	1	0	0	1
INDIGESTION	0	0	1	0	1
INDUSTRIALLY IND	0	0	1	0	1
INTENTIONAL TREM	0	0	1	0	1
INTERMITTENT BRO	0	1	0	0	1
IRON DEFICIENCY	0	1	0	0	1
IRRITABLE BOWEL	0	0	1	0	1
LABYRINTHITIS VI	0	0	0	1	1
TOTAL	85	901	2388	1077	4451

(CONTINUED)

CONCURRENT DISEASES BY AGE

TABLE OF DISEASE BY AGEYEAR

DISEASE AGEYEAR

FREQUENCY	- 35	36 - 50	51 - 64	65 -	TOTAL
CRAMPS IN LEGS	0	0	1	0	1
THYROID GOITRE	0	0	0	1	1
BELLS PALSY	0	0	1	0	1
LIGHT STRUCTURE	0	0	0	1	1
LIPODERMATOSCLER	0	0	1	0	1
VENOUS STASIS UL	0	0	1	0	1
LIPOMAS ON ABDO	0	0	1	0	1
LOST SENSE OF TA	0	0	1	0	1
LOWER RESPIRATOR	0	0	1	0	1
LUMBAR AND CERVI	0	0	1	0	1
LUMBAR ARTHRITIS	0	0	1	0	1
OSTEOARTHRITIS L	0	1	3	1	5
LUMBAR BACK PAIN	0	1	0	0	1
MARKED V.B.I.	0	0	0	1	1
MASTECTOMY	0	1	0	2	3
MASTECTOMY FOR C	0	0	1	0	1
OSTEOARTHRITIS H	0	0	7	2	9
MENIERES DISEASE	0	0	0	1	1
MENOPAUSAL FLUSH	0	1	0	0	1
PALPITATIONS	0	1	0	0	1
AIRWAYS OBSTRUCT	0	0	1	0	1
DERMATITIS	0	0	0	1	1
INNOCENT SYSTOLI	0	0	1	0	1
TOTAL	85	901	2388	1077	4451

(CONTINUED)

CONCURRENT DISEASES BY AGE

TABLE OF DISEASE BY AGEYEAR

DISEASE AGEYEAR

FREQUENCY	- 35	36 - 50	51 - 64	65 -	TOTAL
RESIDUAL WEAKNES	0	0	1	0	1
SOA	0	0	0	1	1
UPPER RESPIRATOR	0	1	0	1	2
WEAKNESS OF HAND	0	0	1	0	1
WEAKNESS RT SIDE	0	0	1	0	1
CHRONIC OBSTRUCT	0	0	1	0	1
BENIGN PROSTASTI	0	0	1	0	1
MINIMAL SIGNS OF	0	0	1	0	1
DRY SKIN CONDITI	0	0	1	0	1
MITRAL REGURGITA	0	0	1	0	1
MITRAL SYSTOLIC	0	0	1	0	1
RHEUMATOID OSTEO	0	0	0	1	1
MYXOEDEMA	0	0	0	2	2
NASAL POLYPS	0	1	0	0	1
NAUSEA	0	0	0	1	1
NERVOUS TENSION	0	0	1	0	1
OBSTRUCTIVE AIRW	2	37	112	62	213
NIGHT CRAMPS	0	0	1	0	1
HIP REPLACEMENT	0	0	0	1	1
OSTEOARTHRITIS K	0	1	4	5	10
Z.N.BASALZELL-CA	0	0	1	0	1
NOCTURIA	0	0	0	1	1
ENLARGED PROSTRA	0	0	1	1	2
TOTAL	85	901	2388	1077	4451

(CONTINUED)

CONCURRENT DISEASES BY AGE

TABLE OF DISEASE BY AGEYEAR

DISEASE AGEYEAR

FREQUENCY	- 35	36 - 50	51 - 64	65 -	TOTAL
ISCHAEMIC ECG	0	0	0	1	1
OSTEOARTHRITIS S	0	0	4	2	6
OSTEOARTHRITIS W	0	0	1	0	1
VAGINITIS, ATROP	0	0	1	0	1
CONJUNCTIVITIS	0	1	0	0	1
LEG INJURIES	0	0	1	0	1
EXERTIONAL S/O/B	1	0	0	0	1
VARICOSE VEINS	0	1	5	1	7
ACNE	0	0	1	0	1
ECTOPIC BEATS, O	0	0	0	1	1
ACCOUSTIC NEUROM	0	0	1	0	1
DEFICIENT CIRCUL	0	0	0	1	1
OSTEOARTHROSIS S	0	0	1	0	1
OVARIAN CYST.	0	0	0	1	1
EYES A.V NIPPING	0	0	1	0	1
PACEMAKER	0	0	0	1	1
PAIN IN BACK	0	0	1	0	1
PAIN UNDER RIBS	0	0	1	0	1
PAIN IN KNEE	0	1	0	0	1
PALE LEFT DISC	0	1	0	0	1
URINE TRACE PROT	0	1	0	0	1
PANSYSTOLIC MURM	0	0	1	0	1
A/V NIPPING	0	0	1	0	1
TOTAL	85	901	2388	1077	4451

(CONTINUED)

CONCURRENT DISEASES BY AGE

TABLE OF DISEASE BY AGEYEAR

DISEASE AGEYEAR

FREQUENCY	- 35	36 - 50	51 - 64	65 -	TOTAL
TRANSIENT VISUAL	0	0	1	0	1
Z.N.PNEUMONECTOM	0	0	0	1	1
SEHSTOERUNG (EIN	0	0	1	0	1
PARTIAL THICKNES	0	0	0	1	1
Z.N.DIABETES	0	1	0	0	1
Z.N.DUCTUS ARTER	0	1	0	0	1
ARTHRITIS FINGER	0	0	0	1	1
PEAK FLOW 220 LI	0	0	1	0	1
PEFR=170	0	0	1	0	1
PEPTIC ULCER	0	0	2	0	2
PERNICIOUS ANAEM	0	0	0	1	1
PERSISTANT COUGH	0	0	1	0	1
PLETHORIC	0	0	1	0	1
POLIO LEG	0	0	0	1	1
POOR PULSES POPL	0	0	1	0	1
ALCOHOL ABUSE	0	0	1	0	1
PROCIDENTIA	0	0	1	0	1
PROSTATIC SYMPTO	0	0	0	1	1
PROSTATISM	0	0	0	1	1
DUPUYTRENS CONTR	0	0	0	1	1
PROSTETIC AORTIC	1	0	0	0	1
PRURITIS ANI	0	0	1	0	1
Z.N.R I H REPAIR	0	0	1	0	1
TOTAL	85	901	2388	1077	4451

(CONTINUED)

CONCURRENT DISEASES BY AGE

TABLE OF DISEASE BY AGEYEAR

DISEASE / AGEYEAR	- 35	36 - 50	51 - 64	65 -	TOTAL
FREQUENCY					
UNDERWEIGHT	0	0	0	1	1
RAISED FASTING L	0	0	1	0	1
CHOLESTEROL 8.0	0	1	0	0	1
RAISED URIC ACID	0	0	1	0	1
CHEST INFECTION	0	0	1	1	2
REFLUX OESOPHAGI	0	0	0	2	2
PARAPLEGIA	0	1	0	0	1
SLURRING SPEECH	0	0	1	0	1
RETINAL VEIN OCC	0	0	1	0	1
RETINITIS PIGMEN	0	0	1	0	1
CATARACTS	0	0	1	0	1
RHONCHI	0	0	1	0	1
CAROTID BRUIT	0	0	1	0	1
HEMIPLEGIA	0	0	1	0	1
ROTATOR CUFF SYN	0	1	0	0	1
CARPAL TUNNEL	0	0	1	0	1
MONOPERISIS	0	0	1	0	1
S O B EXERTION	0	0	1	0	1
SCATTERED RHONCH	0	0	1	0	1
SCATTERED CREPS	0	0	1	0	1
SCIATICA	0	1	0	1	2
HEARTBURN,WATERB	0	1	0	0	1
SHINGLES	0	0	0	1	1
TOTAL	85	901	2388	1077	4451

(CONTINUED)

CONCURRENT DISEASES BY AGE

TABLE OF DISEASE BY AGEYEAR

DISEASE AGEYEAR

FREQUENCY	- 35	36 - 50	51 - 64	65 -	TOTAL
SHORT TERM MEMOR	0	0	1	0	1
HYSTERECTOMY SCA	0	1	0	0	1
SIGNS OF CVA	0	0	1	0	1
SIGNS OF CHRON.O	0	0	0	1	1
SILVER WIRING	0	0	1	0	1
SKIN KERATOSIS	0	0	1	0	1
VALSALVA NEGATIV	0	1	0	0	1
TACHYCARDIA	0	0	1	0	1
WHEEZE	0	1	4	0	5
SMOKERS COUGH	0	1	0	0	1
SPASTIC QUADRAPA	0	0	1	0	1
SPRAINED BACK MU	0	0	1	0	1
SPRAINED WRIST	0	0	1	0	1
STIFF NECK	0	0	1	0	1
SWOLLEN KNEE	0	0	1	0	1
SYSTOLIC MURMUR	0	0	3	0	3
TENDERNESS IN LO	0	0	0	1	1
TENNIS ELBOW	0	1	0	0	1
THYROIDIC	0	0	1	0	1
THYROTOXIC	0	0	1	0	1
TRANSIENT CEREBR	0	0	0	1	1
TREMOR,UPPER LIM	0	0	1	0	1
COLITIS, ULCERAT	0	0	0	1	1
TOTAL	85	901	2388	1077	4451

(CONTINUED)

CONCURRENT DISEASES BY AGE

TABLE OF DISEASE BY AGEYEAR

DISEASE AGEYEAR

FREQUENCY	- 35	36 - 50	51 - 64	65 -	TOTAL
UMBILICAL HERNIA	0	0	1	0	1
URINE, BLOOD ONE	0	0	0	1	1
VARICOSE ECZEMA	0	0	1	1	2
VARICOSE ULCER L	0	0	0	1	1
VARICOSE VEINS E	0	0	0	1	1
POOR VISION	0	0	1	0	1
SPLIT NAILS	0	1	0	0	1
WEAK DIAST.PRESS	0	1	0	0	1
WEAK GRIP HAND	0	0	0	1	1
ISCHEMIC CHANGES	0	0	1	0	1
NOT OTHER SPECIF	0	0	1	0	1
ATR	0	0	0	1	1
ITCHY SKIN	0	1	0	0	1
IMPAIRED BLOOD F	0	1	0	0	1
TOTAL	85	901	2388	1077	4451

APPENDIX 4

Free text adverse events

FREE TEXT
SIGNIFICANT ADVERSE EVENTS

Tiredness on activity.

Burning in chest and feeling awful.

Dizziness therefore drugs stopped.

Tinnitus.

Dry itchy rash on calves.

Red faeces.

Feeling of unreality related to 5 day Adalat.

Marked oedema to knees.

Too bad TP to drive.

Slightly confused.

A skin rash.

Blood shot eyes.

Extreme pain 3 hours after taking each tablet, lasting 4-5 hours.

Sweating.

A rash and being shaky.

Dyspepsia.

Rash in skin flexures.

Heartburn and irritability.

Tachycardia paraesthesia.

A rash on the legs.

Epigastric pain.

Fainting.

Trembling hands.

Finding it difficult to come down steps.

Blood pressure being too low.

Constipation.

Severe headache and patient refused to continue medication.

Generally unwell.

Itching.

Shaking.

Epigastric pain after tablets and nocturnal frequency.

Painful legs.

Jaw pain, paraeshesia in arms and face.

Intolerable dyspepsia.

Severe nocturnal enuresis.

Excessive shaking after 4 days.

Very severe pitting leg oedema.

Being unduly calm and remained so 3 weeks later off drugs.

Acute allergic reaction and oedema.

Irritability.

Pain in muscles, numb, burning in arms, frightening chest pain.

Persistant sore throat, no evidence of infection.

Pain in wrists, hands swelling and then the ache going to back of neck.

Increase in ischaemic chest pain despite slow Beta Blocker being withdrawn.

A skin rash.

Tremour and dullness in ears.

Feeling shaky for about 99 minutes after taking the tablet.

Feeling un-well after taking first dose.

Severe abdominal pain since 14 October, 1985.

Being off balance.

Posturaldrop.

Fainting.

Severe headaches.

Forgetfulness.

Feeling faint and chest pains.

Constipation, hot flushes, bad temper and anxiety.

Reflux dyspepsia.

Cramps in the legs.

Severe right subcostal pain, and right leg went numb.

Postural hypotension.

Insomnia.

Vomiting.

Vomiting and chest pains.

Burning scalp, shoulders and arms and sleeplessness.

Generally achy and unwell.

BP too low.

Insomnia.

Indigestion worse than nausea.

Cramps and parasthesia.

Indigestion.

Generalised oedema.

Light headedness and a floating feeling.

Claustrophobia and agrophobia.

Sweating profusely and depression due to the study.

Feeling as though her body was not her own.

Lightheadedness.

Spots before the eyes.

Facial swelling.

Very red, swollen blistered and weeping skin on the legs.

Insomnia and vomiting.

vomiting.

Irritability.

Slurring of speech.

Aching limbs and being generally tired.

Aches.

Tremours.

Disturbed sleep and muscle cramps.

Depression.

Trembling.

Constipation , dyspepsia and flatulance.

Frequency of micturition and nocturnal.

Tremours.

Postural hypotension.

Tranquilising effect and water retention.

Depression.

Flushing and balance upset.

Arms and legs burning for 3 hours after taking tablets.

Persistent nocturia 5 times a night.

Depression.

Erythemtous eruptions on hands.

Market muzziness.

Burning sensations over legs.

Bilateral whole leg burning feeling.

A feeling of tension after taking the medication.

Eczema of abdomen.

A rash.

Churning sensations in legs.

Swollen hands.

Burning feet.

Sweating.

Burning feet.

Ataxia shivering.

A rash and depression.

Sweating and headedness.

Constipation.

Trembling, very fast pulse, peripheral cyanosis and aching arms.

Sweating and tachycardia.

Shaking and sweating.

Finger swelling.

Leg oedema and erythema.

Pruritis and erythema.

Dizziness and shaking, withdrawal L B Blocker.

Shaking of the limbs.

Reflux and heartburn.

Indigestion.

Feeling generally unwell.

Mild flickering of vision on two occasions.

Cramp and abdominal pains.

Initial insomnia and depression.

Paraesthesia in hands and very trembly.

Nightmares.

Heartburn and rapid weight gain.

Severe indigestion.

Constipation.

Heartburn and vomiting.

Feeling awful and eyes felt dry.

Burning sensations in legs.

Tingling in arms.

Feeling generally unwell.

Feeling generally ill.

Aches and pains and a stomach upset.

Tingling in hands.

Feeling ill therefore tablets stopped.

APPENDIX 5

Comparison of two dosage regimens of nitrendipine in the treatment of mild to moderate hypertension

15.11.88

COMPARISON OF TWO DOSAGE REGIMENS OF NITRENDIPINE IN THE TREATMENT OF MILD TO MODERATE HYPERTENSION

Dr John Marley MBChB FRACGP
Medical Director

John Snaith B Sc
Clinical Research Associate

John Curram PhD
Statistician

Medical Department
Newbury
England

1. Study Summary

1.1 Title of Study

Comparison of two dosage regimens of nitrendipine in the treatment of hypertension.

1.2 Principal Investigators

MULTICENTRE

1.3 Study Number: Bay e 5009/0426

1.4 Study Dates: February 1987 - September 1988

1.5 Study Design

A randomised, double-blind, parallel-group design was employed. Patients underwent an initial 4 week period of placebo therapy before randomisation to nitrendipine given either once daily (10mg mane + placebo nocte) or twice daily (5mg bd). Patients were reviewed after 4 weeks. Responders (seated diastolic blood pressure < 95 mm Hg) were maintained on initial dosage for a further 8 weeks. Non-responders had their dose of nitrendipine doubled and were reviewed after a further 4 weeks. Responders to the increased dose were maintained on this regimen for a further 4 weeks. Patients still failing to achieve target blood pressure received nitrendipine 20mg bd for the final 4 weeks of the study. Seated and standing blood pressures and heart rates were recorded at each visit. Blood pressure was recorded using a bias free sphygmomanometer in the morning prior to tablet administration to ensure trough measurements, i.e. 24 hours post active dose in the once daily group, 12 hours later in the twice daily group. Blood pressure was recorded in the morning prior to tablet administration to ensure trough measurements.

1.6 Patients

From 12 participating centres (6 hospital, 6 general practice) a total of 215 patients entered the study. One hundred and ninety patients were randomised (93 nitrendipine od, 97 nitrendipine bd). One hundred and sixty two valid patients were evaluated for efficacy at Week 8 (82 nitrendipine od, 80 nitrendipine bd).

1.7 Test Drugs

i) Nitrendipine 5mg, 10mg and 20mg look-alike tablets
ii) Matching placebo to nitrendipine 5mg, 10mg and 20mg tablets

All trial medication was administered orally. Total daily dose of nitrendipine varied from 10mg - 40mg daily. Duration of treatment with active medication was 12 weeks.

1.8 Results

1.8.1 Efficacy

After eight weeks treatment, there was no statistically significant difference (P = 0.33) between nitrendipine bd and od for mean response in

seated diastolic BP. There were no statistically significant differences ($P > 0.05$) between treatment groups for mean responses in other blood pressures, seated heart rate and weight. Reductions of BP on monotherapy ($n = 131$) or combined with a beta-blocker ($n = 31$) were of similar magnitude.

In the nitrendipine bd group, mean seated BP fell from 167.3/103.9 mm Hg at Week 0 to 154.4/93.6 mm Hg at Week 8 (mean response 12.9/10.3 mm Hg, $P < 0.001$). In the nitrendipine od group mean seated BP fell from 170.6/103.0 mm Hg at Week 0 to 156.3/93.9 mm Hg at Week 8 (mean response 14.4/9.0 mm Hg, $P < 0.001$). There were no statistically significant differences for responses in mean heart rate or weight within each treatment group ($P > 0.05$).

There were statistically significant differences ($P \leq 0.05$) between Week 12 pre- and post-dose measurements for all mean blood pressures and heart rates.

1.8.2 Tolerability

Fifty two patients in the nitrendipine bd group and 47 in the nitrendipine od group reported adverse events. Most commonly reported events were flushing/vasodilation (28 patients), headache (27 patients), peripheral oedema (15 patients), asthenia (11 patients) and dizziness (8 patients). There appears to be little difference in the overall incidence of adverse events in the two treatment groups.

There was a small but statistically significant ($P \leq 0.05$) increase in mean serum alkaline phosphatase during the study.

1.9 Conclusions

Nitrendipine od was not significantly different from nitrendipine bd in lowering BP. Nitrendipine od was as well tolerated as nitrendipine bd.

2. Introduction

Nitrendipine is a dihydropyridine calcium antagonist with a similar structure and mechanism of action to nifedipine. Various pharmacological and clinical studies (1-6)* suggest that it has a longer duration of action and a greater peripheral activity than nifedipine. Nitrendipine has the potential for controlling blood pressure following once daily dosing.

3. Aim of the Study

To compare the relative efficacy and tolerability of two dosage regimens of nitrendipine given as monotherapy or as an adjunct to beta-blockade in patients with mild to moderate hypertension.

4. Investigators and Study Dates

The study was conducted between February 1987 and September 1988 by the following investigators in 12 centres.

Centre 1	Dr R Petty	Senior Registrar
	Department of Vascular Studies	
	Clinical Research Centre	
	Northwick Park Hospital	
	Harrow. London	
Centre 2	Dr M Dawes	General Practitioner
	58 Hollow Way	
	Oxford	
Centre 3	Dr A B Davies	Consultant Physician
	Neath General Hospital	
	North Glamorgan	
Centre 4	Dr G Porter	General Practitioner
	Shepherds Spring Medical Centre	
	Andover	
Centre 5	Dr B Glekin	General Practitioner
	Dr N Gaw	" "
	Woodside Health Centre	
	Glasgow	
Centre 6	Dr J Langan	General Practitioner
	Baillieston Health Centre	
	Glasgow	
	Dr F Sullivan	" "
	Blantyre Health Centre	
	Blantyre. Glasgow	

(Centres 5 & 6 were co-ordinated by Dr T S Murray Department of General Practice, University of Glasgow)

Centre 7	Dr D E H Llewelyn Department of Medicine Kings College Hospital London	Consultant Physician
Centre 8	Dr C A Seymour Department of Medicine Addenbrookes Hospital Cambridge	Consultant Physician
Centre 9	Dr A Jacob Wallacetown Health Centre Dundee	General Practitioner
Centre 10	Dr C Bowman Weston General Hospital Weston-Super-Mare	Consultant Physician
Centre 11	Dr L D Ritchie Health Centre Peterhead	General Practitioner
Centre 12	Dr D B Owens Diabetes Research Unit University of Wales College of Medicine Cardiff	Director & Hon. Consultant

The study was approved by the local ethical committees between November 1986 and October 1987. DHSS approval under the CTX scheme (ref 0010/0086A) was obtained on 28 November 1986.

5. Materials and Methods

5.1 Study Design (see Fig. 1, Appendix)

A randomised, parallel-group design was employed. Patients selected for entry underwent an initial 4 week period of placebo therapy before randomisation to nitrendipine given either once daily (10mg mane + placebo nocte) or twice daily (5mg bd). Patients were reviewed after 4 weeks. Responders (seated diastolic blood pressure < 95 mm Hg) were maintained on initial dosage for a further 8 weeks. Non responders had their dose of nitrendipine doubled and were reviewed after a further 4 weeks. Responders to the increased dose were maintained on this regimen for a further 4 weeks. Patients still failing to achieve target blood pressure received nitrendipine 20mg bd for the final 4 weeks of the study. Seated and standing blood pressures and heart rates were recorded at each visit. Blood pressure was recorded using a bias free sphygmomanometer in the morning prior to tablet administration to ensure trough measurements, i.e. 24 hours post-active dose in the once daily group, 12 hours later in the twice daily group.

5.2 Test Drug and Control Agents

To maintain blindness a double dummy technique was used. Patients in the once daily arm of the study received one tablet of active medication in the morning. In the evening they received a further tablet of matching placebo. Patients in the bd arm of the study received one tablet of active medication each morning and evening.

Details of the test substances used were as follows:-

Active	Batch No.(s)	Expiry date(s)
Nitrendipine 5mg	520158	9.9.89
Nitrendipine 10mg	929655	30.3.88
	974509	31.3.89
	315367	31.1.89

Active (Continued)

Nitrendipine 20mg	974380	28.11.88
	315257	31.12.89
	315224	30.06.90

Placebo

Nitrendipine 5mg	520159	16.09.89
Nitrendipine 10mg	974557	31.03.90
	315326	30.06.90
Nitrendipine 20mg	929615	25.02.88
	974510	30.06.90
	315328	30.06.89

5.3 Selection of Patients

5.3.1 Primary diagnosis: - Mild to Moderate Essential Hypertension

5.3.2 Inclusion Criteria

Eligible patients were aged over 18 years with seated blood pressure (mean of at least four measurements taken on two separate occasions) in the following ranges depending upon age:

under 65 years	145/95 - 200/120 mm Hg *
over 65 years	160/100 - 210/120 mm Hg *

* The mean of at least 4 measurements taken on 2 separate occasions

Those eligible were either (a) newly diagnosed, (b) hypertensives uncontrolled on beta-blocker monotherapy, or (c) patients on existing medication and electively prescribed nitrendipine as replacement therapy.

5.3.3 Exclusion Criteria

(a) patients under 65 years with seated BP > 200/120 mm Hg or < 145/95 mm Hg and patients over 65 years with a seated BP > 210/120 mm Hg or < 160/100 mm Hg.

(b) accelerated hypertension (grade III or IV fundal changes).

(c) recent (within three months) target organ damage, myocardial infarction or cerebrovascular accident.

(d) clinically significant hepatic, renal or gastrointestinal disease.

(e) heart block, valvular dysfunction or cardiac failure.

(f) insulin-dependent diabetes.

(g) women capable of child bearing.

(h) history of poor attendance or non-compliance.

(i) patients receiving antihypertensive medication other than beta-blockers.

5.4 Procedures and Methods

At the start of the study, the nature of the trial was explained to each patient and their written informed consent was obtained. Suitable patients attended a pre-entry visit to confirm the diagnosis. At the pre-entry visit a full clinical examination was performed including patient history, measurement of height, weight, seated and erect blood pressure and heart rate, laboratory investigations, ECG and x-ray.

All patients received placebo during the pre-entry phase (Weeks -4 to 0). Patients were reviewed at Week 0 and those still satisfying the BP and other entry criteria were randomised to receive either nitrendipine 5mg bd or nitrendipine 10mg od. Patients were reviewed after 4 weeks and based upon their blood pressure response were defined as responders or non-responders. Responders were defined as patients with seated diastolic BP < 95 mm Hg (aged < 65 years) or < 100mm Hg (aged > 65 years). Patients entering the study with a seated diastolic BP in the range 96 - 104 mm Hg were defined as responders if their seated diastolic BP decreased by 10 mm Hg or more.

Responders at Week 4 remained on their existing treatment regimen of nitrendipine for the remainder of the study. Non-responders at Week 4 had their doses doubled for the next four weeks. All patients who were still non-responders at Week 8 received nitrendipine 20mg bd until completion of the study at the end of Week 12.

Blood pressures were recorded at morning clinics using a Hawksley Random Zero Sphygmomanometer or a Copal Electronic Sphygmomanometer (Centres 7 and 9). Patients were instructed not to take their morning dose of nitrendipine on the day of their clinic visit. Blood pressures were therefore measured at "trough" treatment effect, approximately 12 or 24 hours after taking the last active tablet for bd and od groups respectively. At Week 12 patients also took their medication after the "trough" assessment and returned 1 to 2 hours afterwards for reassessment of BP at "peak" treatment effect.

5.5 Assessment Criteria

Assessments performed during the study were as follows:

	Week					
	-4	0	4	8	12(pre-dose)	12(post-dose)
Patient history, ECG, chest X-ray, consent	x					
Blood pressure, heart rates	x	x	x	x	x	x
Weight, other medications & illnesses	x	x	x	x	x	
Adverse events		x	x	x	x	
Biochemistry & haematology		x			x	
Plasma nitrendipine samples					x	x

"Responders" to treatment were defined as the patients demonstrating a fall in seated diastolic BP < 95 mm Hg. Those patients with a baseline DBP in the range 96 - 104 mm Hg had to demonstrate at least a 10 mm Hg reduction.

5.6 Compliance with the Protocol

5.6.1. Inclusion Criteria

Twelve patients with a seated diastolic BP below the defined lower entry limit (95 mm Hg under 65 years, 100 mm Hg over 65 years) were randomised to active treatment. Ten of these patients were aged over 65 years and had a seated diastolic BP > 95 mm Hg. These 12 patients have been included in the analysis of efficacy (2 bd group, 10 od group).

Patients 102 and 153 aged < 65 years had a seated diastolic BP below 95 mm Hg and were excluded from the efficacy analysis.

There were no other patients who clearly violated protocol entry criteria.

5.6.2. Secondary Exclusions

Five patients were secondarily excluded from the efficacy analysis.

Patient 615 was excluded because of non compliance with the protocol. Patients 1107 and 1117 have been excluded from the analysis of efficacy at Week 8 because blood pressures were recorded 1 hour and 2 hours post-dose respectively at this visit.

Patients 202 and 414 withdrew from the study temporarily and recommenced therapy after 4 weeks to eventually complete the study. Data from these patients are excluded from the efficacy analysis at Week 8 and Weeks 8/12 respectively because of the break in treatment.

All patients who entered the study are included in the demography and safety listings.

5.7 Biostatistical Methods

5.7.1 Variables analysed and tests used

Demography: all randomised patients

Age	years	) Descriptive
Sex		) Statistics:
Height	cm	) frequency counts
Weight	kg	) or mean / SD.
Smoking habits		) Sequence groups
Alcohol consumption		) compared using
Race		) 2-sample t-test
Hypertension newly diagnosed		) or X^2 test where
Years since hypertension diagnosed		) applicable.
Antihypertensive therapy		)
Fundal changes (left, right)		)
Chest X-ray		)
ECG result		)
General status of health		)
Sitting diastolic BP	mm Hg	)
Standing diastolic BP	mm Hg	)
Sitting systolic BP	mm Hg	)
Standing systolic BP	mm Hg	)
Sitting heart rate	bpm	)
Standing heart rate	bpm	)

Efficacy data: valid patients

Sitting diastolic BP	mm Hg	) Primary analysis:
Standing diastolic BP	mm Hg	) 2-sample t-test
Sitting systolic BP	mm Hg	) comparing response
Standing systolic BP	mm Hg	) entry - Week 8
Sitting heart rate	bpm	) between groups.
Standing heart rate	bpm	) Secondary analyses
Weight	kg	) see over page

Safety data: all randomised patients

Adverse events	) Tabulation by type) and treatment
Biochemistry Haematology	) Patients outside) normal range) indicated. Paired) t-test on change) pre-entry - Wk 12.

Sitting diastolic BP at Week 8 was identified pre-study as the main efficacy parameter. The analysis of response in sitting diastolic BP from entry to Week 8, comparing between treatment groups, was considered the primary analysis. Any further analyses were considered exploratory, ie to support conclusions from the primary analysis and to help identify hypotheses to be tested in future studies.

The demographic and efficacy variables were tested for normality using the Shapiro-Wilk test. Where data appeared normally distributed, the Student's t-test was used in the statistical analyses. Where the data were categorical, the chi-squared test was used.

Demography was summarised for the following groups of patients: all patients at pre-entry, all patients randomised and all valid patients assessed at Week 8. To avoid the overuse of significance tests, demographic factors were compared between groups for all patients randomised only. In addition to the list of demographic parameters above, replacement antihypertensive therapy, beta-blockade continuing through the study, disease groups and additional therapy were summarised for all patients randomised.

Efficacy parameters were blood pressures, heart rates and weight. Although patients received 12 weeks active therapy, those in the od group may have received nitrendipine bd for the last 4 weeks. The main endpoint was therefore at

Week 8. Responses from entry (Week 0) to Week 8 were compared between treatment groups using Student's 2-sample t-tests for the following groups of patients: all valid patients, monotherapy patients, adjunct patients, patients aged < 65 years, patients aged 65 years and over and all patients on an intention-to-treat basis. Mean efficacy parameters at Weeks 0 and 8 (no statistical tests performed) for each centre are also given.

The following within group comparisons have been performed on efficacy parameters using Student's paired t-tests:

Pre-entry to Week 0, all patients randomised
Week 0 to Week 8, separate treatment groups and subgroups as listed above
Week 0 to Week 12 pre-dose, all valid patients at Week 12
Week 12 pre- to post-dose, all valid patients at Week 12.

The numbers of valid patients who were responders and non-responders at each week were also presented, where responder is defined as sitting diastolic BP < 95 mm Hg.

Statistical analyses were performed using SAS/PC version 6.03.

5.7.2 Significance levels

Statistical significance for the primary comparison (response in sitting diastolic BP Week 0 to Week 8) has been taken as the probability of 0.05 or less ($P \leq 0.05$) of a difference occurring by chance alone. The same statistical significance level has been used for the exploratory analyses. No adjustment for repeated testing has been made for these further analyses, but a large number of statistical tests have been performed.

6. Results and Statistical Analysis

6.1. Demographic and Anamnestic Data

Patient demography split by treatment group is summarised in Table 1 for the 190 patients randomised to active treatment. Demographic data are summarised as mean ± SD. The mean age was 57.2 ± 10.3 years (range 31 - 81 years). Mean weight and height was 78.8 ± 14.4 kg and 166.0 ± 9.7 cm respectively. One hundred patients (53%) were male, 106 patients (56%) had a previous history of smoking of whom 42 (22%) were still smokers at randomisation.

Seventy eight patients (41%) were newly diagnosed and 111 (59%) had previously diagnosed hypertension. The mean duration of hypertension since diagnosis in the latter group was 5.8 years (range 0.12 - 30 years). One hundred and fifty three patients (81%) received nitrendipine as monotherapy and 37 patients (19%) received nitrendipine as an adjunct to beta-blockade. Fifty one patients (27%) were aged > 65 years.

The mean seated blood pressures for all patients randomised were 169.5/103.3 mm Hg ± 18.5/6.3 mm Hg. Mean standing blood pressures were 167.1/105.2 mm Hg ± 18.2/8.6 mm Hg. Seated and standing heart rates were 75.7 ± 10.4 bpm and 78.9 ± 11.4 bpm respectively. There was no statistically significant differences ($P > 0.05$) between the treatment groups for any of the demographic parameters. Patient demography for the 162 valid patients assessed in the efficacy analysis was similar to the above.

6.2. Dosage and Duration of Treatment

The number of patients evaluated at each stage of the study is summarised in Table 2. A total of 215 patients entered the study. Twenty five patients were withdrawn during the placebo run-in phase (12 placebo responders, 3 adverse reactions, 10 for other reasons).

One hundred and ninety patients were randomised to active treatment with nitrendipine (97 bd group, 93 od group). Of these, 23 patients prematurely discontinued study participation and were not assessed at the main end-point assessment at the Week 8 visit. The reasons for withdrawal during the period Weeks 0-8 are as follows:

	Number of patients		
Reason	Nitrendipine BD	Nitrendipine MANE	Total
Adverse reaction*	9	7	16
Non-attendance	1	1	2
Non-compliance*	0	1	1
Other*	4	2	6
Total	13	10	23

* One patient had an adverse reaction and non-compliance as reason for withdrawal. One patient had an adverse reaction and "other" as reason for withdrawal. Hence totals are less than the sum of the individual reasons. One hundred and sixty seven patients received nitrendipine up to Week 8. Five patients were ineligible for efficacy analysis (see Section 5.6.2 for details) leaving a total of 162 valid cases for the main analysis of efficacy.

A further 11 patients discontinued treatment during the final four weeks of the study (Weeks 9-12). A total of 153 and 150 patients respectively were evaluated at the end of the study (Week 12) for pre- and post-dose BP measurements. A summary of reasons for withdrawal during Weeks 9-12 is given below.

Reason	Number of patients in treatment group		
	Nitrendipine BD	Nitrendipine MANE#	Total
Adverse reaction	1	2	3
Non-attendance*	0	3	3
Non-compliance*	0	1	1
Other*	3	4	7
Total	4	8	12

* One patient had non-attendance and "other" as reason for withdrawal. One patient had non-attendance and non-compliance as reason for withdrawal. Hence totals are less than the sum of the individual reasons.

\# Includes one patient who was a non-responder to nitrendipine mane who was receiving nitrendipine 20mg bd during Weeks 9-12.

Full details of individual patients withdrawing from the study can be found in Tables 5-7

Returned tablet counts were undertaken at the end of each assessment period to check for compliance. No patient has been excluded from the analysis of efficacy on the grounds of poor compliance alone. Patients (with equal frequency in both groups), on occasions had compliance less than 80% for a given visit. No patient had consistently poor compliance over the entire treatment period. Compliance is summarised for all valid patients below:-

		Compliance (%) Week		
		0 - 4	5 - 8	9 - 12
Nitrendipine BD	N	88	76	
	Mean	92.8	97.2	N/A
	SD	16.0	20.3	
Nitrendipine OD	N	82	77	
	Mean	91.5	93.0	N/A
	SD	12.0	11.3	
Combined groups	N	170	153	143
	Mean	92.1	95.1	96.1
	SD	14.2	16.4	13.7

There are no statistically significant ($P > 0.05$) differences between treatment groups in compliance, for weeks 0 - 4 and weeks 5 - 8.

Days between visits are summarised for all valid patients in the Table below:

		Number of days between visits Week		
		0 - 4	5 - 8	9 - 12
Nitrendipine BD	N	90	80	
	Mean	27.7	29.6	N/A
	SD	4.3	6.2	
Nitrendipine OD	N	89	82	
	Mean	28.1	27.9	N/A
	SD	6.3	5.0	
Combined groups	N	179	162	153
	Mean	27.9	28.7	29.4
	SD	5.4	5.7	5.2

There were no statistically significant differences between treatment groups ($P > 0.05$) in the number of days between visits, Weeks 0-4, 5-8.

6.3 Efficacy

6.3.1 Number of Patients Evaluable

One hundred and sixty two patients were evaluable for analysis of efficacy at Week 8 (the main end point for efficacy). One hundred and fifty three patients (pre-dose) and 150 patients (post-dose), were evaluable for analysis of efficacy at Week 12 (secondary analysis).

6.3.2 Time since Last Dose Except at Week 0, when all patients were receiving placebo, only patients with trough blood pressure measurements have been included. Patients randomised to nitrendipine od received placebo as the evening dose.

The median time of blood pressure measurement at Week 8 was 13 hours post dose (range 7 - 24 hours). 90% of patients had their blood pressure measured between 11.6 and 21 hours of receiving their previous dose.

Week 12 post-dose blood pressure measurement times are also summarised in the same table. The median time from last dose to post-dose assessment was 1.3 hours (range 1 - 7 hours). 90% of patients were assessed post-dose between 1 and 2.7 hours of taking their last dose.

6.3.3 Blood Pressure Changes between Entry and Week 0 (baseline)

There are statistically significant differences ($P < 0.05$) between pre-entry and Week 0 for sitting diastolic and systolic blood pressure and standing systolic blood pressure. Mean sitting blood pressures were 173.5/105.1 mm Hg at pre-entry and 169.3/103.5 mm Hg at Week 0; mean standing systolic blood pressure was 172.3 mm Hg at pre-entry and 167.0 at Week 0. Despite the removal of placebo responders at Week 0 there was a small but clinically insignificant placebo response in patients still eligible for randomisation.

6.3.4 Primary Efficacy Analysis (Blood Pressure changes Weeks 0 8)

Seated blood pressure and heart rate for valid patients in the study at Week 0 and 8 is displayed in Table 3.

For the primary efficacy analysis, there was no statistically significant difference (P = 0.33) between nitrendipine bd and nitrendipine od for mean response in seated diastolic blood pressure Week 0 - Week 8.

In the nitrendipine bd group, mean seated blood pressure fell from 167.3/103.9 mm Hg at Week 0 to 154.4/93.6 mm Hg at Week 8 (mean response 12.9/10.3 mm Hg, P < 0.001).

In the nitrendipine od group, mean seated blood pressure fell from 170.6/103.0 mm Hg at Week 0 to 156.3/93.9 mm Hg at Week 8 (mean response 14.4/9.0 mm Hg, P < 0.001). Blood pressure changes within each group over Weeks 0, 4 and 8 are displayed in Fig. 2.

The reductions of BP on monotherapy (n = 131) or in combination with a beta-blocker (n = 31) were of similar magnitude. (See Tables 3.2 and 3.3).

		Monotherapy n = 131		Second-line n = 31	
		b.d.	o.d.	b.d.	o.d.
Sitting					
Δ SBP mmHg	Active : Placebo	-15.0	-14.2	-5.3	-15.3
Δ DBP mmHg	Active : Placebo	-10.7	-9.0	-8.9	-9.0
Standing					
Δ SBP mmHg	Active : Placebo	-12.8	-10.3	-8.7	-13.9
Δ DBP mmHg	Active : Placebo	-9.7	-7.2	-7.6	-13.8

There are no statistically significant differences ($P > 0.05$) for responses in heart rates or body weights in each treatment group.

6.3.5 Secondary Analysis

a) All Valid Patients

There were no statistically significant differences ($P > 0.05$) between treatment groups for mean responses in other blood pressures (standing diastolic blood pressure and standing systolic blood pressure), seated heart rate or weight Week 0 to Week 8.

There was a statistically significant difference ($P = 0.036$) for mean response in standing heart rate. In the bd group, the mean change Week 0-8 was 1.9 bpm compared with a mean change of -1.3 bpm in the od group.

b) Subgroup Analysis

Analyses of the mean responses between treatment groups were repeated for patients in the following subgroups:-

i patients receiving monotherapy
ii patients receiving nitrendipine as an adjunct to beta blockade
iii patients over 65 years
iv patients under 65 years

There were statistically significant differences ($P \leq 0.05$) between treatment groups for mean responses in standing diastolic blood pressure and standing heart rate, for the adjunct patients only. There were no statistically significant differences ($P > 0.05$) for any other comparison between treatment groups for the subgroups of patients examined (Tables 3.1 and 3.2).

Within treatment groups, the mean blood pressure responses Week 0 - Week 8 were all statistically significant ($P \leq 0.05$) for each subgroup, except for seated systolic blood pressure in the adjunct group receiving nitrendipine bd. This group had a much lower seated systolic pressure at baseline compared to the od group, however, seated systolic pressures at Week 8 were almost identical in both treatment groups.

c) Intention to Treat Analysis

As a supporting secondary analysis, the responses for Week 0 - Week 8 were analysed on an intention to treat basis. Data for all patients were included where recorded. For these patients who discontinued prior to Week 8 assessment, their last recorded blood pressure measurements on active treatment were used. There were no statistically significant differences ($P > 0.05$) between treatment groups for mean responses in blood pressure or seated heart rate. There is a statistically significant difference ($P = 0.035$) for mean response in standing heart rate.

Within each treatment group there were statistically significant differences ($P < 0.001$) in mean blood pressures Week 0 - endpoint.

d) Dose Titration at Weeks 4 and 8

At Week 8, over 50% of patients in each treatment group had titrated up from the initial dose.

6.3.6 Blood Pressures and Heart Rates at Week 12 Pre- to Post-Dose

For all valid patients there were statistically significant differences ($P \leq 0.05$) between Week 12 pre- and post-dose measurements for all mean blood pressures and heart rates.

Mean seated blood pressures fell 12.6/7.9 mm Hg from pre- to post-dose (Fig. 3). Standing pressures fell similarly by 11.5/7.3 mm Hg after the

same period. Mean increases in seated and standing heart rates over the same period were 1.7 bpm and 2.3 bpm respectively. Similar trends were observed when treatment group and dosage were examined.

The US FDA proposes that blood pressure response at peak effect should be no more than 1.5 - 2 times that at trough effect. "Peak" and "trough" effects on blood pressure in this study were not accurately determined. However the mean seated diastolic blood pressure responses from Week 0 to Week 12 "pre" and "post-dose" were determined and are tabulated with regard to the FDA guidelines in Table 4. In all but two cases (5mg bd and 20mg bd) the actual week 12 post-dose values fall within the described range.

6.3.7 Responders at Each Visit

The number of patients defined as responders (seated diastolic blood pressure < 95mmHg) or non-responders at each visit are summarised for each treatment group in Table 5. At Week 4 and 8, 40% and 56% of patients respectively were responders. There was little difference in response rates between the two treatment groups.

At Week 12 pre- and post-dose, 69% and 89% of patients respectively were responders.

6.4 Safety

All adverse events or intercurrent illnesses recorded during the study were listed whether or not they were thought to be treatment related and were classified according to COSTART terminology. For those patients withdrawn from the study due to adverse events, the major symptom present at discontinuation has been listed as the reason for withdrawal.

For the patients reporting more than one event, each adverse experience was documented.

Of the 215 patients who entered the study 22 patients (including 3 on placebo) were withdrawn due to adverse events. Details of patients withdrawn due to adverse events are displayed in Table 6:-

6.4.1 Adverse Events During Placebo Run-In Phase (Weeks -4 to 0)

Two hundred and fifteen patients received placebo during the run-in phase. Forty seven patients reported 65 adverse events on placebo. The most commonly reported adverse events were headache, 13 patients (6%); dizziness, 8 patients (3.7%); asthenia, 6 patients (2.8%) and somnolence, 5 patients (2.3%).

Three patients experienced adverse events necessitating discontinuation from the study. (1 dizziness, 1 urticarial rash and 1 asthenia).

6.4.2 Adverse Events During Active Treatment Phase (Weeks 0 - 12)

Fifty two patients in the nitrendipine bd group and 47 patients in the nitrendipine od group reported adverse events during the randomised phase of the study. The most commonly reported adverse events (Table 6: all patients) were flushing, 28 (14.7%), headache, 27 (14.2%), peripheral oedema, 15 (7.9%), asthenia, 11 (5.8%) and dizziness, 8 (4.2%). There was little difference in the overall incidence of adverse events in the two treatment groups.

Nineteen patients were withdrawn due to adverse events whilst receiving nitrendipine (headache 6, flushing 3, peripheral oedema 3, dizziness 2, urticaria 2, palpitations 1, nausea 1 and lack of erection 1).

In addition to the above, patient 412 suffered a non-fatal myocardial infarction and patient 516 suffered a minor cerebrovascular accident. Reasons for withdrawal in both cases were not attributed as adverse reactions according to the investigator and were classed as "other".

Details of all adverse reactions necessitating withdrawal are summarised in Table 7.

Full details of individual patients withdrawing from the study can be found in Tables 6 and 7

6.4.3 Laboratory Investigations

Most patients had haematology and biochemistry investigations performed pre-entry and at Week 12.

Mean alkaline phosphatase was significantly increased ($P < 0.05$) from pre-entry to Week 12. Mean alkaline phosphatase increased from 99.6 IU/l at pre-entry to 106.1 IU/l at Week 12; in 12 patients alkaline phosphatase levels moved from normal to above the normal laboratory range, but none of these increases were clinically significant.

6.4.4 Plasma Nitrendipine Analysis

Pre- and post-dose plasma samples were prepared for nitrendipine analysis. The results of these analyses are awaited and will be reported elsewhere.

7. Conclusions

i) 10 - 20mg nitrendipine given as a single dose is as effective as 10 - 20mg nitrendipine given twice daily in reducing blood pressure over 24 hours

ii) over 50% of patients achieved satisfactory blood pressure control on nitrendipine, irrespective of dosage frequency

iii) the differences between peak and trough blood pressure measurements do not fall outside of the range proposed in the new FDA guidelines for assessment of dosage frequency of antihypertensive drugs

iv) Nitrendipine od was as well tolerated as nitrendipine bd

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Glossary

bd	once daily
bpm	beats per minute
BP	blood pressure
CTX	clinical trial exemption
DHSS	Department of Health & Social Security
ECG	electrocardiogram
FDA	Food & Drug Administration
IU	International units
mg	milligram
mm Hg	millimetres mercury
od	once daily
P	probability

Substances

nitrendipine tablets 5mg, 10mg, 20mg

placebo

Key Words

nitrendipine

hypertension

dosage frequency

monotherapy

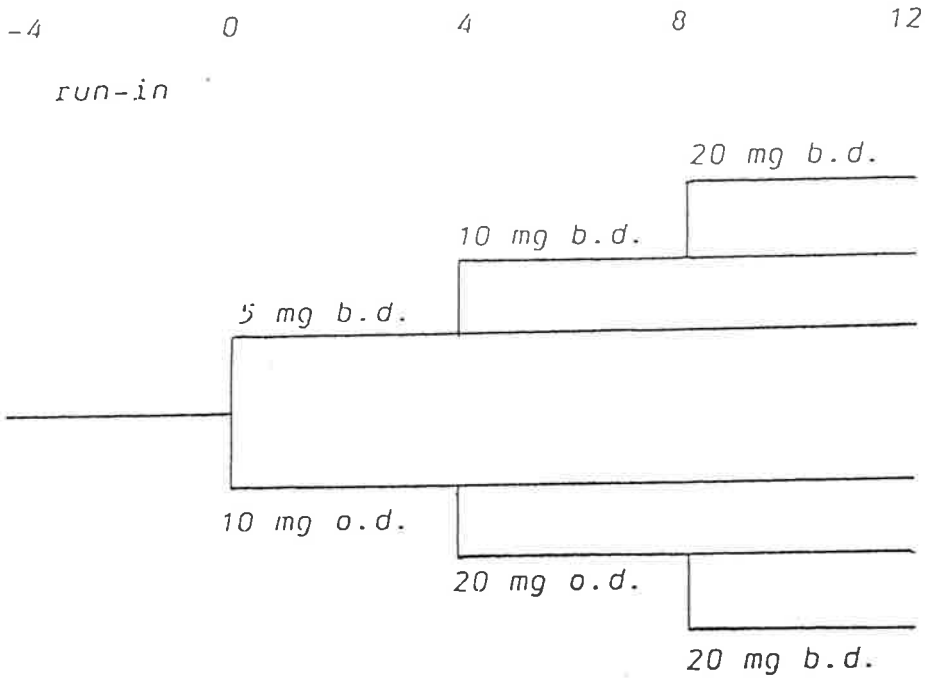
beta-blockade

Summary of Withdrawals

Reason	ntd BD	ntd OD	Total
Adverse reaction	10	9	19
Non attendance	1	4	5
Non compliance	0	2	2
Other	7	6	13
Total*	17	18	35

* Four patients had more than one reason for withdrawal, hence the totals are less than the sum of individual reasons

Fig. 1 NITRENDIPINE MULTICENTRE STUDY (5009/0426)



measurements:					
ECG, X-Ray	X				X
BP, HR	X	X	X	X	X
Laboratory Investigations	X				X
Side effects		X	X	X	X
Compliance		X	X	X	X
Plasma NTD assay					X

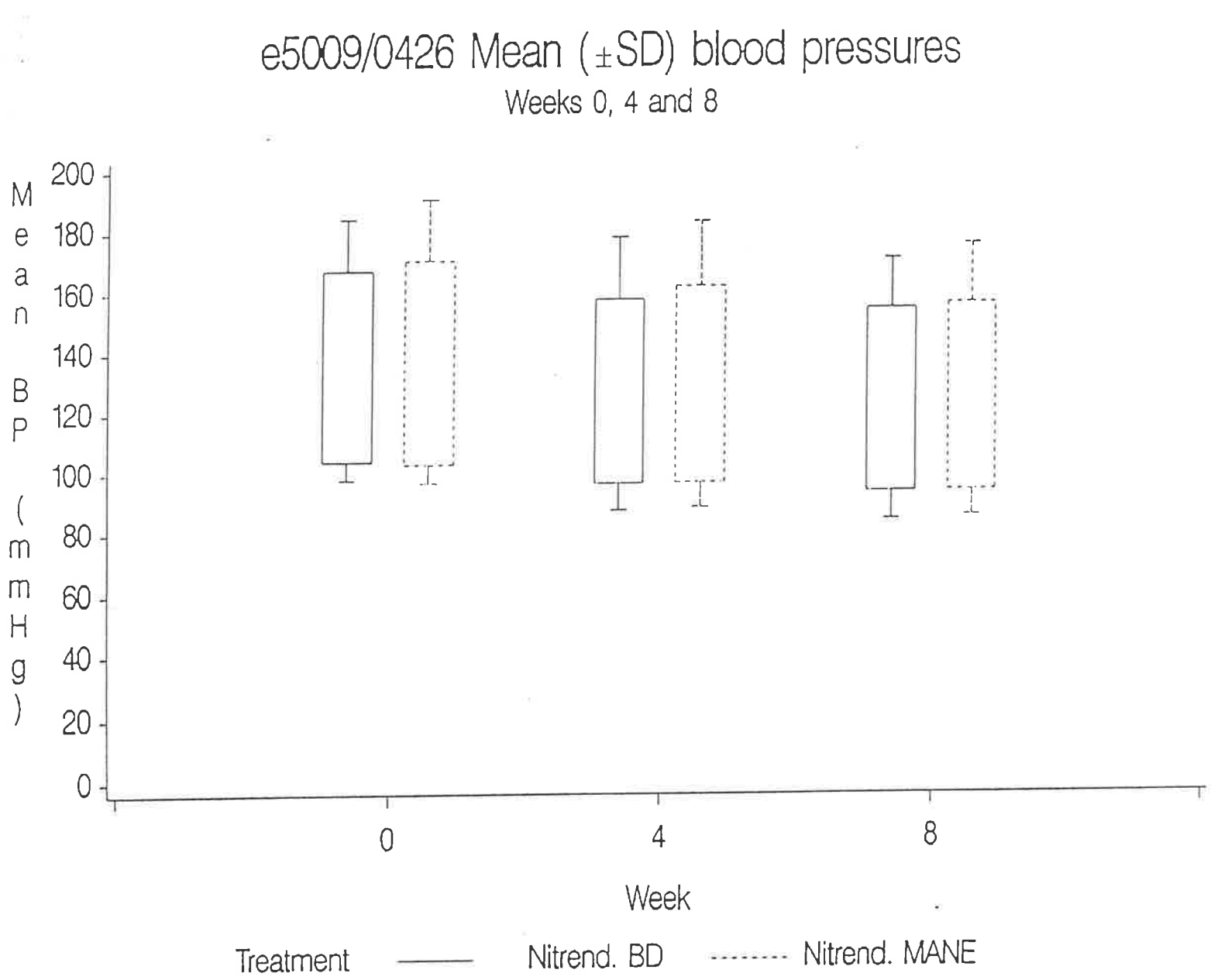

e5009/0426 Mean (±SD) blood pressures
Weeks 0, 4 and 8
Mean BP (mmHg)
200
180
160
140
120
100
80
60
40
20
0
0
4
8
Week
Treatment
Nitrend. BD
Nitrend. MANE

Fig. 3

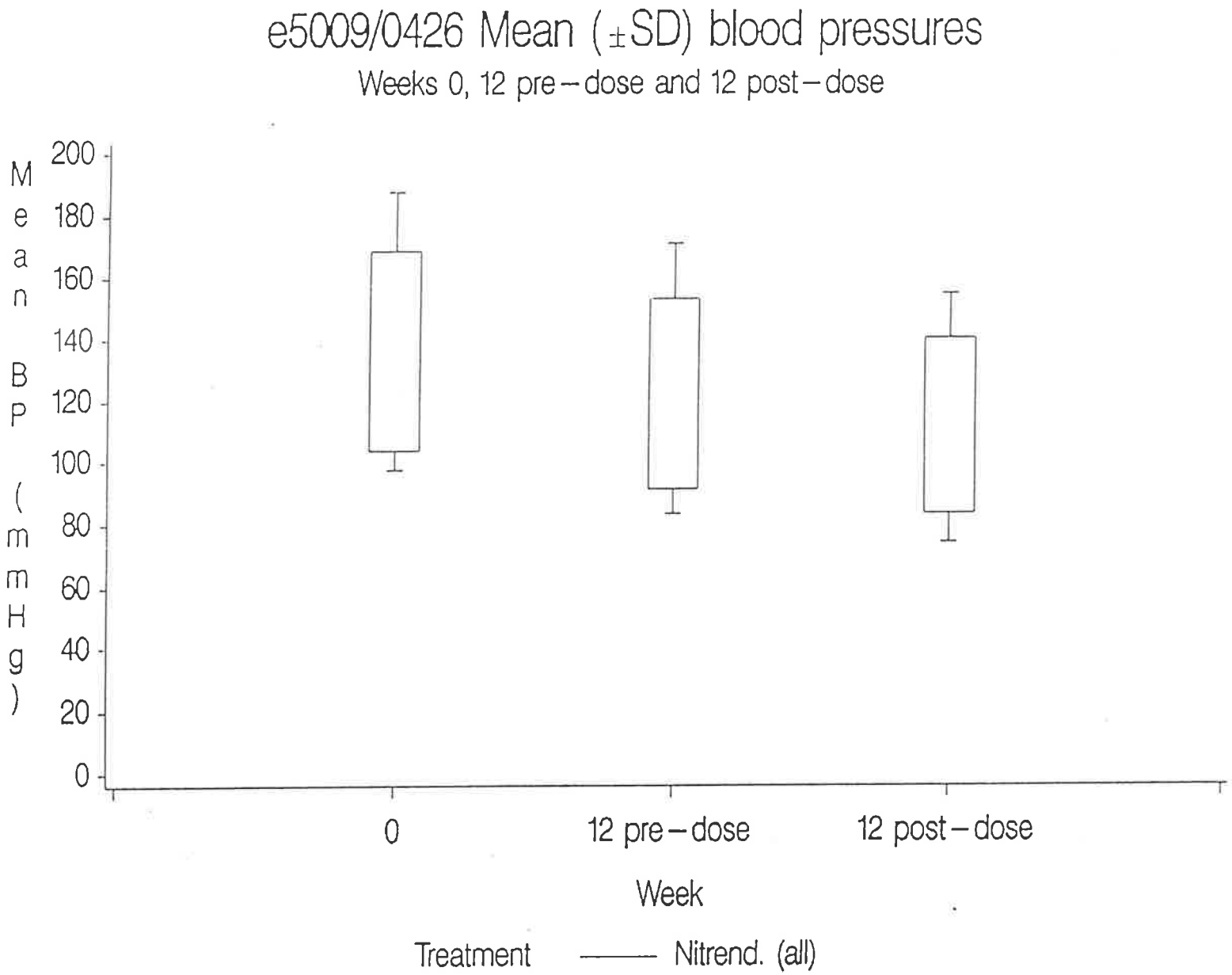

e5009/0426 Mean (±SD) blood pressures
Weeks 0, 12 pre–dose and 12 post–dose
Mean BP (mmHg)
200
180
160
140
120
100
80
60
40
20
0
0
12 pre–dose
12 post–dose
Week
Treatment
Nitrend. (all)

Table 1

Patient demography - all patients randomised

		NTD BD (n=97)	NTD MANE (n=93)	All patients (n=190)
Age (years)	mean	56.0	58.5	57.2
	SD	10.3	10.1	10.3
	n < 65	75 (77%)	64 (69%)	139 (73%)
	n > 65	22 (23%)	29 (31%)	51 (27%)
Sex	male	51 (53%)	49 (53%)	100 (53%)
	female	46 (47%)	44 (47%)	90 (47%)
Height (cm)	mean	166.6	165.5	166.0
	SD	9.5	9.9	9.7
		(n=96)		(n=189)
Weight (kg)	mean	78.6	79.0	78.8
	SD	13.5	15.3	14.4
		(n=93)	(n=91)	(n=184)
Smoking habits	yes	19 (20%)	23 (25%)	42 (22%)
	no	38 (39%)	46 (49%)	84 (44%)
	previous	40 (41%)	24 (26%)	64 (34%)
Alcohol Consumption	yes	65 (68%)	66 (73%)	131 (70%)
	no	31 (32%)	25 (27%)	56 (30%)
		(n=96)	(n=91)	(n=187)
Race	caucasian	92 (95%)	88 (95%)	180 (95%)
	other	5 (5%)	5 (5%)	10 (5%)
Hypertension newly diagnosed?	yes	39 (41%)	39 (42%)	78 (41%)
	no	57 (59%)	54 (58%)	111 (59%)
If no, years since diagnosed	mean	6.2	5.4	5.8
	SD	5.2	5.4	5.3
		(n=57)	(n=53)	(n=110)
Antihypertensive therapy	monotherapy	76 (78%)	77 (83%)	153 (81%)
	adjunct	21 (22%)	16 (17%)	37 (19%)
Sitting BP (mmHg)	mean	168.2/103.6	170.8/102.9	169.5/103.3
	SD	17.1/ 6.6	19.9/ 6.0	18.5/ 6.3
Standing BP (mmHg)	mean	166.3/105.7	167.9/104.6	167.1/105.2
	SD	16.9/ 9.1	19.5/ 8.1	18.2/ 8.6
		(n=96/n=95)	(n=93/n=92)	(n=189/n=187)
Standing HR (bpm)	mean	76.2	75.3	75.7
	SD	10.4	10.5	10.4
		(n=94)		(n=187)
Standing HR (bpm)	mean	79.8	78.0	78.9
	SD	10.8	11.9	11.4
		(n=94)		(n=187)

Table 2
Number of patients in the study

	Nitrendipine BD	Nitrendipine MANE	All patients
No. of patients at pre-entry			215
Withdrawals at or before Week 0			25
No. of patients at Week 0, randomised to active treatment	97	93	190
Protocol violators, excluded from analysis of efficacy #	3	0	3
No. of valid patients at Week 0	94	93	187
Withdrawals after Week 0 to before Week 4	4	4	8
No. of patients at Week 4	90	89	179
Withdrawals at Week 4 to before Week 8	9	6	15
No. of patients at Week 8 (No. of valid patients at Week 8) *	81 (80)	83 (82)	164 (162)
Withdrawals at Week 8 to before Week 12	3	8	11
No. of patients at Week 12: pre-treatment	78	75	153
post-treatment	77	73	150

\# Patients 102, 153 and 615 were excluded from the analysis of efficacy

* Patients 1107 and 1117 were excluded from the analysis of efficacy at Week 8 due to blood pressures being measured at peak

Table 3.1 **Seated BP and HR for Valid Patients in the Study at Week 8 (Monotherapy and Second-line)**

Nitrendipine BD (n=80)	Week 0 (±SD)	Week 8 (±SD)	Mean Response (Wk 0-8)	P
Seated systolic	167.3 (16.8)	154.4 (16.8)	12.9[1]	< 0.001
Seated diastolic	103.9 (6.0)	93.6 (9.2)	10.3[2]	< 0.001
Seated HR	77.1 (10.1)	75.5 (9.7)	1.6[3]	ns
Nitrendipine OD (n=82)				
Seated systolic	170.6 (20.0)	156.3 (19.2)	14.4[1]	< 0.001
Seated diastolic	103.0 (6.1)	93.9 (8.4)	9.1[2]	< 0.001
Seated HR	75.3 (10.5)	75.5 (10.2)	-0.2[3]	ns

P (between groups)

1	0.55
2	0.33
3	0.22

Table 3.2 : BP and HR for Valid Monotherapy Patients at Week 8

Nitrendipine b.d. (n = 63)

	Week 0 (±SD)	Week 8 (±SD)	Mean	P
1. Seated systolic	168.4 (17.3)	153.4 (16.9)	15.0	<0.001
2. Seated diastolic	104.0 (6.3)	93.3 (8.8)	10.7	<0.001
3. Seated HR	78.4 (9.9)	77.0 (9.3)	1.4	NS
4. Standing systolic	165.5 (17.0)	152.7 (15.6)	12.8	<0.001
5. Standing diastolic	106.4 (8.2)	96.7 (9.4)	9.7	<0.001
6. Standing HR	82.5 (10.1)	80.6 (11.0)	1.9	NS

Nitrendipine o.d. (n = 68)

	Week 0 (±SD)	Week 8 (±SD)	Mean	P
1. Seated systolic	170.2 (20.4)	156.0 (18.7)	14.2	<0.001
2. Seated diastolic	102.8 (6.3)	93.8 (8.6)	9.0	<0.001
3. Seated HR	77.0 (10.2)	76.6 (10.1)	0.4	NS
4. Standing systolic	166.8 (20.0)	156.5 (17.8)	10.3	<0.001
5. Standing diastolic	104.2 (7.2)	97.0 (9.8)	7.2	<0.001
6. Standing HR	79.8 (11.8)	80.4 (11.5)	-0.5	NS

P (between groups)

1. Seated systolic	0.77
2. Seated diastolic	0.26
3. Seated HR	0.52
4. Standing systolic	0.39
5. Standing diastolic	0.13
6. Standing HR	0.16

Table 3.3 : BP and HR for Valid Adjunct Therapy Patients at Week 8

Nitrendipine b.d. (n = 17)

	Week 0 (±SD)	Week 8 (±SD)	Mean	P
1. Seated systolic	163.2 (14.4)	157.9 (16.3)	5.3	NS
2. Seated diastolic	103.6 (5.1)	94.7 (10.8)	8.9	<0.001
3. Seated HR	72.4 (9.7)	70.4 (9.3)	2.0	NS
4. Standing systolic	163.6 (14.5)	154.9 (13.5)	8.7	0.029
5. Standing diastolic	105.1 (7.2)	97.4 (11.1)	7.6	0.0011
6. Standing HR	73.8 (10.1)	71.6 (9.5)	2.2	NS

Nitrendipine o.d. (n = 14)

	Week 0 (±SD)	Week 8 (±SD)	Mean	P
1. Seated systolic	172.8 (18.3)	157.5 (22.1)	15.3	<0.001
2. Seated diastolic	103.6 (5.5)	94.6 (7.4)	9.0	<0.001
3. Seated HR	67.2 (7.8)	70.2 (8.8)	-2.9	NS
4. Standing systolic	171.5 (17.4)	157.6 (21.9)	13.9	<0.001
5. Standing diastolic	107.1 (12.8)	93.3 (10.5)	13.8	<0.001
6. Standing HR	70.1 (9.7)	75.3 (10.3)	-5.1	NS

P (between groups)

1.	Seated systolic	0.084
2.	Seated diastolic	0.97
3.	Seated HR	0.12
4.	Standing systolic	0.31
5.	Seated diastolic	0.043*
6.	Seated HR	0.049*

Table 4 **Differences in Blood Pressure Measured Pre- and Post-Dose at Week 12**

Mean Sitting Diastolic BP Response (mmHg)

Group of patients	N	Week 12(pre-dose)	Required wk 12 post-dose range (FDA guidelines)	Actual wk 12 post-dose
All	150	12.4	18.6 - 24.8	20.2
5mg BD	29	13.3	20.0 - 26.6	18.6
10mg BD	26	14.0	21.0 - 28.0	21.0
20mg BD	47	10.1	15.2 - 20.2	20.8
All BD	102	12.0	18.0 - 24.0	20.2
10mg MANE	35	13.0	19.5 - 26.0	20.1
20mg MANE	13	13.0	19.5 - 26.0	19.9
All MANE	48	13.0	19.5 - 26.0	20.1

In all but two cases (5mg BD and 20mg BD) the actual Week 12 post-dose mean values fall within the desired range.

Table 5

Number of Responders and Non-Responders at Each Clinic Visit - valid patients still in the study at Week 8

By Treatment Group at Weeks 0 to 12

Group		Number (%) of patients				
		0	4	8	12(pre-dose)	12(post-dose)
BD	Responder	0 (0%)	32 (40%)	43 (54%)	53 (68%)	65 (84%)
	Non-responder	81 (100%)	49 (60%)	37 (46%)	25 (32%)	12 (16%)
MANE	Responder	0 (0%)	34 (41%)	47 (57%)	53 (71%)	68 (93%)
	Non-responder	83 (100%)	49 (59%)	35 (43%)	22 (29%)	5 (7%)
All	Responder	0 (0%)	66 (40%)	90 (56%)	106 (69%)	133 (89%)
	Non-responder	164 (100%)	98 (60%)	72 (44%)	47 (31%)	17 (11%)

Table 6

Most Commonly Reported Adverse Events

Event	ntd BD (n=97)	ntd OD (n=93)	Total (n=190)
Flushing	15 (15.5%)	13 (14.0%)	28 (14.7%)
Headache	11 (11.3%)	16 (17.2%)	27 (14.2%)
Peripheral oedema	8 (8.2%)	7 (7.5%)	15 (7.9%)
Asthenia	3 (3.1%)	8 (8.6%)	11 (5.8%)
Dizziness	4 (4.1%)	4 (4.3%)	8 (4.2%)
Any adverse event	52 (53.6%)	47 (50.5%)	99 (52.1%)

Table 7

Adverse Reactions Necessitating Withdrawal

	ntd BD	ntd OD	Total
Headache	3	3	6
Flushing	1	2	3
Peripheral oedema	1	2	3
Dizziness	1	1	2
Urticaria	2	-	2
Palpitations	-	1	1
Nausea	1	-	1
Lack of erection	1	-	1
Total	10	9	19

APPENDIX 6

Part sample of demography data

PATIENT	AGE (YEARS)	SEX	WEIGHT (KG)	HEIGHT (CM)	DURATION OF HYPERTENSION (YEARS)	CLINICAL
3703	48	MALE	99	153	1	
3704	58	FEMALE	71	158	2	ARTHRITIS
3710	34	MALE	93	174	1	
3711	43	MALE	69	167	0	
3712	70	MALE	53	163	1	
3713	64	MALE	124	161	4	
3714	52	MALE	143	170	2	
3715	41	FEMALE	45	155	4	
3716	32	MALE	87	181	1	
3717	43	MALE	82	165	6	
3718	32	MALE	112	192	1	
3719	62	MALE	89	175	0	
3720	57	MALE	80	160	1	MYOCARDIAL INFARCT
3721	51	MALE	86	184	0	
3722	57	FEMALE	65	170	7	
3723	48	FEMALE	100	167	1	OBESITY
3724	68	FEMALE	60	155	1	
3725	62	MALE	75	177	2	
3726	44	FEMALE	68	157	1	
3727	57	MALE	76	182	6	OSTEOARTHRITIS
3728	60	FEMALE	57	157	7	
3729	50	FEMALE	57	178	0	
3730	61	FEMALE	65	165	1	
3731	35	MALE	64	176	0	
3732	60	FEMALE	110	170	12	PERIPHERAL VASCULAR D
3733	56	MALE	97	188	0	
3734	60	FEMALE	110	170		PERIPHERAL VASCULAR D OBESITY ISCHEMIC HEART DISEAS
.	.	.	.	.	.	.
.	.	.	.	.	.	.
3735	65	FEMALE	76	165	0	
3736	44	FEMALE	56	161	1	
3737	48	FEMALE	75	182	0	DYSPNOEA LETHARGY
.	.	.	.	.	.	.
3738	45	FEMALE	67	160	3	
3739	62	MALE	97	157	1	
3740	70	MALE	97	167	0	
3741	56	MALE	80	170	1	
3742	39	FEMALE	60	175	0	
3743	57	FEMALE	59	158	0	
3744	62	FEMALE	60	158	1	
3745	53	FEMALE	75	163	1	

3757	54	FEMALE	73	164	[illegible]	SKIN KERATOSIS
3758	51	FEMALE	62	167	[illegible]	
3759	55	FEMALE	79	151	3	OBESITY
3760	54	MALE	75	174	0	
3761	54	FEMALE	61	151	7	ANGINA PECTORIS
3762	50	MALE	73	177	1	
3763	59	FEMALE	65	164	4	
3764	57	MALE	87	175	0	POOR VISION
3765	57	FEMALE	53	161	2	SENSITIVITY (SENSITI
3766	55	MALE	81	185	5	OBSTRUCTIVE AIRWAYS D
3767	50	FEMALE	57	157	[illegible]	SINUSITIS
3768	52	MALE	83	180	3	
3769	70	MALE	87	175	5	DIABETES MELLITUS
3770	53	MALE	95	180	12	
3771	52	MALE	73	179	2	
3772	54	MALE	87	190	3	
3773	48	MALE	90	185	0	
3774	59	MALE	80	185	2	
3775	53	MALE	144	180	1	
3776	54	MALE	86	182	9	
3777	57	MALE	70	175	0	
3778	48	MALE	105	182	8	
3779	55	MALE	84	175	0	
3780	47	MALE	75	177	9	
3781	52	FEMALE	85	160	0	
3782	48	MALE	85	180	5	UEBERGEWICHT
3783	53	MALE	94	175	0	CHEST INFECTION
3784	52	MALE	75	172	0	
3785	58	MALE	78	170	0	ANGINA PECTORIS
3786	54	FEMALE	65	160	2	
3787	47	MALE	80	182	0	RETINOPATHY GRADE3
3788	58	MALE	70	164	0	
3789	53	FEMALE	65	165	0	
3790	48	MALE	69	169	3	ANGSTZUSTAENDE
3791	52	MALE	68	172	0	ANGSTZUSTAENDE
3792	54	FEMALE	70	160	0	
3793	53	FEMALE	90	157	0	DIABETES MELLITUS
3794	54	FEMALE	52	155	1	MITRAL SYSTOLIC MURMU
3795	56	MALE	124	184	0	OBESITY
3796	58	FEMALE	51	160	0	OBSTRUCTIVE AIRWAYS D
.	.	.	.	.	.	WHEEZE
3797	52	FEMALE	53	152	2	
3798	51	MALE	87	187	[illegible]	

3809	65	FEMALE	63	165	0	
3810	44	MALE	80	185	0	
3811	58	MALE	85	170	0	
3812	61	MALE	83	165	0	
3813	33	MALE	70	170	2	
3814	67	MALE	85	172	0	
3815	63	MALE	86	170	2	ANGINA PECTORIS
.	.	.	.	.	.	ANGIOSTOSTENOSE
3816	60	MALE	92	178	0	OBSTRUCTIVE AIRWAYS
3817	61	MALE	117	184	0	
3818	59	FEMALE	70	160	1	DIZZINESS
3819	68	FEMALE	69	157	14	
3820	37	MALE	110	170	0	
3821	64	MALE	93	162	0	
3822	53	MALE	107	175	0	ARTHRITIS KNEES
3823	65	FEMALE	70	160	0	
3824	59	MALE	100	170	2	
3825	60	FEMALE	105	158	4	ANKLE OEDEMA
3826	58	MALE	130	168	1	OBSTRUCTIVE AIRWAYS
3827	55	MALE	100	175	0	
3828	69	FEMALE	76	155	0	
3829	64	FEMALE	90	160	0	VERTIGO
.	.	.	.	.	.	TINNITUS
3830	42	MALE	70	168	0	PERIPHERAL VASCULAR
3831	61	MALE	85	171	0	OBSTRUCTIVE AIRWAYS
3832	61	FEMALE	68	159	9	
3833	69	MALE	70	175	0	OBSTRUCTIVE AIRWAYS
3834	59	FEMALE	80	165	0	
3835	64	FEMALE	60	155	7	
3836	39	MALE	83	168	0	
3837	63	FEMALE	62	153	1	ERYTHROEDEMA PSORIASIS
3838	59	FEMALE	62	152	2	DEPRESSION
3839	67	MALE	85	184	24	PERNICIOUS ANAEMIA
3840	49	MALE	98	173	0	
3841	45	FEMALE	89	155	1	
3842	64	MALE	89	172	0	
3843	61	MALE	71	170	0	
3844	64	FEMALE	59	159	2	ANGINA PECTORIS
3845	63	MALE	70	155	0	
3846	58	MALE	76	165	0	
3847	67	FEMALE	51	157	0	
3848	52	MALE	72	169	0	
3849	35	MALE	82	155	0	

3909	54	FEMALE	83	175	3	
3910	53	FEMALE	91	154	0	
3911	66	FEMALE	82	167	-	
3912	53	MALE	101	184	1	
3913	63	MALE	84	174	14	PERIPHERAL VASCULAR DI
3914	59	FEMALE	89	168	4	
3915	46	FEMALE	71	155	-	
3916	55	MALE	79	177	3	ANGINA PECTORIS
.	.	.	.	.	.	MYOCARDIAL INFARCT
3917	53	FEMALE	85	170	5	ANKLE OEDEMA
3918	66	FEMALE	84	169	1	
3919	67	FEMALE	70	164	7	ANGINA PECTORIS
3920	53	MALE	84	180	3	ANGINA PECTORIS
.	.	.	.	.	.	Z.N. PNEUMONECTOMY
3921	59	FEMALE	81	169	3	ANGINA PECTORIS
3922	48	FEMALE	92	170	6	ANGINA PECTORIS
3923	54	FEMALE	51	168	3	ANGINA PECTORIS
.	.	.	.	.	.	MYOCARDIAL INFARCT
3924	47	FEMALE	85	172	0	
3925	51	MALE	72	181	0	
3926	42	FEMALE	81	154	.	OBESITY
3927	58	FEMALE	71	170	9	ANGINA PECTORIS
3928	52	FEMALE	55	159	3	ACOUSTIC NEUROMA
3929	62	FEMALE	63	169	8	BELLS PALSY
3930	57	MALE	77	170	3	ANGINA PECTORIS
.	.	.	.	.	.	OBSTRUCTIVE AIRWAYS DI
3931	50	MALE	101	180	0	
3932	55	MALE	93	167	8	
3933	50	MALE	115	180	0	
3934	63	MALE	76	168	12	
3935	49	MALE	88	177	9	
3936	66	FEMALE	78	165	0	
3937	64	FEMALE	78	155	-	
3938	59	MALE	83	178	10	ANGINA PECTORIS
3939	61	MALE	98	175	5	MITRAL REGURGITATION
3940	57	MALE	100	172	4	ENLARGED PROSTATE GND
3941	65	MALE	80	167	4	ANGINA PECTORIS
3942	67	FEMALE	72	155	50	
3943	63	FEMALE	79	160	4	
3944	64	MALE	83	178	0	
3945	56	FEMALE	57	160	4	COSTOCHONDRITIS
3946	66	FEMALE	66	160	2	
3947	63	MALE	85	175	1	ANGINA PECTORIS

3958	57	MALE	75	165		
3959	57	FEMALE	62	156	8	DIABETES MELLITUS
3960	45	MALE	87	155		ANGINA PECTORIS
3961	66	FEMALE	71	162	1	MYOKARDINFARKT
.	.	.	.	.	.	.
3962	49	MALE	95	165	8	
3963	59	MALE	84	175		
3964	57	MALE	72	175	6	OBESITY
3965	46	MALE	93	175	2	
3966	58	MALE	78	161	1	
3967	55	MALE	87	162	1	[illegible]
3968	60	MALE	84	175	0	
3969	62	FEMALE	102	157	4	HYPERTENSIVE RETINOPA
.	.	.	.	.	.	OBESITY
3970	51	FEMALE	75	165	1	
3971	48	MALE	75	179	7	
3972	39	FEMALE	60	165	14	
3973	62	MALE	89	168	8	OBSTRUCTIVE AIRWAYS I
3974	66	MALE	92	175		EPILEPSY
3975	65	MALE	75	175	6	
3976	66	MALE	76	175	0	
3977	60	MALE	113	183	3	
3978	42	MALE	83	175	3	OBSERVATIVE ARTHRIT
3979	58	FEMALE	58	165	0	IRRITABLE BOWEL SYNDR
3980	66	FEMALE	64	155	2	
3981	58	FEMALE	60	160	8	
3982	66	MALE	75	173	0	DERMATITIS
3983	69	MALE	73	170	10	DIABETES
3984	59	FEMALE	76	165		
3985	59	FEMALE	81	162	5	PERIPHERAL VASCULAR D
.	.	.	.	.	.	CLAUDICATIO INTERMIT
3986	57	MALE	70	168	5	
3987	64	FEMALE	90	157	0	
3988	58	FEMALE	58	165	10	
3989	50	FEMALE	54	157	0	
3990	59	FEMALE	85	158	14	
3991	63	FEMALE	53	157	1	ANGINA PECTORIS
.	.	.	.	.	.	ANGSTZUSTAENDE
3992	59	FEMALE	75	155	0	
3993	59	FEMALE	70	165	0	
3994	55	FEMALE	66	165	0	
3995	42	FEMALE	63	162	0	
3996	58	FEMALE	93	165	0	

4006	53	MALE	69	174	3	ANGINA PECTORIS
.	.	.	.	.	.	MYOKARDINFARKT
4007	32	FEMALE	63	173		
4008	45	FEMALE	58	165	0	
4009	65	FEMALE	63	155	5	
4010	68	MALE	95	178	0	PERIPHERAL VASCULAR DISEASE
4011	53	FEMALE	54	163	1	
4012	62	FEMALE	45	155	0	ANGINA PECTORIS
.	.	.	.	.	.	MYOKARDINFARKT
.	.	.	.	.	.	THYROTOXIC
4013	62	MALE	82	173	.	ANGINA PECTORIS
4014	43	FEMALE	55	155	9	
4015	65	MALE	62	170	2	
4016	68	FEMALE	50	170	20	ANGINA PECTORIS
4017	55	MALE	120	195	3	ARTHRITIS
4018	37	FEMALE	58	150	4	
4019	70	FEMALE	70	155		
4020	67	MALE	82	183	0	
4021	54	FEMALE	80	165		
4022	47	MALE	90	183	0	
4023	54	FEMALE	58	153		
4024	69	FEMALE	73	155	12	
4025	54	MALE	93	168	3	
4026	65	FEMALE	72	165	2	
4027	70	MALE	93	173		
4028	55	FEMALE	65	160	0	
4029	45	FEMALE	88	155	7	
4030	47	MALE	85	167	0	
4031	43	MALE	83	170	4	
4032	65	MALE	93	179	4	MYOKARDINFARKT
4033	47	MALE	85	167		
4034	44	MALE	107	184	0	
4035	63	MALE	95	180		
4036	66	FEMALE	72	162	18	
4037	59	MALE	80	176	15	
4038	68	MALE	85	172	0	
4039	43	MALE	83	178	2	
4040	44	MALE	107	184	0	
4041	63	MALE	67	186		
4042	62	MALE	85	175	0	
4043	54	MALE	86	171	3	
4044	45	MALE	63	169	0	
4045	57	MALE	74	173	7	

4056	51	FEMALE	59	159	[illegible]	
4057	57	FEMALE	58	156	5	
4058	53	MALE	79	175	2	MYOKARDINFARKT
.	.	.	.	.	.	ULCUS DUODENI
4059	48	MALE	82	168	2	ANGSTZUSTAENDE
4060	61	MALE	76	173	0	
4061	54	MALE	107	173	.	
4062	68	MALE	105	173	0	
4063	61	MALE	84	171	.	
4064	59	FEMALE	70	155	3	
4065	56	MALE	103	180	7	
4066	62	FEMALE	72	158	10	
4067	53	MALE	70	171	.	
4068	69	MALE	69	172	8	
4069	66	MALE	69	159	1	
4070	45	MALE	77	168	0	
4071	55	MALE	100	178	9	
4072	69	FEMALE	75	160	0	
4073	53	MALE	89	175	3	
4074	51	FEMALE	85	150	0	
4075	35	FEMALE	77	157	1	
4076	58	FEMALE	103	166	8	
4077	47	FEMALE	84	170	3	PERIPHERAL VASCULAR DISEASE
4078	35	MALE	99	198	0	
4079	57	MALE	107	186	.	
4080	69	MALE	73	177	17	
4081	55	FEMALE	61	152	4	
4082	60	FEMALE	59	157	0	
4083	69	FEMALE	53	162	12	ANGINA PECTORIS
4084	51	FEMALE	67	157	1	
4085	53	FEMALE	60	152	13	
4086	53	MALE	85	170	0	
4087	67	FEMALE	66	159	.	
4088	69	MALE	73	177	16	
4089	56	MALE	76	170	17	ANGINA PECTORIS
4090	53	MALE	75	174	0	
4091	55	FEMALE	63	170	0	
4092	64	MALE	70	174	6	PERIPHERAL VASCULAR DISEASE
.	.	.	.	.	.	POOR PULSES POPLIT.A.DORSALI
4093	60	FEMALE	80	168	10	WEAKNESS OF HAND (OLD CVA)
4094	69	MALE	74	176	6	
4095	50	MALE	78	176	2	
4096	50	MALE	78	176	7	

.	.	.	.	.	.	DIABETES MELLITUS
.	.	.	.	.	.	OBSTRUCTIVE AIRWAYS
4107	50	MALE	77	175	4	OBSTRUCTIVE AIRWAYS
4108	68	MALE	78	180	5	ANGINA PECTORIS
.	.	.	.	.	.	MYOKARDINFARKT
4109	67	FEMALE	75	170	0	
4110	57	FEMALE	75	157	3	
4111	66	MALE	84	175	0	MYOKARDINFARKT
4112	62	MALE	78	183	1	MYOKARDINFARKT
.	.	.	.	.	.	OBSTRUCTIVE AIRWAYS
.	.	.	.	.	.	WHEEZE
4113	62	FEMALE	81	170	0	OBSTRUCTIVE AIRWAYS
4114	63	FEMALE	113	150	5	OBSTRUCTIVE AIRWAYS
.	.	.	.	.	.	RHONCHI
4115	60	FEMALE	83	170	1	MYOKARDINFARKT
.	.	.	.	.	.	DIABETES MELLITUS
4116	62	FEMALE	75	163	3	ANGINA PECTORIS
4117	67	FEMALE	90	165	0	ANGINA PECTORIS
4118	54	MALE	78	184	3	
4119	62	MALE	75	180	0	
4120	60	FEMALE	78	160	3	
4121	43	MALE	86	180	10	
4122	57	FEMALE	85	168	3	DEPRESSION
4123	62	FEMALE	80	165	0	
4124	66	MALE	76	185	3	
4125	64	FEMALE	85	165	0	
4126	50	MALE	87	175	1	
4127	62	MALE	84	180	0	
4128	61	MALE	96	177	3	
4129	58	MALE	92	180	0	
4130	57	MALE	85	177	1	
4131	63	MALE	88	178	0	OBSTRUCTIVE AIRWAYS
4132	64	FEMALE	86	163	4	
4133	58	FEMALE	92	162	2	
4134	57	MALE	94	178	1	
4135	48	MALE	94	177	1	
4136	58	MALE	96	180	3	
4137	64	MALE	88	175	2	
4138	59	MALE	90	181	3	
4139	56	FEMALE	71	160	2	
4140	61	MALE	85	180	3	
4141	59	FEMALE	68	168	2	ANGINA PECTORIS
4142	70	MALE	72	175	1	
4143	66	MALE	66	155	2	

PATIENT	AGE (YEARS)	SEX	WEIGHT (KG)	HEIGHT (CM)	DURATION OF HYPERTENSION (YEARS)	CONCUR
4153	59	FEMALE	63	159	2	
4154	70	MALE	66	166	2	
4155	57	MALE	93	177	4	
4156	59	FEMALE	64	156	2	
4157	57	MALE	84	177	7	
4158	58	MALE	76	177	1	
4159	47	MALE	76	175	4	
4160	59	MALE	73	169	6	
4161	59	MALE	70	180	2	
4162	50	MALE	79	173	3	
4163	54	MALE	76	177		
4164	52	FEMALE	66	167	6	
4165	51	MALE	79	177	4	
4166	64	FEMALE	68	159	25	
4167	57	FEMALE	73	162	1	
4168	62	FEMALE	68	156	8	
4169	54	MALE	78	179	2	
4170	53	MALE	106	180	9	
4171	54	FEMALE	69	154	4	
4172	65	FEMALE	59	160	8	
4173	66	FEMALE	50	160	2	
4174	53	MALE	75	172	8	
4175	50	FEMALE	62	160	3	
4176	66	FEMALE	57	160	8	
4177	70	FEMALE	70	157	8	
4178	47	MALE	83	182	5	
4179	61	MALE	66	172	4	
4180	68	MALE	83	182	5	
4181	51	MALE	83	177	2	
4182	66	FEMALE	51	160	1	
4183	59	FEMALE	65	160	5	
4184	69	FEMALE	66	167	1	
4185	66	FEMALE	49	155	17	
4186	57	FEMALE	76	160	1	
4187	48	FEMALE	57	160	2	
4188	67	MALE	79	179	2	
4189	59	MALE	70	155	5	MYOCARDINFARKT
4190	59	MALE	90	179	4	
4191	54	FEMALE	69	168	5	
4192	59	FEMALE	68	169	2	
4193	57	FEMALE	75	164	15	
4194	62	FEMALE	67	170	5	

PATIENT	AGE (YEARS)	SEX	WEIGHT (KG)	HEIGHT (CM)	DURATION OF HYPERTENSION (YEARS)	CONCUR
4205	53	FEMALE	57	16+	.	
4207	40	MALE	72	17[illegible]	5	
4208	64	MALE	73	16[illegible]	.	
4209	39	MALE	87	18[illegible]	3	
4210	68	MALE	76	17[illegible]	1	OTCHT
4211	58	FEMALE	69	16[illegible]	1	OSTEOARTHRITIS
4212	45	FEMALE	55	15+	0	
4213	53	MALE	73	177	2	CATARRH
4214	56	MALE	69	17[illegible]	0	OBSTRUCTIVE AIRWAYS
4215	45	FEMALE	84	16[illegible]	2	OBESITY
4216	37	FEMALE	75	152	1	
4217	47	MALE	86	17[illegible]	0	
4218	50	FEMALE	86	160	0	
4219	44	MALE	78	17[illegible]	4	OBSTRUCTIVE AIRWAYS
.	.	.	.	.	.	DYSPEPSIE
4220	42	FEMALE	75	16+	3	OSTEOARTHRITIS
4221	49	MALE	95	16+	5	
4222	56	FEMALE	64	15[illegible]	0	
4223	59	MALE	79	182	0	
4224	55	FEMALE	58	16[illegible]	0	
4225	59	MALE	68	15[illegible]	12	
4226	66	FEMALE	76	16[illegible]	0	
4227	61	MALE	83	18[illegible]	0	
4228	44	MALE	82	18+	1	
4229	52	FEMALE	62	152	5	
4230	56	MALE	83	18[illegible]	1	PERIPHERAL VASCULAR
4231	48	MALE	65	165	2	
4232	65	FEMALE	56	15[illegible]	2	ANGINA PECTORIS
4233	59	MALE	60	160	3	
4234	66	MALE	70	17[illegible]	51	
4235	60	MALE	65	17[illegible]	1	
4236	66	MALE	65	16[illegible]	2	
4237	55	MALE	65	17[illegible]	5	
4238	50	FEMALE	70	16[illegible]	0	
4239	50	MALE	87	17[illegible]	0	
4240	68	MALE	65	17[illegible]	0	
4241	66	MALE	65	16[illegible]	5	ANGINA PECTORIS
4242	55	MALE	67	17[illegible]	0	
4243	64	FEMALE	65	16[illegible]	2	
4244	57	FEMALE	64	160	0	
4245	58	MALE	70	17[illegible]	0	
4246	64	MALE	78	17[illegible]	5	

APPENDIX 7

Part sample of blood pressure data

STUDY A1040/ARMING LISTING OF EFFICACY

PATIENT	DAY OF STUDY	SYSTOLIC BP (MMHG)	DIASTOLIC BP (MMHG)	HEART RATE (BPM)
3996	0	160	100	84
3996	28	150	70	80
3996	56	145	92	86
3997	-7	135	95	88
3997	0	140	115	92
3998	-4	180	96	64
3998	0	170	96	72
3998	29	160	84	66
3998	57	160	90	80
3999	-21	185	110	86
3999	-7	190	110	86
3999	0	190	110	86
3999	30	130	80	78
3999	61	130	80	74
4000	-7	190	105	66
4000	0	185	105	64
4001	-21	160	105	76
4001	-20	165	100	68
4001	0	160	105	68
4001	32	140	80	80
4001	59	150	90	72
4002	-26	240	110	76
4002	-20	180	110	78
4002	0	170	105	70
4002	36	180	90	80
4002	64	150	80	72
4003	-52	170	100	72
4003	-40	175	105	75
4003	0	150	80	74
4003	28	160	90	70
4004	-25	180	115	78
4004	-12	175	110	80
4004	0	180	115	78
4004	29	170	100	72
4004	57	175	110	68
4005	-21	190	110	86
4005	-12	180	105	80
4005	0	180	105	80
4005	29	140	80	74
4005	57	150	80	70

PATIENT	DAY OF STUDY	SYSTOLIC BP (mmHg)	DIASTOLIC BP (mmHg)	HEART RATE (b/m)
4009	-11	180	110	84
4009	0	150	100	72
4009	27	140	80	68
4009	55	150	70	70
4010	-21	180	110	80
4010	-10	160	100	84
4010	0	190	110	84
4010	28	160	90	80
4010	54	180	80	78
4011	-24	180	100	80
4011	-14	190	130	92
4011	0	170	100	80
4011	24	230	110	84
4012	-19	170	110	84
4012	-14	170	110	88
4012	0	170	100	84
4012	29	120	80	80
4012	59	140	80	80
4013	-22	170	110	78
4013	-20	170	100	76
4013	0	180	100	78
4013	29	140	90	76
4014	-22	170	110	80
4014	-14	170	100	84
4014	0	160	110	80
4014	28	170	100	84
4014	57	170	110	82
4015	-24	170	100	76
4015	-11	170	110	80
4015	0	170	100	84
4015	32	160	90	78
4015	60	170	90	84
4016	-22	170	110	78
4016	-15	170	100	84
4016	0	180	110	78
4016	28	170	100	84
4017	.	180	110	80
4017	.	140	100	76
4018	-1	170	110	78
4018	0	170	110	72
4019	-19	160	110	80
4019	0	150	100	76

PATIENT	DAY OF STUDY	SYSTOLIC BP (MMHG)	DIASTOLIC BP (MMHG)	HEART RATE (BPM)
4038	61	150	90	74
4039	-17	140	100	76
4039	0	150	106	111
4039	29	140	100	74
4040	-7	170	110	66
4040	0	160	110	67
4040	34	150	100	72
4040	62	140	70	68
4041	-28	150	100	92
4041	0	170	100	72
4041	31	140	90	88
4041	59	130	80	76
4042	-10	170	100	78
4042	0	150	100	72
4042	29	120	80	78
4042	57	130	100	80
4043	-7	170	110	80
4043	0	160	110	84
4044	-13	190	100	80
4044	0	200	110	74
4044	29	160	100	98
4044	57	150	100	84
4045	-14	160	100	80
4045	0	170	100	76
4045	29	170	90	72
4045	57	150	80	84
4046	-14	180	110	72
4046	0	170	100	80
4047	-27	190	100	88
4047	0	150	110	100
4048	-14	150	110	90
4048	0	150	100	80
4049	-14	190	100	80
4049	0	160	100	80
4050	-14	180	110	108
4050	0	170	100	80
4051	-13	150	90	80
4051	0	160	100	80
4052	-14	200	130	85
4052	0	170	100	80
4053	-26	160	70	92

PATIENT	DAY OF STUDY	SYSTOLIC BP (mmHg)	[illegible] BP (mmHg)	[illegible]
4057	-15	[illegible]		[illegible]
4057	0	[illegible]	[illegible]	[illegible]
4057	29	[illegible]		[illegible]
4057	53	[illegible]	[illegible]	[illegible]
4058	-27	[illegible]	[illegible]	[illegible]
4058	0	[illegible]	[illegible]	[illegible]
4058	29	14[illegible]	[illegible]	[illegible]
4058	57	[illegible]	[illegible]	[illegible]
4059	-9	1[illegible]	[illegible]	[illegible]
4059	-1	1[illegible]	[illegible]	[illegible]
4059	0	1[illegible]	[illegible]	[illegible]
4060	-25	1[illegible]	[illegible]	[illegible]
4060	0	18[illegible]	[illegible]	[illegible]
4060	31	14[illegible]	[illegible]	[illegible]
4060	53	147	[illegible]	[illegible]
4061	-4	1[illegible]	[illegible]	[illegible]
4061	0	160	[illegible]	[illegible]
4061	32	15[illegible]	[illegible]	[illegible]
4062	-12	18[illegible]	[illegible]	[illegible]
4062	0	1[illegible]	[illegible]	[illegible]
4062	29	1[illegible]	[illegible]	[illegible]
4063	-7	1[illegible]	[illegible]	[illegible]
4063	0	1[illegible]		[illegible]
4064	-22	1[illegible]	[illegible]	[illegible]
4064	0	1[illegible]	[illegible]	[illegible]
4065	-14	2[illegible]	[illegible]	[illegible]
4065	-7	2[illegible]	[illegible]	7[illegible]
4065	0	2[illegible]	[illegible]	[illegible]
4065	29	1[illegible]	112	[illegible]
4065	59	1[illegible]	[illegible]	7[illegible]
4066	-14	1[illegible]	[illegible]	[illegible]
4066	-7	1[illegible]	[illegible]	73
4066	0	1[illegible]	1[illegible]	74
4066	29	17[illegible]	[illegible]	74
4066	57	15[illegible]	[illegible]	72
4067	-14	2[illegible]	[illegible]	[illegible]
4067	-7	2[illegible]	[illegible]	[illegible]
4067	0	2[illegible]	[illegible]	[illegible]
4067	24	156	[illegible]	[illegible]
4068	-14	1[illegible]	[illegible]	[illegible]
4068	-7	136	[illegible]	[illegible]
4068	0	1[illegible]	11[illegible]	[illegible]

PATIENT	DAY OF STUDY	SYSTOLIC BP (MMHG)	DIASTOLIC BP (MMHG)	HEART RATE (BPM)
4072	-7	210	112	74
4072	0	210	110	68
4073	-18	160	112	90
4073	-3	150	110	64
4073	0	150	110	90
4074	-28	190	110	90
4074	-21	170	110	94
4074	0	190	110	90
4075	-13	170	110	76
4075	-6	170	110	78
4075	0	170	110	76
4076	-28	190	110	76
4076	-14	220	110	84
4076	-7	220	110	84
4076	0	220	110	84
4077	-21	150	110	78
4077	-14	150	110	78
4077	0	150	110	78
4077	29	145	110	78
4078	-14	150	110	76
4078	0	160	110	72
4078	32	140	90	76
4078	60	140	90	76
4079	-16	200	110	78
4079	0	210	110	78
4079	29	170	90	76
4079	63	160	90	76
4080	-27	170	110	80
4080	-14	140	90	76
4080	0	150	90	76
4081	-25	210	110	80
4081	-21	210	110	80
4081	0	170	110	76
4081	30	160	90	80
4081	57	160	95	74
4082	-13	160	110	76
4082	-12	170	110	74
4082	2	170	110	74
4082	32	180	105	85
4082	55	180	100	80
4083	-18	160	90	84
4083	-7	140	90	80

PATIENT	DAY OF STUDY	SYSTOLIC BP (MMHG)	DIASTOLIC BP (MMHG)	HEART RATE (BPM)
[illegible]	-6	150	[illegible]	[illegible]
[illegible]	0	[illegible]	[illegible]	[illegible]
4085	38	180	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
4087	-12	[illegible]	[illegible]	[illegible]
[illegible]	-4	[illegible]	[illegible]	[illegible]
4087	0	220	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
4087	59	[illegible]	[illegible]	[illegible]
[illegible]	-19	[illegible]	[illegible]	[illegible]
4088	-5	[illegible]	[illegible]	[illegible]
[illegible]	0	[illegible]	[illegible]	[illegible]
4088	28	[illegible]	[illegible]	[illegible]
[illegible]	-28	[illegible]	[illegible]	[illegible]
4089	0	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
4089	58	[illegible]	[illegible]	[illegible]
[illegible]	-24	[illegible]	[illegible]	[illegible]
4090	0	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
4090	54	[illegible]	[illegible]	[illegible]
[illegible]	-26	[illegible]	[illegible]	[illegible]
4091	0	[illegible]	[illegible]	[illegible]
[illegible]	-26	[illegible]	[illegible]	[illegible]
4091	51	[illegible]	[illegible]	[illegible]
[illegible]	-25	[illegible]	[illegible]	[illegible]
4092	0	175	[illegible]	[illegible]
[illegible]	-27	[illegible]	85	[illegible]
4092	55	[illegible]	[illegible]	[illegible]
[illegible]	-27	[illegible]	[illegible]	[illegible]
4093	0	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	162	[illegible]	[illegible]
4093	51	[illegible]	[illegible]	[illegible]
[illegible]	-23	[illegible]	[illegible]	[illegible]
4094	0	[illegible]	[illegible]	[illegible]
[illegible]	25	[illegible]	[illegible]	[illegible]
4094	52	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
4095	[illegible]	175	[illegible]	[illegible]
[illegible]	-25	[illegible]	[illegible]	[illegible]
4095	0	175	[illegible]	[illegible]
[illegible]	25	[illegible]	[illegible]	[illegible]

PATIENT	DAY OF STUDY	SYSTOLIC BP (MMHG)	DIASTOLIC BP (MMHG)	HEART RATE (/MIN)
4099	51	150	75	74
[illegible]	-24	170	[illegible]	[illegible]
4100	0	175	175	68
[illegible]	-27	[illegible]	[illegible]	[illegible]
4100	49	160	85	68
[illegible]	-22	[illegible]	[illegible]	[illegible]
4101	0	170	170	48
[illegible]	27	[illegible]	85	[illegible]
4101	49	155	85	74
[illegible]	-23	[illegible]	[illegible]	[illegible]
4102	0	175	175	68
[illegible]	27	[illegible]	80	68
4102	49	160	80	76
[illegible]	-20	[illegible]	[illegible]	[illegible]
4103	0	190	175	75
[illegible]	-25	[illegible]	90	[illegible]
4103	51	160	85	[illegible]
[illegible]	-25	[illegible]	[illegible]	[illegible]
4104	0	175	170	67
[illegible]	-23	[illegible]	90	[illegible]
4104	50	155	85	75
[illegible]	-24	[illegible]	[illegible]	[illegible]
4105	0	185	175	[illegible]
[illegible]	-24	[illegible]	[illegible]	[illegible]
4105	47	155	85	90
[illegible]	-24	[illegible]	[illegible]	[illegible]
4106	0	190	175	90
[illegible]	-23	[illegible]	[illegible]	[illegible]
4106	57	150	80	75
[illegible]	-25	[illegible]	[illegible]	[illegible]
4107	0	175	110	85
[illegible]	-23	[illegible]	[illegible]	[illegible]
4107	51	150	75	70
[illegible]	-26	[illegible]	[illegible]	[illegible]
4108	0	195	175	83
[illegible]	-26	[illegible]	90	[illegible]
4108	52	150	75	72
[illegible]	-24	[illegible]	[illegible]	[illegible]
4109	0	180	180	75
[illegible]	-27	[illegible]	70	[illegible]
4109	52	145	75	72

PATIENT	DAY OF STUDY	SYSTOLIC BP (mmHg)	DIASTOLIC BP (mmHg)	HEART RATE (/min)
4128	57	150	100	68
4129	-3	160	100	80
4129	-1	150	100	75
4129	0	150	100	76
4129	29	130	85	84
4129	57	130	90	84
4130	-5	170	100	85
4130	-3	170	100	76
4130	0	170	100	84
4130	29	160	100	80
4130	57	155	100	84
4131	-4	140	100	84
4131	-2	150	100	86
4131	0	140	100	80
4131	29	140	100	88
4131	57	130	80	80
4132	.	175	110	84
4132	.	160	110	84
4134	-23	150	100	84
4134	-16	160	100	82
4134	0	165	100	80
4134	29	150	100	84
4135	-3	165	100	78
4135	-3	170	100	80
4135	0	180	100	84
4135	29	160	100	82
4135	57	150	90	78
4136	-14	200	110	76
4136	-7	175	110	76
4136	0	200	110	82
4136	29	180	110	74
4136	57	140	110	76
4137	-14	190	105	88
4137	-4	160	110	80
4137	0	160	110	82
4137	29	150	100	82
4137	57	160	105	86
4138	-9	140	100	76
4138	-3	170	105	72
4138	0	170	100	76
4138	29	160	105	72

PATIENT	DAY OF STUDY	SYSTOLIC BP (MMHG)	DIASTOLIC BP (MMHG)	HEART RATE (BPM)
4150	0	170	100	80
4150	28	150	90	80
4150	55	140	90	80
4150	-15	200	130	70
4150	0	230	115	90
4150	34	160	90	90
4150	62	155	95	80
4151	-17	170	110	90
4151	0	170	110	90
4151	27	160	90	80
4151	58	150	70	100
4153	-20	200	110	70
4153	0	220	110	70
4153	30	170	110	80
4153	56	160	90	80
4153	-2	140	100	80
4153	0	170	100	80
4153	28	140	80	80
4153	56	140	80	80
4155	-10	170	100	72
4155	0	160	100	72
4155	28	130	90	80
4155	56	140	80	80
4161	-3	200	100	80
4161	0	200	100	80
4161	29	140	90	80
4161	57	140	80	80
4162	-11	150	110	80
4162	0	122	110	80
4162	27	120	90	80
4162	55	120	80	80
4163	-10	170	110	70
4163	0	170	110	70
4163	24	140	100	80
4163	52	140	90	80
4164	-8	200	110	80
4164	0	200	110	80
4164	24	160	100	80
4164	52	150	100	80
4165	-9	160	110	82
4165	0	160	110	82

PATIENT	DAY OF STUDY	SYSTOLIC BP (MMHG)	DIASTOLIC BP (MMHG)	HEART RATE (BPM)
4184	0	190	100	80
4184	28	170	90	84
4184	56	130	80	92
4185	-22	200	110	88
4185	0	200	110	80
4185	24	180	110	0
4185	56	190	100	80
4186	-20	160	100	84
4186	0	180	100	80
4186	28	160	100	84
4186	44	140	80	80
4187	-24	170	110	84
4187	0	195	100	80
4188	-24	200	110	76
4188	0	210	100	84
4188	28	190	100	84
4188	54	150	80	80
4189	-24	190	100	84
4189	0	190	100	80
4189	28	160	90	84
4189	51	170	90	80
4190	-26	190	100	84
4190	0	190	100	80
4190	28	190	90	84
4190	54	145	90	80
4191	-26	210	110	84
4191	0	210	110	80
4191	28	190	100	84
4191	46	170	80	80
4192	-24	180	100	84
4192	0	180	100	80
4192	28	190	90	84
4192	52	180	90	80
4193	-24	210	110	84
4193	0	200	110	80
4193	24	210	90	84
4193	55	190	90	80
4194	-25	180	100	84
4194	0	190	100	80
4194	30	180	90	84
4194	54	180	90	80

APPENDIX 8

BMI and diastolic blood pressure

DATA EBENE01 & 03 SAMPLE

OBS	PATNR	RRSIDIAS	TTYPE	BETA	VISIT	WEIGHT	HEIGHT	BMI
1	1	110	1	0	1	57	161	21.9899
2	3	100	1	0	1	61	163	22.9591
3	4	100	1	0	1	94	163	35.3796
4	5	95	3	2	1	57	151	24.9989
5	6	95	1	0	1	63	160	24.6094
6	7	100	1	0	1	82	165	30.1194
7	8	100	237	1	1	46	159	18.1955
8	9	100	1	0	1	77	162	29.3400
9	10	95	1	0	1	79	164	29.3724
10	11	100	1	0	1	82	167	29.4023
11	12	100	1	0	1	73	158	29.2421
12	13	100	1	0	1	82	164	30.4878
13	14	110	1	0	1	69	152	29.8650
14	15	100	7	1	1	62	161	23.9188
15	16	95	1	0	1	65	154	27.4077
16	17	110	1	0	1	95	177	30.3233
17	18	98	3	2	1	76	172	25.6896
18	19	98	3	2	1	76	172	25.6896
19	20	108	1	0	1	72	170	24.9135
20	21	110	1	0	1	64	167	22.9481
21	22	110	1	0	1	77	181	23.5036
22	23	106	1	0	1	82	188	23.2005
23	24	110	1	0	1	76	150	33.7778
24	25	102	1	0	1	76	163	28.6048
25	26	115	1	0	1	83	161	32.0204
26	27	110	1	0	1	87	180	26.8519
27	28	115	1	0	1	63	162	24.0055
28	29	110	3	2	1	97	182	29.2839
29	30	115	37	1	1	105	165	38.5675
30	31	105	7	1	1	85	176	27.4406
31	32	105	1	0	1	86	185	25.1278
32	33	115	1	0	1	99	188	28.0104
33	34	100	1	0	1	85	179	26.5285
34	35	100	1	0	1	63	160	24.6094
35	36	100	3	2	1	72	175	23.5102
36	37	102	3	2	1	76	180	23.4568
37	38	98	3	2	1	89	165	32.6905
38	39	98	37	1	1	65	175	21.2245
39	40	104	1	0	1	79	170	27.3356
40	41	96	3	2	1	72	180	22.2222
41	42	96	3	2	1	61	155	25.3902
42	43	96	3	2	1	54	155	22.4766
43	44	98	3	2	1	67	160	26.1719
44	45	110	1	0	1	72	165	26.4463
45	46	98	1	0	1	72	165	26.4463
46	47	98	1	0	1	60	155	24.9740
47	48	100	3	2	1	75	177	23.9395
48	49	104	37	1	1	80	182	24.1517

OVERALL MEAN BP AND BMI

OBS	_NAME_	N	MEAN	STD	MAX	MIN
1	BMI	4154	27.075	4.8873	61.461	13.605
2	RRSIDIAS	4154	104.159	5.8228	115.000	70.000
3	RRSISYST	4154	174.479	20.1571	250.000	100.000

MEAN BP BY BMI LT AND GE 31

NAME OF FORMER VARIABLE=RRSIDIAS

OBS	BMIF	N	MEAN	STD	MAX	MIN
1	< 31 KG/M2	3375	104.003	5.76040	115	70
2	>= 31 KG/M2	779	104.833	6.04315	115	76

NAME OF FORMER VARIABLE=RRSISYST

OBS	BMIF	N	MEAN	STD	MAX	MIN
3	< 31 KG/M2	3375	174.440	20.0866	250	100
4	>= 31 KG/M2	779	174.646	20.4718	240	115

MEAN BP BY BMI LT 21, 21-30, 31-32, GE 33

NAME OF FORMER VARIABLE-RRSIDIAS

OBS	BMIF	N	MEAN	STD	MAX	MIN
1	< 21 KG/M2	174	103.782	6.58238	115	70
2	>= 33 KG/M2	470	105.081	5.99483	115	86
3	21-30 KG/M2	3201	104.015	5.71326	115	80
4	31-32 KG/M2	309	104.456	6.10638	115	76

NAME OF FORMER VARIABLE=RRSISYST

OBS	BMIF	N	MEAN	STD	MAX	MIN
5	< 21 KG/M2	174	175.034	21.7154	230	120
6	>= 33 KG/M2	470	175.145	20.8865	240	125
7	21-30 KG/M2	3201	174.408	19.9974	250	100
8	31-32 KG/M2	309	173.887	19.8338	240	115

RELATIONSHIP BETWEEN BMI AND SITTING DIASTOLIC BP
TREATED PATIENTS

DEP VARIABLE: RRSIDIAS DIASTOLIC BP
ANALYSIS OF VARIANCE

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PROB>F
MODEL	1	389.98345	389.98345	12.165	0.0005
ERROR	1320	42318.05286	32.05913095		
C TOTAL	1321	42708.03631			

ROOT MSE	5.662078	R-SQUARE	0.0091
DEP MEAN	103.2057	ADJ R-SQ	0.0084
C.V.	5.486204		

PARAMETER ESTIMATES

VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T FOR HØ: PARAMETER=0	PROB > |T|	VARIABLE LABEL
INTERCEP	1	100.03691	0.92180844	108.522	0.0001	INTERCEPT
BMI	1	0.11673772	0.03347064	3.488	0.0005	

RELATIONSHIP BETWEEN BMI AND SITTING DIASTOLIC BP
TREATED PATIENTS

VARIABLE	N	MEAN	STD DEV	SUM	MINIMUM	MAXIMUM
RRSIDIAS	1322	103.2057	5.685955	136438.0	80.00000	115.0000
BMI	1322	27.1450	4.654365	35885.7	13.88889	61.1402

PEARSON CORRELATION COEFFICIENTS / PROB > |R| UNDER HO:RHO=0 / N = 1322

	RRSIDIAS	BMI
RRSIDIAS	1.00000	0.09556
	0.0000	0.0005
BMI	0.09556	1.00000
	0.0005	0.0000

RELATIONSHIP BETWEEN BMI AND SITTING DIASTOLIC BP
UNTREATED PATIENTS

DEP VARIABLE: RRSIDIAS DIASTOLIC BP
ANALYSIS OF VARIANCE

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PROB>F
MODEL	1	466.21855	466.21855	13.762	0.0002
ERROR	2830	95869.26027	33.87606370		
C TOTAL	2831	96335.47881			

ROOT MSE	5.820315	R-SQUARE	0.0048
DEP MEAN	104.6038	ADJ R-SQ	0.0045
C.V.	5.564152		

PARAMETER ESTIMATES

VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T FOR HO: PARAMETER=0	PROB > |T|	VARIABLE LABEL
INTERCEP	1	102.40580	0.60250134	169.968	0.0001	INTERCEPT
BMI	1	0.08128066	0.02190983	3.710	0.0002	

RELATIONSHIP BETWEEN BMI AND SITTING DIASTOLIC BP
UNTREATED PATIENTS

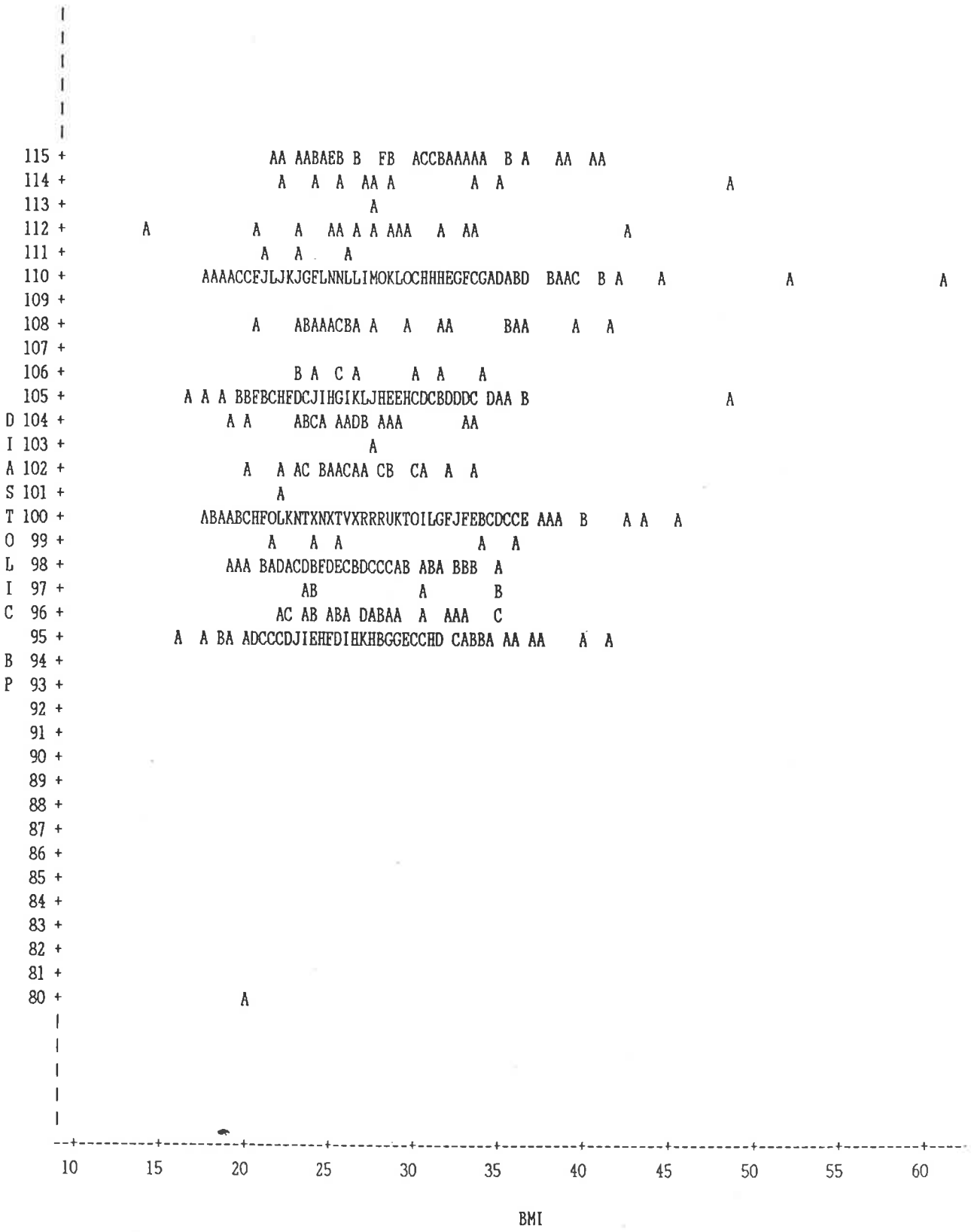
VARIABLE	N	MEAN	STD DEV	SUM	MINIMUM	MAXIMUM
RRSIDIAS	2832	104.6038	5.833419	296238.0	70.00000	115.0000
BMI	2832	27.0423	4.992725	76583.7	13.60544	61.4612

PEARSON CORRELATION COEFFICIENTS / PROB > |R| UNDER HO:RHO=0 / N = 2832

	RRSIDIAS	BMI
RRSIDIAS	1.00000	0.06957
	0.0000	0.0002
BMI	0.06957	1.00000
	0.0002	0.0000

RELATIONSHIP BETWEEN BMI AND SITTING DIASTOLIC BP
TREATED PATIENTS

PLOT OF RRSIDIAS*BMI LEGEND: A = 1 OBS, B = 2 OBS, ETC.



RELATIONSHIP BETWEEN BMI AND SITTING DIASTOLIC BP
UNTREATED PATIENTS

PLOT OF RRSIDIAS*BMI LEGEND: A = 1 OBS, B = 2 OBS, ETC.

NOTE: 313 OBS HIDDEN

APPENDIX 9

Publications and Presentations

Relating to Chapter 2:

Publications

Safety and Efficacy of Nifedipine 20mg Tablets in Hypertension using Electronic Data Collection in General Practice. Marley J. E. Journal of Royal Society of Medicine 1989,82:272-5

General Practice Data derived tolerability of Antihypertensive Drugs. Marley J, Curram J. International Journal of Clinical Research 1989;17:473-8

Body mass index and diastolic blood pressure. Marley J, Curram J. British Medical Journal 1989;299:1102

Alleviation of motion sickness by nifedipine. Marley J, Joy M. Lancet 1987;2:1265

Presentations

General Practice Computers in Pharmaceutical Safety Assessment. Marley J. 5th Royal Australian College of General Practitioners Computer Conference, Melbourne, Australia, 1987.

Nifedipine 20mg Tablets in General Practice; Efficacy and Tolerability in a large Hypertensive Population. Marley J. Calcium Antagonists in Hypertension 25th Anniversary Symposium, Basel, Switzerland, February 1988. Journal of Cardiovascular Pharmacology 1988 (Suppl;2) .

A Large Population Study of Age-related Efficacy and Tolerability of Nifedipine 20mg Tablets. 12th Scientific Meeting of the International Society of Hypertension. Marley J. Kyoto, Japan, May 1988.

Nifedipine 20mg Tablets in Hypertension: A population Study of Efficacy and Tolerability. Calcium Channel Blockers: Their Evolving Role in Hypertension. Marley J. San Francisco, April 1988.

Relating to Chapter 3:

Publications

Are Multicentre Study Investigators Meetings Worthwhile? Marley J, Snaith J, Lal D. British Journal of Clinical Practice 1989;82:776

Relating to Chapter 4:

Publications

Is the non-pharmacological treatment of hypertension neglected? Marley J, Davis N, Joy M. J Roy Soc Med 1991;84:540-542.

Presentations

Database directed hypertensive care audit. Marley J. Medical Computing in the 1990s. Proceedings RACGP 6th Computer Conference, RACGP, Sydney, 1990.

Marley, J. E. (1989). Safety and efficacy of nifedipine 20 mg tablets in hypertension using electronic data collection in general practice. *Journal of the Royal Society of Medicine, 82*(5), 272–275.

NOTE:

This publication is included in the print copy
of the thesis held in the University of Adelaide Library.

'he Journal of International Medical Research 1989; 17: 473 – 478

General Practice Data Derived Tolerability Assessment of Antihypertensive Drugs

J.E. Marley and J.B. Curram
Bayer UK Ltd, Newbury, UK

A large hypertensive population of patients in general practice was used to assess the tolerability of nifedipine in previously untreated patients and was compared with other antihypertensive drugs in previously treated patients. A total of 3972 patients with a sitting diastolic blood pressure between 95 and 115 mmHg were treated with 20 mg nifedipine twice daily for 1 month. In non-responders the dose was increased to 40 mg twice daily for a second month; responders continued to take 20 mg twice daily. A total of 2772 patients had been previously untreated for hypertension, whereas 857 had previously been treated with β-blockers alone or in combination and 346 had received diuretics alone or in combination. Adverse events were recorded for 28 days prior to treatment being initiated with or changed to nifedipine and for two 28-day nifedipine treatment periods. Flushing and headache, which diminished with time, occurred during nifedipine treatment. Ankle oedema did not diminish with time. Reductions were seen in occurrences of dyspnoea, impotence, lethargy and cold extremities.

KEY WORDS: Nifedipine; β-blockers; diuretics; hypertension; antihypertensive treatment; tolerability; general practice.

INTRODUCTION

Essential hypertension is a common condition affecting many people. It is likely that as many as one person in six in the population may require life-long treatment.[1] Treatment for hypertension became available with the introduction of ganglion-blocking drugs in the 1950s. Essential hypertension, unless severe, is a symptomless condition and patients usually feel well until they are treated.[2] Patients readily default from treatment because of adverse effects so that the tolerability of antihypertensive drugs is of great importance.

Nifedipine (20 mg) tablets are made of film-coated, micronized compressed nifedipine and, in this form, have low solubility. In this study the tolerability of nifedipine tablets was assessed in patients whose mild to moderate essential hypertension had not previously been treated and, in a second

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group of patients, tolerability was compared with other antihypertensive drugs with which these patients had previously been treated.

The study was conducted in general practice, the data being collected from a large computerized database.

PATIENTS AND METHODS

Patients

Patients were eligible for entry to the study if they had essential hypertension: sitting phase V diastolic blood pressure (DBP) of between 95 and 115 mmHg. Patients were either newly identified as hypertensive or were those in whom a change of treatment was indicated because of poor efficacy or tolerability. A total of 3972 patients from 486 general practices entered the study, 2772 patients being newly diagnosed. The remainder had been treated with β-blockers alone or in combination (857 patients), or with diuretics alone or in combination (346 patients). A full medical history, general examination and informed consent were obtained before entry. Demographic details are shown in Table 1.

Treatment

After two pre-entry blood pressure checks eligible patients were treated with 20 mg nifedipine twice daily. Blood pressure was reviewed after 4 and 8 weeks' open treatment. At the first review patients whose sitting phase V DBP was greater than 90 mmHg had their nifedipine dose increased to 40 mg twice daily.

Tolerability assessment

The incidences of 10 specific adverse events

Table 1
Demographic details of patients entered into the study (values given as mean ± SD)

Measure	Male	Female	All patients
No. of patients	2041	1931	3972
Age (years)	56.4 ±9.2	58.0 ±8.4	57.2 ±8.9
Weight (kg)	80.8 ±13.7	70.2 ±13.7	75.6 ±14.7
Height (cm)	172.7 ±8.6	161.2 ±6.9	167.1 ±9.7

Table 2
Mean (± SD) systolic and diastolic blood pressures and heart rates at each visit for all patients

Treatment period (weeks)	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)*	Heart rate (beats/min)
0	174.6 ±20.1 (*n*=3972)	104.2 ±5.8 (*n*=3972)	78.6 ±8.9 (*n*=3872)
4	154.8 ±19.8 (*n*=3332)	90.6 ±14.6 (*n*=3324)	79.2 ±9.4 (*n*=3320)
8	150.5 ±17.9 (*n*=2820)	87.4 ±9.3 (*n*=2820)	78.7 ±9.0 (*n*=2818)

* Sitting phase V diastolic blood pressure.

common to antihypertensive drugs were sought at entry and at the end of each 4-week treatment period. Other volunteered events were recorded. At entry the events were related to drugs taken or to those experienced while untreated in the previous 4 weeks, whereas at subsequent visits the events were related to treatment with nifedipine.

The adverse event data were entered into a central computer using remote terminals in the general practitioners' surgery. Adverse events were graded on the following scale: 1, mild; 2, moderate; 3, severe; 4, intolerable. At any time the patient could be withdrawn from the study. If an event was graded as 3 or 4 the patient was routed into an automatic withdrawal pathway.

RESULTS

The mean blood pressure and heart rate recorded at each visit are shown in Table 2.

Table 3
Type, number and severity of reported adverse events before and after treatment with nifedipine[a]

Adverse event/ severity	0 weeks (*n*=3972)	4 weeks (*n*=3332)	8 weeks (*n*=2820)	Adverse event/ severity	0 weeks (*n*=3972)	4 weeks (*n*=3332)	8 weeks (*n*=2820)
Lethargy				Nausea			
Mild	150	74	61	Mild	39	52	26
Moderate	221	51	27	Moderate	24	23	10
Severe	53	13	12	Severe	13	16	7
Intolerable	5	8	3	Intolerable	1	8	1
Ankle swelling				Dyspnoea			
Mild	51	123	125	Mild	115	40	27
Moderate	21	84	78	Moderate	101	21	14
Severe	9	27	20	Severe	31	12	7
Intolerable	-	15	5	Intolerable	-	-	2
Impotence				Skin flushing			
Mild	16	8	5	Mild	15	249	203
Moderate	32	6	4	Moderate	7	171	70
Severe	31	8	7	Severe	18	55	32
Intolerable	6	1	2	Intolerable	-	16	6
Headache				Cold extremities			
Mild	108	280	167	Mild	98	20	14
Moderate	107	130	60	Moderate	134	7	5
Severe	25	41	40	Severe	55	6	5
Intolerable	-	34	3	Intolerable	7	-	1
Dizziness				Palpitations			
Mild	81	79	65	Mild	26	54	26
Moderate	86	39	17	Moderate	24	29	14
Severe	23	16	11	Severe	12	10	10
Intolerable	3	11	3	Intolerable	-	1	1

[a] Adverse events reported at 0 weeks are from pre-entry treatment, those reported at 4 and 8 weeks are from treatment with nifedipine.

Table 4
Type and number of adverse events, according to previous antihypertensive therapy, before and after treatment with nifedipine[a]

Adverse event/ previous treatment	0 weeks (*n*=3972)	4 weeks (*n*=3332)	8 weeks (*n*=2820)	Adverse event/ previous treatment	0 weeks (*n*=3972)	4 weeks (*n*=3332)	8 weeks (*n*=2820)
Lethargy				Nausea			
Any antihypertensive	381	89	62	Any antihypertensive	60	48	21
β-Blocker	282	49	27	β-Blocker	31	29	9
Diuretics	25	12	6	Diuretics	7	4	1
Untreated	48	57	41	Untreated	17	51	23
Ankle swelling				Dyspnoea			
Any antihypertensive	59	149	123	Any antihypertensive	181	38	27
β-Blocker	23	68	58	β-Blocker	119	15	9
Diuretics	13	30	24	Diuretics	16	8	5
Untreated	22	100	105	Untreated	66	35	23
Impotence				Skin flushing			
Any antihypertensive	70	14	11	Any antihypertensive	23	256	147
β-Blocker	48	4	4	β-Blocker	10	124	55
Diuretics	9	3	2	Diuretics	3	44	30
Untreated	15	9	7	Untreated	17	235	164
Headache				Cold extremities			
Any antihypertensive	139	250	119	Any antihypertensive	273	25	13
β-Blocker	61	113	45	β-Blocker	222	13	5
Diuretics	20	38	18	Diuretics	9	4	1
Untreated	101	235	125	Untreated	21	8	12
Dizziness				Palpitations			
Any antihypertensive	133	83	42	Any antihypertensive	41	52	22
β-Blocker	83	36	19	β-Blocker	25	28	11
Diuretics	19	9	5	Diuretics	4	3	1
Untreated	60	62	54	Untreated	21	42	29

[a]Adverse events reported at 0 weeks are from pre-entry treatment, those reported at 4 and 8 weeks are from treatment with nifedipine.

The results of the specific adverse event enquiries at each of the visits are shown in Tables 3 and 4. Table 3 lists the events by severity at each visit, Table 4 lists the events in relation to previous treatment.

Significant free format adverse events were: one report of onychogryphosis, one of postural hypotension, two reports of moderate left ventricular failure and one report of drowsiness and syncope. During the course of the study three patients died: a 63-year old male, whose blood pressure was well controlled, had a cerebrovascular accident; a 63-year old female with pancreatitis, angina pectoris and cardiomyopathy; and a 59-year old male who noted increasing angina, was withdrawn from the study for appropriate treatment but died 10 days later from a myocardial infarction. A total of 561 patients withdrew from the study because of adverse events and 269 patients withdrew for other reasons.

DISCUSSION

The adverse event reports recorded during the nifedipine treatment period showed the large majority of events to be graded as mild (grade 1) or moderate (grade 2). As would be expected,[3] treatment with a dihydropyridine calcium antagonist produced the expected incidence of skin flushing and headache in all patients. The incidence of reports of headache and flushing diminished in number and intensity with continuing treatment, the reduction not being accounted for in total by patients withdrawing. Reports of ankle oedema, however, increased in all patient groups and did not diminish in number or intensity with time. This suggests that, if ankle swelling is present after 4 weeks of treatment it will remain and, if unacceptable, treatment should be stopped. There was a small increase in the number of patients noticing palpitations after 4 weeks' treatment; the number reduced with continuing treatment. Incidences of dyspnoea, cold extremities, lethargy, dizziness and impotence all diminished with nifedipine treatment; nausea was clinically unaltered.

Events common to treatment with diuretics and β-blockers,[4] were seen in those patients who had been taking them before entry to the study. Large reductions were seen in the frequency of cold extremities, lethargy, dyspnoea and impotence in those patients who had previously taken a β-blocker. In those who had previously been taking a diuretic, reductions were seen in the incidences of impotence, lethargy, nausea, dyspnoea, cold extremities and dizziness. In patients who had not been previously treated, reports of dyspnoea were almost halved, confirming that nifedipine may have a small, but useful effect on airways obstruction as previously observed.[5] Curiously, the reports of impotence in this previously untreated group were almost halved, suggesting that there may have been a true effect of nifedipine in relieving this condition. Penile erection due to nifedipine in impotence has been previously reported.[6]

This study has confirmed that all antihypertensive medication has undesirable effects in some patients. For some, the flushing, headache and ankle swelling associated with nifedipine may prove unacceptable. For those patients taking diuretics or β-blockers who experience unacceptable cold extremities, lethargy and dyspnoea, and those with obstructive airways disease, nifedipine may constitute a useful alternative treatment.

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Body mass index and diastolic blood pressure

SIR,—We would like to add our experience on the relation between body weight and blood pressure to that of Dr Stig Sonne-Holm and colleagues,[1] using data from our previous study.[2] We recently reviewed the relation between sitting diastolic blood pressure and body mass index in 4152 patients with essential hypertension. Mean diastolic blood pressure was 104·2 (SD 5·8) mm Hg and mean body mass index was 27·1 (4·9) kg/m^2; they had a weak positive correlation ($r=0·076$, $p=0·0001$). An increase in body mass index of 1 kg/m^2 was associated with a rise in diastolic blood pressure of approximately 0·09 mm Hg. The population in the study by Dr Sonne-Holm and colleagues was more obese, having a body mass index of ≥ 31 kg/m^2. We did not discriminate between obese and non-obese patients, and the relation between body mass index and diastolic blood pressure was, at best, weak in our study.

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1 Sonne-Holm S, Sorensen TIA, Jensen G, Schnohr P. Independent effects of weight change and attained body weight on prevalence of arterial hypertension in obese and non-obese men. *Br Med J* 1989;299:767-70. (23 September.)
2 Marley JE. Safety and efficacy of nifedipine 20 mg tablets in hypertension using electronic data collection in general practice. *J R Soc Med* 1989;82:272-5.

ALLEVIATION OF MOTION SICKNESS BY NIFEDIPINE

SIR,—A 39-year-old man had experienced severe motion sickness throughout his life. He could travel by air but in a car, bus, or ship he suffered frequent vomiting. Most antiemetics gave little relief. His occupation entailed frequent trips by cross-channel ferry and being driven in France in large soft-suspension cars; thus his ability to suppress his nausea was often tested.

At a routine blood-pressure screening he was found to have moderate essential hypertension and he was referred for treatment. He agreed to take part in a clinical trial in which all patients received one month of treatment with atenolol 50 mg daily in a single-blind fashion after which they were randomised double-blind to receive atenolol 50 mg daily either alone or with sustained-release nifedipine 20 mg once daily for 3 months. All drugs were encapsulated.

The patient was randomised to atenolol and nifedipine and during this treatment phase he commented spontaneously that his travel sickness had resolved. He said that at last he had "got his sea-legs and grown out of it". He had not taken any antiemetic agent during the study, having assumed that it might interact with the trial medication. He had not recorded any reduction in symptoms whilst taking atenolol alone. At the completion of the study his medication was reduced to atenolol 50 mg daily alone and although his hypertension was well controlled, the motion sickness returned. On three cross-channel voyages sustained-release nifedipine 20 mg twice daily was given in an open fashion on the day of travel, and every time the journey was trouble-free.

Drugs currently available for the treatment of motion sickness are antihistamines, phenothiazines, or atropine derivatives. These can cause drowsiness or blurred vision which could be dangerous, for example, for someone driving after taking these drugs on a cross-channel ferry. Cinnarazine is indicated for the treatment of motion sickness and has calcium antagonist properties.[1] It appears to exert a significant depressant effect on the vestibular nuclei, possibly by antagonising the stimulated influx of calcium ions from the endolymph into the vestibular sensory cells.[2] Cinnarazine can cause drowsiness,[3] possibly due to its antihistamine activity. Dihydropyridine calcium antagonists are potent blockers of calcium flux, neurotransmitter release, and calcium-dependent biochemical responses in the brain.[4] It is therefore possible that nifedipine reduced motion sickness by antagonising the influx of calcium ions into vestibular cells.

This patient inadvertently took part in the double-blind trial of nifedipine, a calcium antagonist not usually associated with drowsiness and with no antihistamine action. An effective drug for motion sickness that does not impair mental function or reactions would be valuable, and formal trials of nifedipine in this indication seem to be worth while.

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NOTE:

This publication is included in the print copy
of the thesis held in the University of Adelaide Library.

Marley, J., Davis, N., & Joy, M. (1991). Is the non-pharmacological treatment of hypertension neglected? *Journal of the Royal Society of Medicine, 84*(9), 540–541.

NOTE:

This publication is included in the print copy
of the thesis held in the University of Adelaide Library.

APPENDIX 10

Chapter 4; interview record and database structure

HYPERTENSION ADVICE QUESTIONNAIRE

PLEASE COMPLETE THIS QUESTIONNAIRE FOR ALL PATIENTS WITH HYPERTENSION AS A PRIMARY OR SECONDARY DIAGNOSIS.

The factors in this questionnaire have all been shown to be beneficial to patients with hypertension. Patients may or may not be advised about them by their G.P.s and/or hospital doctors. They may also deny having received the advice. Do not record advice as given, if given for the first time at this consultation.

Please answer all questions in columns 1, 2 and 3. If the the answer to a question is 'no' in all of columns 1, 2 and 3, please complete column 5:- scale 0 to 4: 0=definitely not given; 4=definitely given.

IS HYPERTENSION THE PRIMARY DIAGNOSIS? **Y/N**

IS THE PATIENT: A SMOKER? **Y/N**, EX-SMOKER? **Y/N**, LIFE NON-SMOKER? **Y/N**

HAS THE PATIENT BEEN TOLD THEY HAVE HYPERTENSION? **Y/N**

IS THE PATIENT OVERWEIGHT? Now **Y/N** In Past **Y/N**

	1. Previous advice given by: G.P.	Hosp. doc	**2.** Advice documented in notes as given:	**3.** Advice followed by patient:	**4.** No record; assess probability of advice previously given:				
Lose weight	Y/N	Y/N	Y/N	Y/N	0	1	2	3	4
Reduce or stop alcohol	Y/N	Y/N	Y/N	Y/N	0	1	2	3	4
Stop smoking	Y/N	Y/N	Y/N	Y/N	0	1	2	3	4
Reduce meat or vegetarian diet	Y/N	Y/N	Y/N	Y/N	0	1	2	3	4
Yoga	Y/N	Y/N	Y/N	Y/N	0	1	2	3	4
Biofeedback	Y/N	Y/N	Y/N	Y/N	0	1	2	3	4
Reduce salt intake	Y/N	Y/N	Y/N	Y/N	0	1	2	3	4
Increase exercise	Y/N	Y/N	Y/N	Y/N	0	1	2	3	4
Progressive muscle relaxation	Y/N	Y/N	Y/N	Y/N	0	1	2	3	4

SCALE 0 to 4:
0 = definitely not given.
4 = definitely given.

```
Structure for database: C:LIFESPH.dbf
Number of data records:      70
Date of last update   : 03/02/91
Field  Field Name  Type       Width    Dec
    1  HYPPRIM     Logical        1
    2  SMOKER      Logical        1
    3  EXSMOKER    Logical        1
    4  NONSMOKER   Logical        1
    5  HYPTOLD     Logical        1
    6  OVERWEIGHT  Logical        1
    7  EXOVERWT    Logical        1
    8  WTGP        Logical        1
    9  ALCOHOLGP   Logical        1
   10  SMOKEGP     Logical        1
   11  VEGEGP      Logical        1
   12  YOGAGP      Logical        1
   13  BIOGP       Logical        1
   14  SALTGP      Logical        1
   15  EXERGP      Logical        1
   16  PMRGP       Logical        1
Press any key to continue...
   17  WTHOSP      Logical        1
   18  ALCHOSP     Logical        1
   19  SMOKEHOSP   Logical        1
   20  VEGEHOSP    Logical        1
   21  YOGAHOSP    Logical        1
   22  BIOHOSP     Logical        1
   23  SALTHOSP    Logical        1
   24  EXERHOSP    Logical        1
   25  PMRHOSP     Logical        1
   26  WTNOTES     Logical        1
   27  ALCNOTES    Logical        1
   28  SMOKENOTES  Logical        1
   29  VEGENOTES   Logical        1
   30  YOGANOTES   Logical        1
   31  BIONOTES    Logical        1
   32  SALTNOTES   Logical        1
Press any key to continue...
   33  EXERNOTES   Logical        1
   34  PMRNOTES    Logical        1
   35  WTFOLLOW    Logical        1
   36  ALCFOLLOW   Logical        1
   37  SMOKEFOLLO  Logical        1
   38  VEGEFOLLOW  Logical        1
   39  YOGAFOLLOW  Logical        1
   40  BIOFOLLOW   Logical        1
   41  SALTFOLLOW  Logical        1
   42  EXERFOLLOW  Logical        1
   43  PMRFOLLOW   Logical        1
   44  WTPROB      Numeric        1
   45  ALCPROB     Numeric        1
   46  SMOKEPROB   Numeric        1
   47  VEGEPROB    Numeric        1
   48  YOGAPROB    Numeric        1
Press any key to continue...
   49  BIOPROB     Numeric        1
   50  SALTPROB    Numeric        1
   51  EXERPROB    Numeric        1
   52  PMRPROB     Numeric        1
** Total **                      53
```