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Addendum

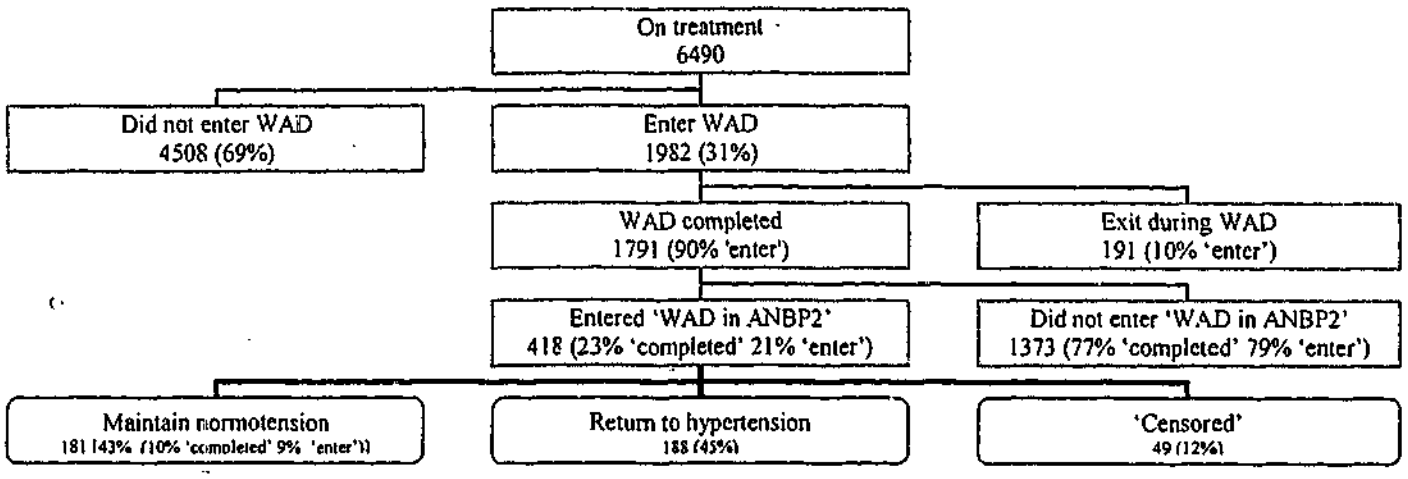

Figure 4.6. Flow chart of classification of patients screened in Victoria for ANBP2 between 10/9/96 and 30/6/98 who were currently receiving antihypertensive drugs.

Figure 4.6 is a supplementary figure for Chapter 4 that follows the progress of all patients screened in Victoria for ANBP2 over the period during which 'WAD in ANBP2' was conducted. The 418 is less than the 503 subjects who entered 'WAD in ANBP2' because 85 of these subjects had been screened prior to 10/9/96. This figure is provided to permit a comparison of the 'WAD in ANBP2' cohort to the general practice population screened for ANBP2 and discussed in Chapter 3. Three quarters of the subjects who completed drug withdrawal recommenced medication prior to the qualifying period for 'WAD in ANBP2' and subsequently only 10% of all subjects who completed drug withdrawal remained 'normotensive' 54 weeks later. This figure however has to be interpreted with caution. Patients were offered drug withdrawal as part of the run in phase for ANBP2, i.e. the investigators wanted them to be hypertensive off medication so they could enter the study. Therefore patients were offered withdrawal who would not be offered withdrawal in normal clinical practice, for example those with known cardiovascular disease and those who were hypertensive on drug therapy. Patients were also not given behavioural interventions that would assist maintenance of normotension as shown in Chapter 2.

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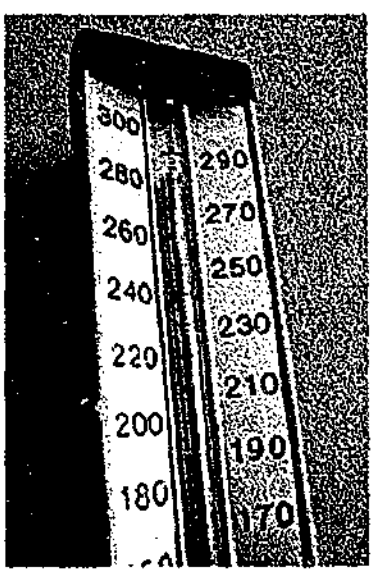
Aspects of pharmacological management of hypertension in general practice.

A thesis submitted to the Faculty of Medicine in candidacy for the Degree of Doctor of Philosophy

Department of Epidemiology and Preventive Medicine



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May 2002

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Summary

Cardiovascular disease (CVD) ranks third internationally and first in Australia on the burden of disease in disability-adjusted life years. In an aging first world society and as countries in the third world develop, this burden is likely to increase over the coming decades.

Strategies to combat CVD include preventive measures prior to it becoming apparent (primary prevention) or after (secondary or tertiary prevention). To this end over 250 independent risk factors risk factors have been identified from large epidemiological studies. The major ones include age, male gender, a family history of premature cardiovascular disease, smoking, elevated blood pressure, elevated total cholesterol, and diabetes mellitus. The first three risk factors are immutable but the other four are modifiable by medical intervention and behavioural change.

Hypertension is the arbitrary designation of a certain measurement of blood pressure as a risk factor / disease state. It is arbitrary because the relationship of blood pressure to all cause mortality and cardiovascular morbidity is a linear one[1]. Clinical trials on diastolic blood pressure have established that lowering of these levels through drug therapy or behavioural modification reduced these risks by typically 40% for stroke and 15-25% for ischaemic heart disease. Historically the definition of hypertension has trended downwards and isolated systolic hypertension has also been recognised. The

1. MacMahon, S. Antihypertensive drug treatment: the potential, expected and observed effects on vascular disease. *J Hypertension* 1990; 8 (suppl 7): S239-S244.

consequence of this is that the population now considered at risk and likely to benefit from therapy has expanded.

With this expansion into a larger proportion of the population comes an increased potential for individuals to be commenced on therapy who do not require it. However once a clinician has commenced someone on medication they are reticent to cease it. This thesis seeks to identify patient characteristics that may assist clinicians to select patients who may have their medication ceased.

A systematic review of predictors of maintenance of normotesion post cessation of all antihypertensive drugs established that approximately 42% of selected mild to moderate hypertensive patients could have their medication ceased and remain normotensive for periods in excess of twelve months. It suggested that a patient well controlled long-term on a single drug agent is the ideal candidate especially if they are willing to adopt lifestyle changes such as sodium restriction and weight loss.

Short-term predictors of maintenance of normotension after stopping all antihypertensive medication in the elderly (65-84 years) were identified from a *post hoc* analysis of 25,826 who were offered such a strategy during the run-in phase of the Second Australian National Blood Pressure Study (ANBP2). Predictors identified were younger age and monotherapy to complete drug withdrawal, and lower on therapy systolic and diastolic blood pressure, younger age, type of agent and monotherapy as for successful drug withdrawal and maintenance of blood pressure control.

Long-term predictors of maintenance of normotension after stopping all antihypertensive medication were identified by a prospective cohort study of 503 elderly subjects over a 12-month period. Predictors identified were younger age, on treatment systolic blood pressure, monotherapy, and a higher waist-hip ratio.

All of these findings suggest that the clinician may include the strategy of drug withdrawal in their population of patients currently receiving antihypertertensive medication for hypertension. This strategy is most likely to be successful if the patient is younger, well controlled on single drug therapy and is willing to undertake behavioural change. In practice this may be a patient who requests such a strategy and thus is more likely to be motivated to change their lifestyle.

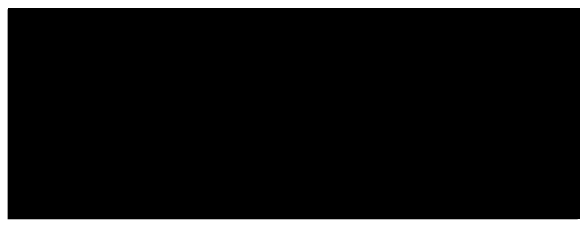
Further chapters deal with possible reasons why patients may have been inappropriately commenced on therapy and its consequences. It was found that general practitioners generally believe that newer antihypertensive agents are more efficacious and have better short and long-term side-effect profiles. The preference for these agents increases the estimated cost to the Federal Government's pharmaceutical schemes of $43-92 million per annum in 1998 figures. Guidelines were only a minor influence on the small numbers of practitioners who actually knew them. It seems that they have pre-empted the results of trials such as ANBP2 despite evidence to date showing no additional benefit for newer agents.

The research conducted for this thesis has increased our understanding of the management of mild to moderate hypertension in the general practice environment where most of this condition is managed through:

1. The conduct of the first systematic review of predictors of successful drug withdrawal and its predictors.
2. General practice based observation studies identifying such predictors in an elderly Australian cohort.
3. A cost minimisation analysis of Federal Government pharmaceutical benefit schemes relating to clinician preference to newer over older agents.
4. A survey of Victorian general practitioners seeking to explain this preference.

Declaration of originality

This thesis contains no material that has been accepted for the award of any other degree or diploma in any university or institution. I affirm to the best of my knowledge this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.



Mark Raymond Nelson

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Chapter 1

Introduction

Global and local burden of cardiovascular disease

Cardiovascular disease ranks third on the burden of disease in disability-adjusted life years (DALYs) estimated by the World Health Organization (WHO) in 1999 [1]. According to WHO Global Burden of Disease 2020 estimates as the quality of life improves in the third world it is likely that the number one position currently held by infectious diseases will be supplanted by the current second and third ranking diseases, those of neuropsychiatric and cardiovascular diseases respectively [2].

In Australia cardiovascular disease is the leading cause of death. in 1998 it was responsible for 50,797 deaths (40% of all deaths) [3]. Coronary heart disease (mostly acute myocardial infarctions) was the leading single cardiovascular cause of death with 27,825 deaths (22% of all deaths). Stroke ranked second for mortality with 11,982 deaths (9% of all deaths).

This burden shows no sign of abating. Assuming current trends continue, it is estimated that for a 40-year-old, the risk of having coronary heart disease at some time in their future life is one in two for men and one in three for women, and for a 45-year-old, the risk of having a stroke before age 85 is one in four for men and one in five for women [3].

This risk is disproportionately adverse for Australian indigenous populations with rates twice that of other Australians [3]. This inequality is even greater for those aged 25–64 where Aboriginal and Torres Strait Islander peoples' death rates were seven and ten times those of men and women respectively from the rest of the population [3].

Socioeconomic status also emphasises inequalities in health status. People aged 25–64 living in the most disadvantaged group died from cardiovascular disease at around twice the rate of those living in the least disadvantaged group [3].

On a regional level for the provincial areas (Ballarat and Geelong) that are included in Chapter 4 cardiovascular disease was ranked number one in 1996 for the burden of disease in disability-adjusted life years for both areas [4]. Ischaemic heart disease with 204 deaths (27.6%) and stroke with 75 (10.1%) also ranked first and second respectively in cause of deaths in Ballarat for males and females in 1996 [4]. The figures for Greater Geelong in the same period are almost identical, ischaemic heart disease 377 deaths (25.3%) ranked first and stroke 150 (10.0%) ranked second.

Cardiovascular disease risk factors

The classic risk factors for adverse cardiovascular disease risk are age (males >55 years, females >65 years), elevated blood pressure, male gender, smoking, high total cholesterol, diabetes mellitus, or a family history of premature cardiovascular disease [5]. Other factors contributing to risk are low high density lipoproteins (HDL), high low density lipoproteins (LDL), microalbuminuria in diabetes, impaired glucose tolerance, obesity, physical inactivity, high fibrinogen levels, and individuals who

belong to high risk socioeconomic, ethnic (e.g. Han Chinese and stroke risk) or geographic populations (e.g. Eastern Europe) [5].

These risk factors have a high prevalence in the Australian population. In 1995 it was estimated that more than 10 million adult Australians (over 80% of the adult population) had at least one of the following cardiovascular risk factors: tobacco smoking, sedentary lifestyle, hypertension, or being overweight [3]. About four in five men and three in four women had at least one of these risk factors.

Associated clinical conditions (ACC) also impact adversely on cardiovascular disease risk. These include cerebrovascular disease (cerebrovascular accident, reversable ischaemic neurological deficit, or transient ischaemic attack), heart disease (acute myocardial infarction, angina, heart failure, or the need for coronary revascularization), renal disease, diabetic nephropathy or renal failure, vascular disease (dissecting aneurysm, symptomatic arterial disease), and advanced hypertensive retinopathy (haemorrhage, exudate, or papilloedema) [5]. Absolute risk of further major cardiovascular events is very high with, for example, annual stroke risk of 3-5% for those who have already had a stroke or transient ischaemic attack, and myocardial infarction or related death of ≥4% for those who have a history of myocardial infarction or unstable angina [6, 7].

The presence of target-organ damage (TOD) also increases the risk of cardiovascular events) [5]. TOD includes left ventricular hypertrophy, proteinuria with or without elevated creatinine, demonstrated presence of atherosclerotic plaque, or narrowing of retinal arteries.

Blood pressure (mm Hg)			
Other risk factor(s) or disease	Grade 1 140-159/90-99	Grade 2 160-179/100-109	Grade 3 ≥ 180/≥ 110
I no other risk factor	**LOW RISK**	**MED RISK**	**HIGH RISK**
II 1-2 risk factors	**MED RISK**	**MED RISK**	**V HIGH RISK**
III ≥ 3 risk factors, or target organ damage, or diabetes	**HIGH RISK**	**HIGH RISK**	**V HIGH RISK**
IV Associated Clinical Condition	**V HIGH RISK**	**V HIGH RISK**	**V HIGH RISK**

LOW RISK = <15% CVD event in 10 years
MED RISK = 15-20% CVD event in 10 years
HIGH RISK = 20-30% CVD event in 10 years
V HIGH RISK = >30% CVD event in 10 years

Table 1.1. Hypertension and absolute risk. Adopted from WHO/ISH guidelines page 163 [5].

Hypertension

More recent clinical practice guidelines have recognised the preceding facts by the promotion that hypertension should not be managed in isolation to other risk factors [5, 8-11] (Table 1.1). The concept of absolute risk underlies this shift in emphasis. Absolute risk is the

risk of an individual, expressed as a percentage, having defined cardiovascular events over a specified period of time. The guidelines have also promoted new differential initiation and goal blood pressure criteria for patients with renal disease, diabetes or established cardiovascular disease, in recognition of these patients increased absolute risk of future cardiovascular events. These differential criteria are the recognition of

adverse absolute risk profile according to the number of associated risk factors, associated clinical conditions, or the presence of target organ damage (e.g. stroke or peripheral vascular disease). Other popular absolute risk tables that are in current clinical use are the New Zealand tables that estimate a person's absolute 5-year risk of a cardiovascular event, and the Framingham Point Scores Estimate of 10-Year Risk for Coronary Heart Disease [12, 13].

Hypertension and drug therapy

Hypertension was first recognised in the 1950s as a risk factor for cardiovascular disease and mortality in patients with severe hypertension. These patients were known to have high morbidity and mortality due to end organ damage caused by these very high (malignant) blood pressure levels. With the development and clinical use of effective agents such as the ganglion blockers and centrally acting agents, it could be demonstrated that these very high-risk patients could benefit from blood pressure lowering. These initial therapeutic agents however, often had relatively severe side effects that were nevertheless acceptable in these patient groups because of their very high absolute risk for adverse cardiovascular events.

Subsequent development of effective and more tolerable drugs such as the beta-adrenoreceptor blockers and thiazide diuretics, permitted clinicians to question if such benefits would be seen in patients with mild to moderate hypertension. Epidemiological studies suggested that such benefits would be expected with relative risk reductions of 30% for stroke and 20% for cardiac events for each sustained 5-6 mmHg reduction in diastolic blood pressure [14]. Large scale clinical trials conducted in the 1970s and 1980s, such as the Australian mild hypertension trial

(ANBP), the Veterans Study, and the Medical Research Council (MRC) mild hypertension trial, demonstrated such benefits with stroke reductions of 40% and cardiac event reductions of between 15 to 25% compared to placebo [15-18]. These findings have been supplemented by the identification and management of other cardiovascular disease risk factors such as dyslipidaemia [7].

Blood pressure is a continuous variable that is directly related to adverse cardiovascular outcomes [14]. It occupies its central role in cardiovascular disease prevention due to its historic role as the first recognised risk factor that was modifiable by therapeutic intervention. In 1999–00, almost three million Australians aged 25 and over had hypertension or received medication for it [3]. The proportion of Australians (aged 25–64 years) with high blood pressure has actually declined since 1980.

Cardiovascular disease also is the cause of significant morbidity and health care costs. Stroke is the leading cause of long-term disability in adults. In 1998–99, there were 437,717 hospitalisations where cardiovascular disease was the principal diagnosis (7% of all hospitalisations) [3]. Cardiovascular disease is the most costly disease for the health system in Australia being responsible for 12% ($3.9 billion) of total recurrent health expenditure in 1993–94 with estimated costs due to coronary heart disease of $894 million, hypertension $831 million, and stroke $630 million.

Hypertension in the elderly

In western societies as we age our blood pressure trends upward [19]. Hence it was estimated in 1995 that approximately 41% of people aged 65-69 were hypertensive by

contemporary definitions compared with 17% of men and 15% of women in the general Australian population aged over 18 years [20].

Further clinical trials have extended the benefit of therapy from elevated diastolic blood pressure to isolated systolic hypertension, a phenomenon found in the elderly where increasing aortic stiffness leads to reduced arterial compliance [21, 22].

Arteriosclerosis and the loss of elastin activity in older age (it has a chemical half-life of 50 years) leads to a stiffening of the aortic wall and a lack of expansion and recoil which normally dampens the systolic and accentuates the diastolic blood pressure. This leads to a 'standing wave' where the ejection volume of systole is reflected back towards the heart from arterial branches leading to an increase in systolic blood pressure [23]. Thus we observe a rise in systolic and a fall in diastolic blood pressure in aging with a consequential high pulse pressure which has been shown to have adverse cardiovascular disease outcomes and subsequent benefit from therapy in many studies [24-29].

The hierarchy of blood pressure parameters, systolic, diastolic or pulse pressure is the topic of intellectual debate at the moment. As clinicians we measure our patients' blood pressure and are reliant on clinical trials to guide on us on which levels to treat and therefore who may benefit. Historically such evidence came from studies whose blood pressure inclusion criteria were based on diastolic blood pressure (DBP) measurements. These studies therefore excluded those subjects who had elevated systolic blood pressure (SBP) but normal or low diastolic blood pressure, so called 'isolated systolic hypertension' (ISH). If we look at any given population, systolic

blood pressure trends upward throughout life but diastolic blood pressure tends to peak in the 50s and thence trends downward. Hence the population who have ISH are also those most at risk of coronary and cerebrovascular adverse events, the elderly. Large-scale clinical trials in the 1990s have demonstrated that such patients benefit from having their ISH treated [22, 30, 31].

As systolic blood pressure and diastolic blood pressure diverge with aging, the pulse pressure (PP = SBP – DBP) increases. Framingham data has shown that systolic blood pressure and pulse pressure are independent predictors of cardiovascular disease risk [19]. Herein is the debate, is diastolic blood pressure, systolic blood pressure or pulse pressure a more important predictor?

Franklin *et al* studied 6500 men and women aged 20-79 who were not on anti-hypertensive medication and who did not have coronary heart disease (CHD) [32]. They found that in the <50 year olds diastolic blood pressure was a stronger predictor of CHD risk per 10mmHg increment [hazard ratio (HR) 1.34; 95%CI 1.18-1.51] than systolic blood pressure (HR 1.14; 95%CI 1.06-1.24) or PP (HR 1.02; 95%CI 0.89-1.17). At age 50-59 the groups were comparable. In the 60 and over group the strongest predictor was pulse pressure (HR 1.24; 95%CI 1.16-1.33).

Withdrawal of antihypertensive drug studies

A review of the literature of drug withdrawal studies pertaining to predictors of maintenance of normotension post withdrawal is provided in Chapter 2. All identified studies are summarised in Tables 1 and 2 in the appendix. As can be seen in

Table 1.2 the most consistent predictors were blood pressure (lower pretreatment, on treatment and post withdrawal), pharmacotherapy (fewer agents, lower dose and shorter duration), and left ventricular mass (absence of left ventricular hypertrophy).

Predictor	+	-
Blood pressure;		
Pre treatment	7	4
Pre treatment number of recordings	0	1
On treatment	5	3
Post withdrawal	2	1
Ambulatory	1	0
Pharmacotherapy;		
Duration	2	4
Type of agent	1	1
Number of agents (fewer)	3	1
Dose level (lower)	2	1
Subject profile;		
Age at treatment	0	1
Older age at withdrawal	1	5
Gender	0	4
Race	0	1
Family history	0	1
Lower body weight		
at withdrawal	2	3
after withdrawal	1	1
Smoking	0	2
High alcohol consumption (negative)	1	1
Vascular disease	0	1
Cardiovascular system		
Increased LV mass (negative)	2	1
Increased heart rate (negative)	0	2
Electrolytes	0	1
Renin profile	1	1
24 hour Na/K excretion	0	1
Other		
Diet (Na restriction, weight loss)	3	1
(K supplementation)	0	1

Table 1.2. Withdrawal of antihypertension drug studies that tested predictors of success (N = 17). + = statistically significant association, - no statistically significant association.

Figure 1.1 is a scatter plot with regression curve of antihypertensive drug withdrawal studies that had published data on percentages of subjects without a lifestyle intervention remaining normotensive over the first 12 month period (n = 10). One study (not plotted here) had data with a lifestyle intervention (counseling) and had 6

and 12 month survival rates of 80% and 67% respectively [33]. It shows that most subjects return to hypertension in the first six months.

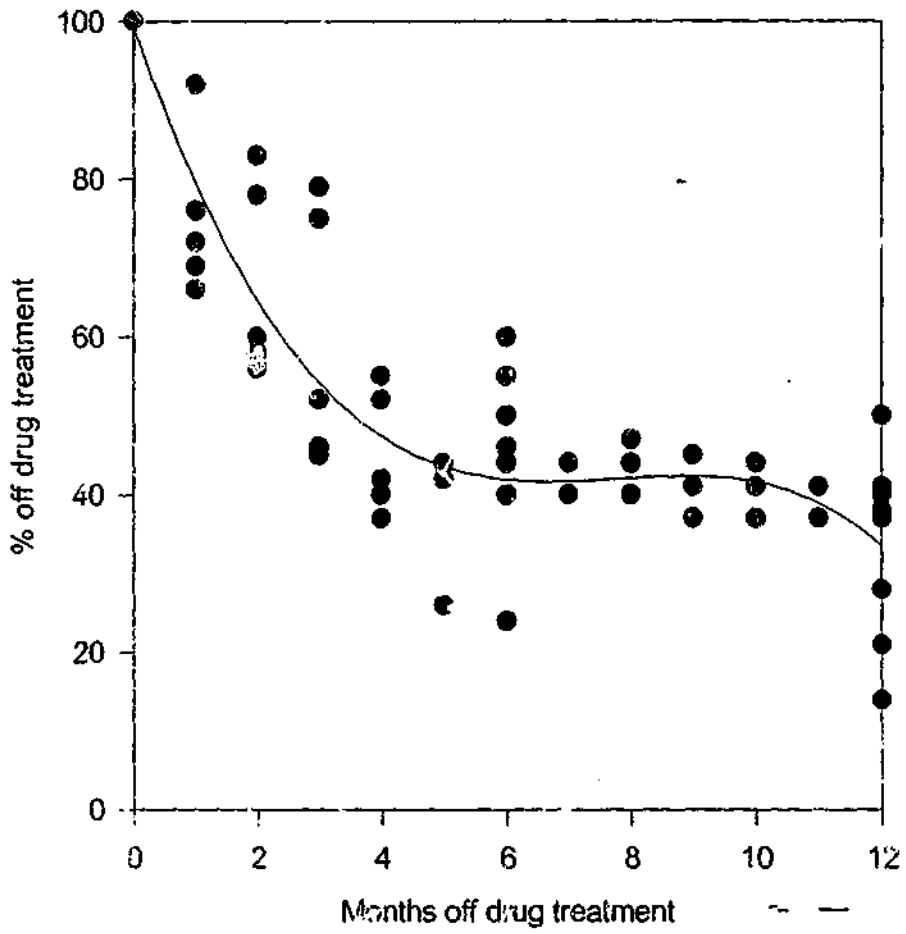


Figure 1.1. The percentage of patients remaining normotensive at varying times after drug withdrawal.

Observational antihypertensive drug withdrawal studies

Aylett and Ketchin reported an 83% success rate, defined as maintaining blood pressure below pretreatment levels (DBP ≤100 mmHg on 3 visits) for drug withdrawal at 12 months in a study conducted in general practice in rural

Northumberland [34]. This study was poorly researched (no prior studies identified), had no detail on subject selection, was a small sample (9) and came to conclusions far beyond anything that could be deduced from it.

Alderman *et al* reported on withdrawal of antihypertensive drugs in a general population, i.e. an attempt to have unselected group enter withdrawal of antihypertensive drugs [35]. Subjects were members of a retail shop union therefore there were more whites and females than in a true cross section of the general US community. Of the 4022 members, 3020 were screened and 737 were identified as hypertensive of whom 302 had their hypertension managed on a work site treatment program. A program of systemic withdrawal of antihypertensive drugs was introduced on January 1 1981 and all 196 subjects in the treatment program constituted the study population. Of these subjects, 157 met criteria of enrolment related to proof of hypertension and no added cardiovascular problems. Criteria for hypertension varied for those under 65 and over 65 although the authors did not justify this distinction (see appendix Table 1). Eighty-eight subjects were considered by these criteria to be on effective treatment of which 66 entered withdrawal of antihypertensive drugs. At one year follow up 3 subjects were lost to follow up, 19 had recommenced therapy and 44 were still off antihypertensive medication. A three-year follow up was possible with 17 subjects of whom 15 remained off all antihypertensive medication.

Van Kraaij *et al* investigated retrospectively the hospital medical records of elderly (aged 75 years or older) subjects on diuretic therapy for any reason who had subsequently undergone withdrawal for any reason [36]. One thousand five hundred

and forty seven subjects were identified. Those who underwent withdrawal had a one-year follow-up investigation and collection of additional updated information from their primary care physician. A total of 593 patients (38.3%) were using diuretics for any reason. Diuretics had been withdrawn in 218 patients (36.8%). In 101 subjects this was because of doubts about the initial or persistent indication for diuretic use and in 91 subjects because of adverse effects. No reasons for withdrawal were reported in 26 patients. Withdrawal of diuretics was attempted for hypertension in only 35.4%. The likelihood of remaining free of diuretic therapy for one year was 41%, however this could not be assumed to be antihypertensive drug free status. Hence this study was excluded from the analysis in chapter 2.

Boyle, Price and Hamilton conducted an observational trial on a highly selected unspecified group of 20 subjects with mild hypertension (18 essential) treated for five years (treated DBP <100 mmHg), and controlled on diuretics alone [37]. No method of subject selection or indeed specification of the population from which they were drawn was provided. No method of blood pressure measurement was specified except that they were performed on a 'standard sphygmomanometer'. Diastolic blood pressure was defined as the fourth Korotkow sound whereas the current recommendation is the fifth, therefore diastolic blood pressure would be overestimated by modern standards. All subjects bar two females (at 38 and 95 weeks post withdrawal) eventually returned to hypertension. The authors concluded "there appears ... to be no simple way of detecting hypertensive patients who remit after a period of treatment" [37]. This conclusion cannot be justified from this small and inadequately documented study.

Fotherby and Potter conducted a drug withdrawal study in an elderly hypertensive population attending a hospital hypertension clinic [38]. One hundred and five consecutive hypertensive primary prevention subjects had antihypertensive drug therapy withdrawn and lifestyle advice given. The sample was 47% male, mean age 76 years (range 65-84 years) on antihypertensive drug therapy for more than one year. Clinic blood pressure and weight were recorded monthly for 12 months in all subjects and at every three months in those who had a possible follow-up period of 24 months. Ambulatory blood pressure was measured at baseline and repeated one month off therapy. Seventy-four (70%) subjects had a potential follow-up of 12 months (four were withdrawn from the study) and 64 were available for two years of follow-up.

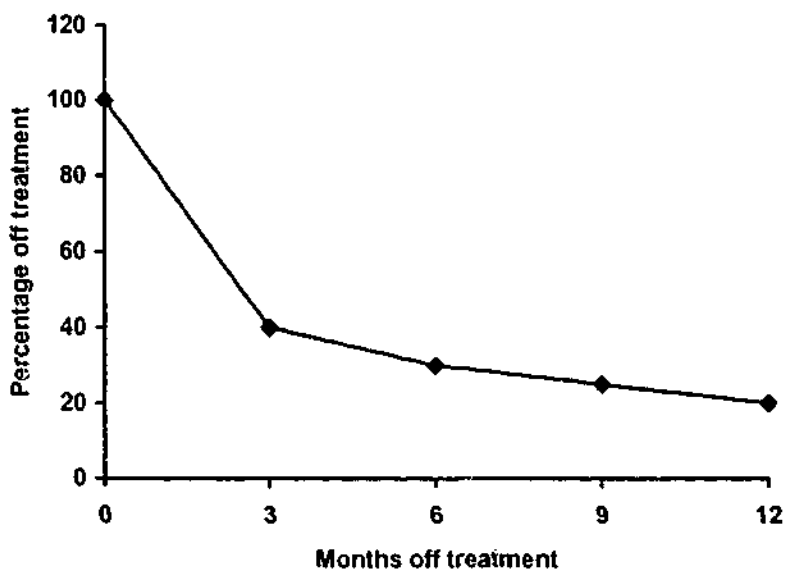


Figure 1.2 From Fotherby and Potter [38] pg 860 figure 1 (n = 105).

Antihypertensive treatment was restarted by blood pressure criteria shown in Table 2 in the appendix. Twenty percent maintained normotension at one year (Figure 1.2).

The Medical Research Council reported on the course of blood pressure in mild hypertensives after withdrawal of long term antihypertensive treatment [39]. This

was an add on study to their trial of treatment of mild hypertension [18]. Younger subjects (35-64 years) were offered medication cessation following their completion of the follow-up period in the main study. Follow-up of these withdrawal subjects was stopped when the main study was completed and therefore only 23.4% of 2765 had had the 2½-year follow up that was planned. Predictors of maintenance of normotension identified were younger age in those withdrawn from propranolol, and pre and on treatment blood pressure in males who ceased bendrofluazide.

Imataka *et al* investigated the effects of monotherapy and withdrawal of antihypertensive drugs in the treatment of hypertension [40]. They conducted a retrospective examination of the records of 282 patients with mild to moderate hypertension who had been treated for 5 years or more (average 9.7 years). They found that antihypertensive drugs had been withdrawn in 17% for 12 months or more in this cohort. Lower pretreatment systolic blood pressure and lower pretreatment QRS voltage were signs favorable for withdrawal of the drugs.

Jennings and colleagues conducted a review of the literature on antihypertensive drug withdrawal and also presented data on a study they had conducted themselves [41]. Eighty-three subjects had their medication withdrawn and were followed for a twelve-month period. A significant proportion (28%) stayed normotensive off therapy for a year although by two years all subjects had met the criteria for resumption of antihypertensive medication. The novel aspect of this study was a demonstration of the predictive effects of left ventricular hypertrophy on rate of redevelopment of hypertension. Duration of therapy was also a significant predictor. Their conclusion

was that echocardiography may indicate the li. lihood of a rapid return to hypertension when drug therapy is ceased.

Lernfelt *et al* conducted a small study (n = 32) on casual blood pressure, blood pressure during isometric exercise, and left ventricular morphology and function on the recurrence of hypertension after cessation of drug therapy [42]. The subjects were aged 70-years, had a blood pressure of less than 175/95 mmHg and had no overt cardiovascular disease. Treatment was withdrawn in 25 of the 32 subjects who were then followed over two years. A significant increase in mean systolic and diastolic blood pressures was observed in the 14 patients who completed the study. No change was observed with respect to left ventricular morphology and left ventricular diastolic function. A statistically significant decrease in left ventricular fractional shortening, but no clinical signs of congestive heart failure were observed.

Mitchell *et al* conducted a longitudinal descriptive study in that it sought to determine the proportion and characteristics of mild hypertensives who remained normotensive after withdrawal from drug treatment that was partially conducted in a university family practice unit [43]. Mitchell's study also included subjects from a large steel company (DOFASCO) in Hamilton, Ontario. One hundred and seven of 125 (86%) eligible hypertensives at the two sites entered the study. One hundred and three (96%) of the subjects completed the study. Subjects discontinued all antihypertensive medication and were followed until blood pressure became elevated by study criteria or for 12 months, whichever was the least. Thirty-eight (37%, 95% CI 27- 46%) subjects remained normotensive at 12 months. Predictors of maintenance of normotension were lower on treatment standing diastolic blood pressure (87.6 versus

91.8 mmHg, 95% CI 2.2-6.2, $p < 0.001$) and longer duration of blood pressure control on medication (12.6 months versus 8.7, 95% CI 0.9-6.9, $p = 0.012$). No predictive relationship was found for maintenance of normotension for age, medication potency, duration of hypertension, weight, lying blood pressure, change in heart rate, or blood pressure during mental or physical stress tests.

Neusy and Lowenstein's study on "blood pressure and blood pressure variability following withdrawal of propranolol and clonidine" had hydrochlorothiazide given throughout successive 4 to 5 week periods of placebo, propranolol, and clonidine administration [44]. Hence antihypertensive medication was never completely stopped.

Perry and Shroeder's pioneering paper published in 1956 looked mainly at the need for continued treatment once therapy had been commenced [45]. They took 114 patients whose diagnosis was firmly established by hospital admission and whose hypertension was controlled on hexamethonium and hydralazine. The subjects were classifed by their pretreatment diastolic blood pressure into 40 mild (diastolic blood pressure 100-114 mmHg), 41 moderate (diastolic blood pressure 115-129 mmHg), and 33 severe (diastolic blood pressure 130-180 mmHg). These levels are by modern standards very high. They were taught home monitoring and were put on a sliding scale of hexamethonium and a physician determined hydralazine regimen. Subjects were considered to be 'controlled' if they had a diastolic blood pressure <100 mmHg on home blood pressure measurements for the fortnight prior to review at one month and one, two and three years post discharge. The authors demonstrated that the lower the pretreatment diastolic blood pressure the more likely that a subject be controlled

and cease medication. However no confidence levels were given. Ten patients over periods from 12-39 months had been able to successfully discontinue their medication though no record was present over which period they were successfully off medication or if there were any relapses.

Schmieder *et al* also examined possible predictors of the recurrence of hypertension in patients who remained normotensive after withdrawal of drug therapy [46]. The subjects were thirty untreated male patients with WHO stage I essential hypertension (mean age 43 +/- 6 years). Baseline characteristics investigated were pretreatment blood pressure at rest, during mental arithmetic and during the cold pressor test (plunging hands into iced water). Each subject was then randomly allocated to oxprenolol or nitrendipine groups. After 6 months of effective monotherapy, all drugs were withdrawn and subjects followed up for 5 months. Two weeks after cessation of therapy 26% had returned to hypertension, after 4 weeks 28%, after 12 weeks 48% and after 21 weeks 74%. Predictors for return to hypertension were age, pretreatment blood pressure, and systolic and diastolic blood pressure increase to the cold pressor test. Analyses of covariance for age and pretreatment blood pressure confirmed that reactivity to the cold pressor test was a predictor of the return of hypertension.

Takata *et al* contrasted the experience of withdrawing non-thiazide diuretics and angiotensin converting enzyme inhibitors in essential hypertensive subjects [47]. One hundred and thirteen subjects with essential hypertension receiving one or more antihypertensive agents were enrolled in the study. Entry level diastolic blood pressure was less than 90 mmHg. In half of the subjects, diuretics (n = 35) or angiotensin- converting enzyme inhibitors (n = 37) were discontinued, and their

remaining drugs were maintained throughout the study. The other subjects (n = 41) continued all their medications. Forty-one percent of subjects remained normotensive for 12 months after withdrawal of diuretics, and 37% of subjects with angiotensin-converting enzyme inhibitors discontinuation remained normotensive. Diuretic withdrawal resulted in an increase in serum potassium and a decrease in serum uric acid and creatinine. Angiotensin converting enzyme inhibitor withdrawal induced a decrease in serum potassium. Withdrawal of either diuretics or angiotensin converting enzyme inhibitors significantly reduced plasma renin activity.

Levinson *et al* in a study involving mild hypertensives who were well controlled on monotherapy (diuretics) found no significant corelation with any of the predictors they investigated [48]. Predictors investigated were pretreatment blood pressure, presence of end organ damage, duration of known hypertension, family history of hypertension, heart rate, body weight, weight gain after stopping hypertension, 24 hour urinary sodium and potassium excretion, serum electrolytes and renin profile.

From the aforementioned studies it can be seen that there have been many observational antihypertensive drug withdrawal studies. However very little of this work has been conducted in a general practice environment where the bulk of mild to moderate hypertension is managed.

Interventional and randomised controlled antihypertensive drug withdrawal studies

Among the historic large scale prospective trials that established the efficacy of the treatment of hypertension was the Veterans Administration Cooperative Study [16,

17]. At the termination of the study a number of patients remained normotensive on treatment and were entered into a subsequent trial studying the return of hypertension after the withdrawal of antihypertensives [49]. Eighty-six subjects who had received treatment with hydrochlorothiazide, reserpine and hydralazine for two years or longer in the Veterens Study and whose diastolic pressures averaged below 96 mmHg for the last year of treatment were enrolled in the subsequent study. Sixty patients were assigned double-blind to placebo and 26 were continued on active drugs. Forty-two of the placebo group of subjects returned to hypertension over the 18 month follow-up period because of return of elevated blood pressures. The majority (39) had done so in the first six months. Six patients in the placebo group and none in the treated group had morbid events. Nine (15%) of the placebo subjects maintained normotension. Predictors of the rate of return to hypertension were higher pretreatment blood pressure and age. Serum uric acid fell significantly while serum potassium rose significantly in the placebo group.

The Dietary Intervention Study of Hypertension (DISH) study utilised subjects who had previously participated in the Hypertension Detection and Follow-up Program. After stratification by weight, subjects were randomized into one of seven groups as shown in Table 2. The main results of the DISH study were published by Langford *et al* [50]. This randomised prospective study looked at dietary modification (sodium restriction 70 mEq/day and potassium 100 mEq/day or weight loss by caloric restriction with little emphasis on exercise) as an intervention to increase the success of withdrawal of antihypertensive drugs. Controls remained on antihypertensive medication. Other predictors of success for withdrawal of antihypertensive drugs investigated were age, weight and previous level of hypertension. Those who

returned to hypertension in the withdrawal of antihypertensive medication group were remedicated. Those overweight subjects randomised to weight reduction lost 4.5 kgs on average. Those who lost more weight were less likely to return to hypertension but this was not statistically significant. Sodium reduction in the sodium restriction group lead to a reduced sodium excretion but again not to a statistically significant level. At 56 weeks post withdrawal the percentage remaining off therapy were over-weight weight reduction group (59.5%), non-overweight sodium-restriction (53.4%), and no intervention (35%).

Ho *et al* examined the relationship of plasma renin activity (PRA) as a predictor of maintaining normotension after withdrawal of antihypertensive drugs [51]. The renin profile is helpful in drug selection in the management of hypertension. Among 496 DISH subjects 75 were randomly selected for PRA measurement at 4 months after intervention. All had their blood pressure under control at that time. Subjects were followed up for 56 weeks after randomization. The endpoint was return to antihypertensive medication due to elevated diastolic blood pressure. Kaplan-Meier survival analysis showed that subjects with PRA less than or equal to 53.3 ng/100 mL/h (the median level) had a lower cumulative success rate for remaining off antihypertensive drug than those with PRA above the median ($p = 0.046$). In Cox regression analysis controlling for 24 hour urinary sodium level, baseline diastolic blood pressure, age, sex, race, obesity, and dietary intervention group, a unit decrease in log PRA was associated with a 2.78-fold increase in risk of returning to drug ($p = 0.006$). This inverse relationship was independent of dietary intervention and change in diastolic blood pressure in the first four months before PRA was measured. The

authors concluded that patients with low PRA are less likely to maintain blood pressure control without drugs than patients with high PRA.

A similar but later study than DISH was TONE (Trial Of Nonpharmacological interventions in the Elderly) [52]. TONE was a randomised controlled trial investigating nonpharmacologic interventions for treatment of hypertension in the elderly. The study population consisted of 875 men and women aged 60 to 80 years with systolic blood pressure lower than 145 mmHg and diastolic blood pressure lower than 85 mmHg while receiving monotherapy.

Obese subjects ($n_1 = 585$) were randomised to reduced sodium intake, weight loss, both, or usual care. Non obese subjects ($n = 390$) were randomised to reduced sodium intake or usual care. After three months of the intervention withdrawal of antihypertensive medication was attempted. Subjects were then followed up for return to hypertension, treatment with antihypertensive medication, or a cardiovascular event. The follow-up period ranged from 15-36 months with a median of 29 months.

Significant results were:

(a) The combined outcome measure was less frequent among those assigned versus not assigned to reduced sodium intake (RR 0.69; 95% CI 0.59-0.81, $p < 0.001$).

(b) In obese subjects, among those assigned versus not assigned to weight loss (relative hazard ratio, 0.70; 95% CI, 0.57-0.87; $p < 0.001$). Relative to usual care, relative risk among the obese subjects were 0.60 (95% CI, 0.45-0.80; $p < 0.001$) for reduced sodium intake alone, 0.64 (95% CI, 0.49-0.85; $p = 0.002$) for weight loss

alone, and 0.47 (95% CI, 0.35-0.64; $p < 0.001$) for reduced sodium intake and weight loss combined.

(c) The frequency of cardiovascular events during follow-up was similar in each of the six treatment groups.

The authors therefore concluded that "reduced sodium intake and weight loss constitute a feasible, effective, and safe nonpharmacologic therapy of hypertension in older persons".

Blom and Sommers conducted a randomised placebo controlled study to investigate 'inappropriate' antihypertensive therapy in elderly patients [53]. Forty subjects were recruited from a hospital outpatient clinic and randomly allocated to either remain on treatment which included methyldopa or placebo. Only two patients in the placebo group required reintroduction of methyldopa tablets.

Grimm and colleagues conducted a study investigating if the use of potassium chloride would reduce the need for antihypertensive drug therapy [54]. To this end they conducted a randomized, placebo-controlled, double-blind clinical trial on 287 men aged 45 to 68 years. Subjects had their antihypertensive medication withdrawn and were then randomised to potassium chloride (142 subjects receiving 96 mmol of microcrystalline potassium chloride per day) or placebo (145 subjects). They were then followed for an average of 2.2 years. Both groups received instructions on following a low sodium diet. Overnight urinary sodium excretion fell from 63 mmol per eight hours at base line to an average of 45 mmol per eight hours during follow-up indicating that subjects were following their dietary advice. Those in the

intervention arm had a significantly higher ($p < 0.001$) serum potassium levels and urinary potassium excretion (averaging 4.5 mmol per liter and 42.5 mmol per eight hours, respectively) during follow-up than those in the placebo arm (4.2 mmol per liter and 20.0 mmol per eight hours). Seventy-nine subjects in each arm required reinstitution of antihypertensive medication according to the protocol criteria and there was also no significant differences in systolic or diastolic blood pressure between the two arms of the study. It was concluded that supplemental potassium chloride did not reduce the need for antihypertensive medication in hypertensive men on a restricted-sodium diet, nor did it increase their success of maintenance of normotension post antihypertensive drug withdrawal.

Morgan and Anderson demonstrated that sodium restriction can delay the return of hypertension in patients previously well-controlled on drug therapy [55]. Their paper demonstrated that 90% of post withdrawal subjects on a normal salt diet returned to hypertension within 6 months, while the rate was only 40% for subjects on a reduced sodium diet. They proposed that "a high sodium intake activates a number of amplifiers that causes a shift of the dose-response curve to sodium to the left and if not prevented or interrupted leads to the development of hypertension".

Walma *et al* investigated if long-term diuretic therapy could be withdrawn in a Dutch general practice setting. Their studies were reported as a pilot (n = 52) [56] and main study (n = 202) [57]. The indication for therapy was not exclusively hypertension. Two hundred and two subjects taking long-term diuretics without manifest heart failure or hypertension were allocated to either placebo or continuation of diuretic treatment. Diuretic therapy was required in 50 patients in the withdrawal group and

13 in the control group (risk difference 36%; 95% CI 22-50%). Heart failure was the most frequent cause of prescribing diuretic therapy (n = 25). A mean increase in systolic blood pressure of 13.5 (9.2 to 17.8) mmHg and in diastolic pressure of 4.6 (1.9 to 7.3) mmHg was noted.

Maland, Lutz and Castle conducted a randomised controlled study looking at previously well-controlled patients on diuretics alone and considered aspects of success of the maintenance of normotension, side-effects and laboratory parameters [58]. This double-blinded placebo-controlled prospective study was conducted on 62 subjects in aged 30 and above (mean 60.3 years) although more than half (37) were aged 60 and above. Subjects were screened (diastolic blood pressure 90-104 mmHg, treated at least 5 years and controlled on diuretic alone for one year) before randomisation into treatment or placebo arm. The treatment arm was the patient's prior diuretic and the control a placebo of their prior diuretic. Twenty-six percent of placebo and 3% of actively treated subjects reached predetermined hypertension criteria at or before 12 months.

The importance of behavioural change in post drug withdrawal successful maintenance of normotension is underlined by the aforementioned studies.

Special aspects of antihypertensive drug withdrawal

Ambulatory blood pressure monitoring

Beltman *et al* tested whether ambulatory blood pressure monitoring would be a superior predictor of return to hypertension than seated clinical measurement [59]. Twenty-nine subjects who were well controlled on medication for one year were

withdrawn from their medication and had ambulatory blood pressure monitoring at 8 weeks post withdrawal. At twelve months all subjects had returned to pretreatment levels of ambulatory and seated diastolic blood pressures.

Myers *et al* discontinued medication in 98 patients without target organ damage who were receiving long term antihypertensive therapy under the care of their family physician [60]. Development of hypertension was defined as an increase in the patient's ambulatory blood pressure to greater than or equal to 160/95 mmHg recorded during usual daily activities. Target organ damage was sought by using echocardiography to measure changes in left ventricular mass during the period off therapy. Fifty subjects remained off treatment at one year. Mean ambulatory blood pressure increased ($p < 0.001$) from baseline 128 +/- 2 mmHg systolic and 76 +/- 1mmHg diastolic, to 139 +/- 1 mmHg and 82 +/- 1 mmHg respectively at 1 year. Ambulatory blood pressure measurements remained lower ($p < 0.001$) than corresponding clinical readings performed by general practitioners. Clinical measurements were 138 +/- 2 mmHg systolic, 83 +/- 1 mmHg diastolic at baseline, and 150 +/- 2 mmHg systolic and 89 +/- 1 mmHg diastolic at one year. At one year, ambulatory blood pressure was <140/90 mmHg in only 21 patients. Withdrawal of therapy did not produce any statistically significant changes in left ventricular mass index with the mean value at one year (104 +/-3 g/m^2) being similar to baseline (103 +/- 3 g/m^2). Of the remaining patients, 35 returned to hypertension and 13 recommenced antihypertensive medication for reasons other than hypertension.

Side effects

An important consideration in withdrawal of antihypertensive drugs for the patient is the reversability of symptoms associated with the treatment of hypertension as the condition itself is considered asymptomatic. Cooper, Glover and Hornbrey looked at this in an opportunistic study during post marketing surveillance for enalapril [61]. The study had 11,710 hypertensive subjects of whom 4500 were newly diagnosed. At initiation of withdrawal of antihypertensive drugs subjects were questioned regarding their symptoms and it was not surprising to find statistically significant differences between treated and untreated groups. Symptoms reflected well recognised side-effects of the various drug groups. For example beta-adrenoreceptor blockers had a significant prevelance of wheezing and fatigue. Two weeks post withdrawal of antihypertensive drugs there was a significant reduction in frequency of most symptoms with the exception of headache. Headache had a significant increase with the exception of previously untreated and those who had received calcium channel blockers. Calcium channel blockers are associated with headaches due to their vasodilation effects. The short follow up (two weeks) and the opposite effect noted in calcium channel blockers suggests that headache is an effect of antihypertensive withdrawal *per se* rather than a marker of return to hypertension.

The authors concluded that *"the burden of symptoms reported by treated hypertensive patients is probably the result of a combination of their disease, drug- related adverse effects and inappropriate use of drugs in certain patient groups"* [61]

Fotherby and Potter investigated the effect of withdrawing or continuing anti-hypertensive therapy on orthostatic blood pressure change in elderly hypertensive

subjects [62]. This is a potential area to benefit from antihypertensive drug withdrawal as postural hypotension is associated with adverse events in the elderly, especially falls. Subjects meeting study criteria for antihypertensive drug withdrawal had supine and standing blood pressure measurements taken on treatment, and at 1, 3, 6, 9 and 12 months post withdrawal. Lifestyle advice to lower blood pressure was also given. Subjects not meeting blood pressure criteria for treatment withdrawal or who were unwilling to stop treatment had blood pressure measurements taken after 6 and 12 months whilst also receiving non-pharmacological advice. Orthostatic hypotension was defined as a mean systolic blood pressure fall equal to or greater than 20 mmHg on standing from a supine position. Forty-seven subjects (median age 76 years, range 65-84 years) had treatment withdrawn. Thirteen subjects (median age 73 years, range 68-82 years) continued on their drug treatment. Twelve months after treatment withdrawal there was a significant reduction in the number demonstrating orthostatic hypotension from eleven (23%) to four (11%) ($p < 0.05$), whilst the group continuing on treatment showed no change. In the withdrawal group those with orthostatic hypotension on treatment ($n = 11$) were older (79 versus 74 years, not significant), had higher on treatment systolic blood pressure (164 +/- 21 mmHg versus 147 +/- 17 mmHg, $p = 0.02$) compared to those without, although there was no difference in body mass index, gender, number or type of anti-hypertensive drugs taken. The results of this study must be interpreted with caution due to the lack of randomisation, subject self-selection, and the unequal size of the groups.

This group published further work on postural hypotension in the same year [63]. They sought to identify factors associated with postural hypotension in elderly treated hypertensive subjects and to determine the effects of antihypertensive drug

withdrawal on postural hypotension. Eighty-six subjects on antihypertensive drug therapy for over 6 months were enrolled in the study. Only forty-seven subjects underwent repeat blood pressure measurement five weeks after withdrawal of antihypertensive medication. Twenty-six (30%) of the subjects had postural hypotension (defined as previously). Baseline characteristics were similar in the groups with and without postural hypotension. The authors noted a significant correlation between the orthostatic blood pressure fall for all subjects and day-night systolic blood pressure difference ($r = -0.30$, $p = 0.01$) and urinary sodium:creatinine ratio ($r = -0.33$, $p = 0.04$). However multiple regression analysis revealed only the day-night systolic blood pressure difference was a significant predictor. Again they concluded that a trial of antihypertensive drug treatment withdrawal could reduce the risk of potural hypotension.

Fotherby summarised his findings in the journal Drugs and Aging the following year [64]. He suggested that at least 20% of selected older patients with hypertension can remain normotensive without drug treatment for periods of up to 5 years. As will be seen in the following chapters this is a frequently quoted figure but is likely to be conservative if the selection process is based on predictors identified in other studies. He reported that predictors of success of drug withdrawal is (lower) on-treatment blood pressure, not being overweight and the absence of left ventricular hypertrophy on ECG evidence. As will be seen in the following chapters, the evidence does not support not being overweight as a predictor. It will be demonstrated that it is weight loss post drug withdrawal that is the predictor not the baseline weight *per se*. It will also be shown that those with an adverse waist-hip ratio are more likely to maintain normotension possibly because of their ability to benefit from weight loss. He

acknowledges this as "compliance with lifestyle advice may increase the chance of successful drug withdrawal". His final recommendations for those who may have drug withdrawal are those unhappy with such therapy and who also:

(a) Have well-controlled blood pressure on monotherapy with no sign of target organ damage.

or

(b) Have 'white-coat' hypertension,

or

(c) Are very elderly (> 80 years).

Those in (a) are perhaps the ideal patients for withdrawal of antihypertensive drugs providing there is a gradual reduction in drug dosages and close follow-up to detect a return to hypertension. It has also been shown that white coat hypertension may not be a completely innocuous condition [65-67]. Lastly clinical trials have shown benefit in treating blood pressure up to the age of 84 and it is reasonable to suspect that this benefit would continue into the very old age group [21]. Indeed as age is the single most important risk factor for adverse cardiovascular events the very elderly are most likely to benefit from a reduction in these events.

Ljungman *et al* studied renal function before and after withdrawal of long term antihypertensive treatment in primary hypertension [68]. Glomerular filtration rate (GFR) and renal plasma flow were measured in a random sample of 17 normotensive and 20 untreated patients with primary hypertension. At the 7- year follow-up all 20 were back on medication. GFR was more reduced in the hypertensive (-17%) than in the normotensive group (-9%). The percentage decrease in renal blood flow was the

same in both groups. No significant renal function changes appeared after withdrawal of treatment.

Middeke and colleagues investigated the effect of withdrawal from antihypertensive long-term therapy with beta blockers and diuretics on lipid metabolism [69]. These agents may have adverse effects on lipids and it is important to investigate that these effects are reversible. Serum lipoprotein concentrations were assessed in forty men with essential hypertension at the end of a long-term (5.2 +/- 1.4 years), controlled intervention study (HAPPHY study). Subjects had been treated with hydrochlorothiazide (n = 23) or atenolol (n = 17). After withdrawal from antihypertensive medication, the low density lipoprotein cholesterol decreased by 17 and 12 mg/dl, respectively, in the diuretic and beta blocker groups ($p < 0.05$). Total cholesterol decreased by 16 mg/dl ($p < 0.05$) in the diuretic group. High density lipoprotein cholesterol increased by 8 mg/dl ($p < 0.01$) and triglycerides decreased by 27 mg/dl ($p < 0.05$) in the beta blocker group at the end of the withdrawal period. The authors claimed "for the first time, it was clearly demonstrated that the well-known unfavorable effects of diuretics and beta blockers on lipid metabolism are reversible after cessation of long-term therapy of several years' duration" [69].

Psaty *et al* conducted a population-based, case-control study of risk factors for first events of coronary heart disease in patients with high blood pressure [70]. Their relevant findings to this thesis were that the relative risk of incident coronary heart disease associated with recently stopping the use of beta-adrenoreceptor blockers. Their evidence for cessation of these agents was derived from a health maintenance organization's computerized pharmacy database. They classified subjects who did not

fill their prescriptions regularly enough to be at least 80% compliant as 'stoppers'. All subjects had hypertension treated with medication. The cases were 248 patients who had presented with new coronary heart disease from 1982 through 1984, and the 737 controls were a probability sample of health maintenance organization patients free of coronary heart disease. After adjustment for potential confounding factors, subjects who had recently stopped using beta-adrenoreceptor blockers had a transient fourfold increase in the relative risk of coronary heart disease (relative risk 4.5; 95% CI 1.1 to 18.5). The association was specific to beta-adrenoreceptor blockers but not diuretics. This association, as discussed elsewhere, has biological feasibility (reflex sympathetic stimulation) but should strictly be described as with adherence to drug therapy rather than drug withdrawal.

Review articles

Froom *et al* produced a review article that also contained a survey of 1000 family physicians in New York state of stated practice of withdrawal of antihypertensive drugs [71]. The survey had a response rate of 57% most of whom were male (76.0%), middle years (31-50, 76.8%), board certified (92.9%), and taught medical students or residents (64.9%). These family physicians stated that they sometimes stopped antihypertensive medication in patients (79.1%) who are well controlled and free of side-effects and that they had ceased an average of 5.6 patients during the preceding 6 months. Statistically significant physician characteristics that predicted withdrawal of antihypertensive drugs were being less than 50 years, finishing residency training after 1990, being board certified, and teaching medical students.

A more valid and reliable review of the literature was conducted by Fletcher and colleagues [72]. They investigated predictors of return of high blood pressure after withdrawal. Factors that predicted the return of high blood pressure after withdrawal included high level of pre-treated blood pressure, marked obesity, male gender, short duration of treatment and left ventricular hypertrophy (LVH). They concluded that many subjects would therefore not be suitable candidates for withdrawal of treatment in view of their high blood pressures (both treated and pre-treated), obesity, and also their unwillingness to stop therapy.

Schmieder *et al* also published a review on antihypertensive drug withdrawal [73]. Predictors documented here were young age, normal body weight, low salt intake, low pre-treatment blood pressure, successful therapy with one drug, and only minimal signs of target organ damage. Lifestyle dietary interventions such as a low salt or a weight-loss diet were also reported to extend the period of drug free therapy.

Safety

Alderman and Lamport report that "no studies of drug withdrawal in hypertension have reported any substantial adverse consequences" [74]. If studies have shown for many years that patients can come off their medication safely, why don't physicians withdraw medication? Alderman and Lamport identified three possible areas of concern for drug withdrawal, loss to follow up, a withdrawal syndrome, and an unanticipated loss of a cardioprotective effect.

No difference in loss to follow-up has been demonstrated between continued treatment and withdrawal of antihypertensive medications groups [35]. A withdrawal

syndrome is a concern to a clinician and is defined as a cardiovascular event or symptom due to rapid return to pretreatment blood pressure or beyond (rebound phenomenon) but may also occur without such blood pressure changes. Withdrawal of antihypertensive medication with now infrequently used centrally acting agents such as clonidine and methyldopa has been associated with the rebound phenomenon but little evidence exists for increased risk of cardiovascular events or symptoms in its absence.

However antihypertensive drugs may have effects beyond their antihypertensive action. The HOPE study is the first study to show that this may be so notwithstanding that it had high absolute risk subjects that would not routinely be candidates for antihypertensive drug withdrawal [75].

Hypertension may be considered by practitioners a life long illness that should therefore require life long medication [76]. It must be reinforced that medication is not aimed at the cause of a cardiovascular event but is designed to modify a predisposing risk factor. To this it must be added that "not all hypertensive persons are candidates for for stroke and heart attack", indeed "most..would live a long..life..in the absence of therapeutic intervention" [74]. Ekbom *et al* in a five year prospective observational study of those subjects who withdrew medication to enter the pilot of the STOP-Hypertension study demonstrated a significantly lower death ratio than would be expected from the general Swedish population (19 cases observed versus 30 expected; $p < 0.05$) [77].

Lernfelt *et al* demonstrated no change with respect to left ventricular morphology and left ventricular diastolic function but a statistically significant decrease in left ventricular fractional shortening without clinical signs of congestive heart failure [42]. Franks *et al* however did claim that they had demonstrated an increased mortality relative risk in a retrospective analysis of medical records for prior management of hypertension in patients who had their antihypertensive therapy changed [78]. Difficulties associated with this study were sample size, establishing exactly when medication was withdrawn, and including those with established evidence of cardiovascular disease. Thus it was not 'directed' drug withdrawal, withdrawal of antihypertensive drugs occurred due to side-effects or metabolic abnormalities. Also subjects may still be on drug treatment and it therefore more correctly refers to change of medication rather than withdrawal. There also was no comparison of pre and post withdrawal blood pressures although the authors suggest that for the few where it was available there was no difference. There are also quality of life considerations given that the patients had adverse effects of one group and that an alternative was available.

Outcomes

One study has looked at outcomes for withdrawal of antihypertensive drugs subjects and was associated with the STOP - Hypertension study [77]. This Swedish multicentre observational study had the objective to observe blood pressure, cardiovascular events, and total mortality after withdrawing antihypertensive treatment in patients aged 70-84 years. It had a 5-year follow- up of 333 elderly subjects in the pilot study who had remained normotensive post withdrawal of antihypertensive drugs (mean age 75.2 +/- SD 3.8 years, 68% females). In all, 74 out

of the 333 patients (22%) died during the study period. After withdrawal of the antihypertensive therapy, all patients started in the untreated state and during the 5-year follow-up they could then either remain in the untreated state, or be reverted to blood pressure lowering drug treatment because of hypertension or other diseases, e.g. angina pectoris, oedema, congestive heart failure, etc. The authors found the probability of remaining without treatment for 5 years was approximately 20%. During the state of no drug treatment, patients had a lower total mortality risk than that of the general Swedish population, matched for age and sex. They also had a lower risk of cardiovascular events than those on drug treatment. These results suggest that with frequent check-ups, withdrawal of antihypertensive therapy in the elderly can be tried without increased risk of cardiovascular events.

This group identified low dose monotherapy and relatively low blood pressure before withdrawal as predictors of success of maintenance of normotension. Predictors investigated were, age in years at initiation of therapy, age in years at withdrawal of therapy, duration of treatment, gender, number of pretreatment blood pressure recordings, pretreatment systolic and diastolic blood pressure, monotherapy versus combined therapy, dose level before withdrawal of antihypertensive medication, and pre-withdrawal of antihypertensive medication systolic and diastolic blood pressure.

Rationale for antihypertensive medication withdrawal

Who therefore can have their antihypertension medication withdrawn and what is the rationale for such a strategy? In a review article Fletcher, Franks and Bulpitt suggested that the

"Patients who are likely to remain normotensive are non-overweight women with normal ventricular mass and untreated blood pressures in the mild hypertension range, and with well controlled hypertension, treated for several years." [72]

Fotherby more specifically recommends that the following well controlled elderly hypertensive groups should be considered for drug reduction and withdrawal [64].

(i) Monotherapy > 1 year with no target organ damage and who request it.

(ii) Commenced treatment after only two or three blood pressure recordings.

(iii) Suspected 'white coat hypertension' particularly where hypotensive symptoms are present or other symptoms of drug therapy intolerance.

(iv) Symptomatic orthostatic hypotension.

(v) Where lifestyle changes have been introduced and maintained.

(vi) The very elderly (> 80 years of age) except where there are additional benefits for concomitant conditions (e.g. congestive cardiac failure or angina) or if the patient has no side-effects and is happy to continue.

Dannenberg and Kannell, based on the Framingham Heart Study, suggested the following candidates [79].

(a) Controlled and stable for 6-12 months on multiple antihypertensive medications should be offered 'step down'.

(b) Controlled and stable for 6-12 months on single low dose antihypertensive medication should be considered for cessation provided;

(i) The pre-treatment BP levels were only mildly elevated.

(ii) That substantial behavioural change has been established.

(iii) Withdrawal of antihypertensive drugs patients are to be closely monitored for the duration of their life, receive encouragement to maintain behavioural change and be informed that they are unlikely to remain off their medication permanently.

There are many potential reasons for ceasing antihypertensive medication in selected elderly patients. 'Unmedication' (the reduction of drug dosage and drug cessation) is a common practice for geriatricians to apply to the elderly admitted to hospital or nursing homes under their care [80]. They recognise the problems associated with pharmacotherapy in the elderly such as drug-drug interaction (the elderly are more likely to be on more than one medication) which has the potential to lead to increased side-effects and may potentiate toxicity [64]. The altered physiological responses in the major organs of aged patients may also exacerbate this, e.g. renal impairment, or more potentially harmful concomitant diseases of aging, e.g. renal failure.

Adverse metabolic effects (electrolyte, carbohydrate and lipid) are also more likely to be seen in this age group and again be exacerbated by the above factors. The elderly are also more likely to have problems with compliance to medication with the potential for accidental overdose [81].

The elderly are also over represented in the lower socioeconomic groups and therefore the cost of antihypertensive medication [estimated at 11-104c per day per patient in 1998 on a single agent (see Chapter 5)], medical treatment for the condition and any associated iatrogenic disease has to met by the individual and the general community.

In the cost of antihypertensive medication alone ($447.6 million in 1998 see chapter 5), a 20% reduction would represent a significant cost saving to the community.

Patients may also be on inappropriate therapy. The patient may not currently require antihypertensive drugs because they never had hypertension by recognised diagnostic criteria (inappropriate diagnostic methodology). If general practioners do not follow guidelines they have the potential to initiate inappropriate therapy due to poor blood pressure measurement technique, too few measurements at a single visit, too few measurements over a number of visits at appropriate time gaps, lack of knowledge of diagnostic criteria, or failure to initiate behavioural modification first. Evidence for the unreliability of clinical recordings compounded by variability of the patient's blood pressure [82] or too few clinical recordings (up to 70% of general practitioners diagnose on as few as two or three recordings [83]) and repeat measurement may also lead to resolution of the blood pressure elevation [35].

Elderly patients who were appropriately commenced on antihypertensive medication may also be able to have such medication ceased if they become 'cured' or 'in remission' from their hypertension (treated hypertension). Possible mechanisms include reversal of vessel wall hypertrophy that developed due to the primary disease process (structural-regression) [84], or the resetting of baroreceptors [85]. Blood pressure recordings may also, with time, return to the normal range. Only 48% of the placebo control group of the Australian Therapeutic Trial in Mild Hypertension had a persistent elevated blood pressure for up to three years [86]. In moderate to severe hypertension the results are poorer with rates of 10% or less and the recommendation is that patients require medication for life [87].

The underlying condition may also have been cured in secondary hypertension. For example a patient may have had percutaneous transaortic angioplasty and stenting for renal artery stenosis.

Lifestyle changes may also ameliorate the condition, e.g. loss of weight, commencing regular exercise or dietary change (low sodium, high potassium, reduced alcohol) [52]. Patients may also have ceased other drugs (e.g. prednisolone or non steroidal anti-inflammatory drugs) that elevated blood pressure.

It is also possible that the patient commenced therapy before the recognition of 'white coat hypertension' or may not have this condition recognised in their particular case. Here the circumstances of measuring the blood pressure leads to recordings that are elevated. However recent evidence has suggested that this may not be a benign condition as previously thought [65-67].

Some physicians also are concerned by what they see as confusing messages being sent to the patient regularly reinforcing the need for the patient to take their medication and then telling them to stop it! What is confused here in both the physician's and patient's mind is the difference between non compliance, taking medication irregularly or not at all without the physician's knowledge such that its true efficacy is not known, versus withdrawal, where stopping the medication is part of the management.

In summary selected patients may benefit from withdrawal of antihypertensive drugs but the selection of such individuals would be assisted by the identification of predictors of maintenance of normotension.

As previously outlined current management of hypertension is predicated upon an individuals absolute risk of cardiovascular disease. Dealing with this concept of absolute risk begs the following question. If antihypertensive medication is withdrawn from patients, are they at adverse risk of subsequent cardiovascular events due to their absolute risk profile for risk factors other than hypertension?

The HOPE study was a double-blind placebo controlled, two-by-two factorial randomised clinical trial evaluating the efficacy of ramipril, an ACE-inhibitor, and vitamin E on cardiovascular events in subjects at high risk of such events [75]. This study has demonstrated that ramipril, when compared to placebo, significantly reduces cardiovascular event rates in a broad range of high-risk patients including those who were in the currently accepted normotensive range. The authors attributed only some of the benefit of ramipril to its blood pressure lowering properties as the majority did not have hypertension at baseline and the mean reduction in blood pressure was only 3/2 mmHg. It was estimated that only 40% of the reduction in strokes and 25% of the reduction in myocardial infarctions was due to this small blood pressure reduction. This reinforces that hypertension is arbitrary and that factors other than blood pressure need to be considered when antihypertensive drug withdrawal is considered as a therapeutic option.

Current recommendations on withdrawal of antihypertensive drugs

A meta-analysis of hypertension treatment trials estimated a 5-6 mmHg reduction in diastolic blood pressure was shown to produce a 14% reduction in CHD risk and a 42% reduction in stroke risk [14]. Because of these benefits approximately ten percent of adults in Western countries are receiving long-term treatment with antihypertensive drugs [88]. However, as outlined in the previous section, a proportion of these may be receiving treatment inappropriately either because therapy was commenced without appropriate justification or because their hypertension has resolved. Once treatment is commenced, physicians are often reluctant to withdraw therapy because of the difficulty in distinguishing between those who need and those who do not need continued treatment.

Unnecessary drug treatment is costly to society and to individuals, and places subjects at risk of the adverse effects of drug treatment. However drug withdrawal may also be a concern because of issues such as drug withdrawal effects and possible legal liability if cardiovascular events occur during or shortly after ceasing therapy.

The current recommendation for withdrawal of antihypertensive drugs in Australia is contained in 'The management of hypertension: a consensus statement' and is;

> *"...studies suggest that only a small number of patients with well controlled blood pressure can withdraw from drug therapy and maintain normal blood pressure for extended periods. Patients most likely to benefit are those prepared to make the appropriate lifestyle changes with regard to weight*

control, increased physical activity and reduction of alcohol and salt intake". [9].

Such a statement recognises the importance of behaviour modifying interventions and reinforces the need to identify predictors to improve outcomes following withdrawal of antihypertensive drugs.

The more recent Australian guidelines contain no statement on withdrawal of antihypertensive drugs [8]. Likewise the British Hypertension Society guidelines make no specific recommendation on drug withdrawal stating only that "treatment can be stepped down later if the blood pressure falls substantially below the optimal level" [11].

The World Health Organisation and International Society of Hypertension (WHO/ISH) do not support drug withdrawal but rather drug dose and number reduction. Their 1999 guidelines state:

"Cessation of therapy in patients who have been correctly diagnosed as hypertensives .... is usually followed, sooner or later, by the return of the blood pressure to pretreatment levels. Nevertheless, after prolonged blood pressure control it may be possible to attempt a careful progressive reduction in the dose or number of drugs used, especially in patients strictly observing non-drug treatment" [5].

In the US the sixth report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure states that:

"An effort to decrease the dosage and number of antihypertensive drugs should be considered after hypertension has been controlled effectively for at least 1 year. The reduction should be made in a deliberate, slow, and progressive manner. Step-down therapy is more often successful in patients who also are making lifestyle modifications. Patients whose drugs have been discontinued should have scheduled follow-up visits because blood pressure usually rises again to hypertensive levels, sometimes months or years after discontinuance, especially in the absence of sustained improvements in lifestyle." [10].

These recommendations are summarised in Table 1.3.

	Australian consensus guidelines [8]	JNC VI [9].	BHS [10]	WHO/ISH [4]
Dosage reduction	NS	✓	✓	✓
Reduction in number of agents	NS	✓	✓	✓
WAD + behavioural change	✓	✓	NS	×
WAD	✓	✓	NS	×

Table 1.3 Current recommendations of national and international expert committees on withdrawal of antihypertensive drugs. Key; ✓ = recommended, × = not recommended, NS = not stated.

Withdrawal of antihypertensive drugs in the general practice environment

Mild to moderate hypertension is now largely managed in general practice with referral often only occurring for secondary hypertension and refractory cases [89]. The general practice environment is quite different from the clinical practice

environment of specialist centres where these initial withdrawal trials were conducted. There are issues in this environment of recommended diagnostic criteria versus actual practice (criteria of commencement of therapy) and the variability of blood pressure leading to the possibility of inappropriate therapy.

The medico-legal aspects of a patient having a cardiovascular event after the cessation of such drugs, whether appropriate or inappropriate, may temper any concern general practitioners may have regarding unnecessary medication. Given these circumstances how can a general practitioner identify who may be able to have their medication safely ceased? The development of 'desk-top' predictors, i.e. data that is simply obtained from the general practitioner held medical record or routine practice pathology testing, may help the general practitioner to identify such patients. Once identified these patients, under close supervision, may have their medication ceased with the greatest chance of success. As will be seen in Chapter 2 this success can be further enhanced by the instigation of non-drug measures such as salt restriction, weight loss and exercise regimens.

Thesis aims and questions

This thesis centres on the issue of withdrawal of antihypertensive drug therapy and management of hypertension in the elderly in the general practice environment. Primarily a cohort study was conducted entirely in the Victorian general practice setting on subjects of either sex who were 65-84 years of age who were receiving antihypertensive drugs at the time of identification. Subjects who met inclusion and exclusion criteria and who had this medication ceased entered the study after remaining normotensive at 2 weeks post-withdrawal. Subjects were classified at 12

months according to whether they remained normotensive off all antihypertensive medication or had returned to antihypertensive medication for hypertension by study criteria. Baseline subject characteristics were then compared between these groups to identify which predicted who remained normotensive off all antihypertensive medication for the specified twelve months. These characteristics were also subject to a survival analysis for those who returned to medication to identify which predicted time to return to hypertension. This study has attempted to take the step from the repeated measurement over thirty years of typical success rates of 20% of maintenance of normotension post antihypertensive drug withdrawal and give the general practitioner a practical guide for implemention of these findings by providing 'predictors of success' that are available in the general practice setting.

In Chapter 2 the aim is to identify subject characteristics reported in the literature that predict maintenance of normotension for a period of 12 months after all antihypertensive drugs have been withdrawn.

The aim of Chapter 3 is to identify subject characteristics in a large comparative outcome study that predict successful withdrawal of medication and thereafter maintenance of normotension for a period of 2-18 visits. This is essential to do, as it investigates antihypertensive drug withdrawal prior to the entry point into the study reported in Chapter 4.

Chapter 4 as outlined previously, aims to identify subject baseline characteristics that are predictors of maintenance of normotension at 12 months, and time to return to hypertension in an elderly hypertensive general practice based cohort. An additional

aim is to compare major cardiovascular outcomes and death of those who maintain normotension for a twelve month period with those who returned to hypertension.

In Chapter 5 the aim is to examine trends in the use of the major antihypertensive drug groups and to determine the cost implications resulting from these trends.
In Chapter 6 the aim is to investigate the approach taken by general practitioners to the use of various antihypertensive drugs as monotherapy for mild to moderate hypertension. It is hoped to identify reasons used by doctors for choosing one antihypertensive drug rather than another and to examine the characteristics of doctors associated with particular prescribing patterns.

The following approach seeks to achieve these aims and answer the following questions.

i. Chapter 1. This chapter contains the justification for the thesis.

ii. Chapter 2. This chapter contains a systematic review of the literature pertaining to the central research question, 'which subject characteristics predict who remains normotensive when antihypertensive drugs are ceased?'

iii. Chapter 3. This chapter contains an analysis of all subjects in the Second Australian National Blood Pressure Study (ANBP2) who were offered drug withdrawal as part of the run in phase of this study (n = 25,867). ANBP2 is a comparative outcome study of a diuretic and ACE-inhibitor based regimen in the management of hypertension in the elderly being conducted entirely in

Australian general practice. It is being conducted by the High Blood Pressure Research Council of Australia and is jointly funded by the federal government and the pharmaceutical industry [90, 91].

This analysis is considered first as it was the observation of failure of a significant minority (approximately 18%) of the subjects who had antihypertensive drugs withdrawn to return to hypertension to enable them to be randomised into ANBP2 that generated the main research question. This analysis also has important methodological implications for 'WAD in ANBP2' as it examines the experience of the subjects from identification as on antihypertensive drugs till at least two weeks post withdrawal of all antihypertensive drugs which is the entry point of 'WAD in ANBP2'. It aims to answer the question 'which characteristics of an elderly general practice sample predict who may have their antihypertensive medication successfully withdrawn and remain normotensive in the short-term?'

iv. Chapter 4. This chapter investigates predictors of maintenance of normotension at 12 months post withdrawal of antihypertensive medication in the elderly in this clinical setting. It also investigates which baseline characteristics predict the time to return to hypertension in those that do so in this time period.

v. Chapter 5. A number of auxiliary questions were raised by 'WAD in ANBP2' and Chapter 5 will consider the first of these. If a significant number of general practice patients can have their antihypertensive medications stopped what are the economic implications of this and what might be the explanation for this success? This was approached from a public health perspective with a cost

minimisation analysis of pharmacological management of hypertension and its implications for Federal Government pharmaceutical schemes. A comparison was made between current guideline recommendations and current practice of the initiation of antihypertensive medication in uncomplicated mild to moderate hypertension. As previously outlined failure to follow guidelines may influence success rates of withdrawal of antihypertensive medication.

vi. Chapter 6. The success of withdrawal of antihypertensive drugs has a number of possible explanations that will be considered in the body of this thesis. This and the cost implications of the analysis in Chapter 5 raises the questions, 'how do general practitioners decide when to initiate drug therapy for hypertension and what influences their decision making in choice of agent?'

This chapter is a cross-sectional survey of Victorian general practioners' knowledge, attitude and stated practice of the management of mild-moderate uncomplicated hypertension. It investigates why general practioner management differs from guideline recommendations and how this may have implications for the inappropriate initiation of therapy and hence withdrawal of antihypertensive drug success rates.

vii. Chapter 7 The final chapter includes a general discussion of issues raised by the literature review, what has been addressed by the studies and what remains to be answered. It will be argued that a meta-analysis of withdrawal of antihypertensive drugs studies is required to establish beyond surrogate

measures the safety of withdrawal of antihypertensive drugs as this is of concern to clinicians.

In summary investigating withdrawal of antihypertensive drugs in a general practice environment ensures:

1. Appropriate treatment. Only those who require continued medication get it.
2. Quality of life (pharmacotherapy). Those who no longer need medication avoid its complications.
3. Health economics in an aging society. Cost saving in medication and the treatment of iatrogenic disease.

Chapter 2

A systematic review of subject baseline characteristics as predictors of maintenance of normotension after withdrawal of antihypertensive drugs.

Introduction

Approximately ten percent of adults in Western countries are receiving long-term treatment with antihypertensive drugs [1]. A proportion of these patients may be receiving treatment inappropriately, either because pharmacological therapy was commenced without appropriate justification or because their hypertension has resolved with lifestyle change. Once treatment is commenced doctors are often reluctant to withdraw therapy because of the difficulty in distinguishing between those who need and those who do not need continued treatment.

Unnecessary drug treatment is costly to society and to individuals, and places subjects at risk of the adverse effects of drug treatment. However, drug withdrawal may also be a concern because of issues such as drug withdrawal effects and possible legal liability should cardiovascular events occur during or shortly after cessation of therapy.

The following is a systematic review of published studies on withdrawal of antihypertensive drugs. The main aim of this review is to identify consistent predictors of successful cessation of therapy through an analysis of subject baseline

characteristics and study criteria. A secondary aim is to present the information as an algorithm that might be of value to general practitioners.

Method

Articles examining withdrawal of antihypertensive drug therapy were identified from Medline using various topic-related key words. Additional papers were identified from the bibliographies of these publications.

Each article was analyzed and key data concerning study design, definitions of hypertension and normotension and baseline predictors were extracted. The criteria used for normotension varied amongst the individual studies. Successful withdrawal was therefore defined as the maintenance of blood pressure levels below those where recommencement of drug treatment was advised twelve months after cessation of therapy. Studies with follow up periods less than 12 months, and those where the blood pressure levels requiring recommencement of therapy were not specified, were therefore excluded. Studies with very long follow-up periods were also excluded if it was not possible to estimate a 12-month success rate from the data provided by the authors.

The monthly hazard (risk) of returning to hypertension was produced by computing the risk within each reported time interval and averaging over the interval time span. Summary relative risks on the likelihood of requiring recommencement of therapy were determined using the DerSimonian and Laird random effects model, together with tests for heterogenity of effects across the studies [2]. These described the

effects of gender, body weight reduction post withdrawal of antihypertensive drugs, and sodium reduction post withdrawal of antihypertensive drugs. As little heterogeneity was demonstrated the summary relative risks reduce to those obtained from a fixed effect model.

Results

Forty-one studies were identified, the majority of which described observational studies or patients withdrawn from drug therapy during the run in phase of a clinical trial [3-45]. Seven studies were excluded because of a follow up period of less than 12 months [14][17][20][32-34][37], nine because of the absence of any estimate of success at 12 months [4][9][10][13][15][28][35][40][43], five because of the absence of criteria related to the recommencement of therapy [3][5][11][18][20], and eight because baseline characteristics provided could not be linked to an estimate of success at 12 months [12][14][16][21][23][31][41][45]. The remaining twelve studies were considered to represent the pivotal studies and are summarized in Table 2.1 (overleaf) [3][6-8][19][22][24-27][36][38][39][42][44].

Table 2.2 (page 55) shows that the most consistent predictors identified amongst these studies were blood pressure (lower pretreatment, on treatment and post withdrawal), pharmacotherapy (fewer agents and lower dose) and dietary intervention (weight and sodium reduction). In most of the individual studies, information about potential predictors of return to hypertension was not provided in a form that allowed a summary measure of effect to be determinined. Most commonly the characteristics of those with normotension were compared to those with recurrent hypertension at 12

Study	Study type and sample population	N (N WAD)	Pre-treatment DBP (mmHg)	Duration of treatment (years)	DBP at withdrawal (mmHg)	Recommence therapy BP level (mmHg) DBP	SBP	% (n) normotensive at 12 months
Alderman et al [3]	Observational. Unselected union members (mean age 55.7).	157 (88)	≥95 on 2 visits	≥ 0.5	<85 (<65y) <90 (≥65y)	1 visit ≥110 2 visits ≥95 ≥95	≥200 ≥160(<65) ≥165 (≥65)	28% (44)
DISH [6-8]	Multi-center RCT in 30-69 yo with dietary intervention (Na/K or wt reduction)	496 (415)	1st visit ≥95 2nd visit ≥90	≥5	<95 SBP <180	1 visit ≥105 2 visits ≥100 3 visits ≥95		Placebo 35% Wt loss 60% Salt restrict 52%
Grimm et al [19]	RCT, placebo-controlled with double blinding. Males aged 45-68 given KCl or placebo post WAD plus low sodium diet.	(287 - 145 placebo)	NP	≥3.5	<90	1 visit ≥115 2 visits ≥95 3 visits ≥90		56% (160) 57% (81) KCl 54% (79) Placebo
Levinson et al [22]	Observational placebo controlled: mild controlled on diuretics alone. No age given.	(24)	90-109	≥1	≤90	1 visit >114 2 visits >99 3 visits >94 6 month av >90		21% (5)
Medical Research Council [24]	Randomised controlled study on 35-64 year olds at entry.	2765 (783)	90-109	6	<90	> 90		Diuretic M 44% F 54% β-blocker M 47% F 28%
Mitchell et al [25]	Longitudinal descriptive study of 30-70 yo in a family practice and a work site.	125 (107)	NP	10.5 (average)	NP	>90		37% (38)
Morgan et al [26]	Placebo controlled randomized double blind trial on 60-79 years with dietary advice intervention.	(102)	>100	≥ 2	<90	2 visits >90		10%

Study	Study type and sample population	N (N WAD)	Pre-treatment DBP (mmHg)	Duration of treatment (years)	DBP at withdrawal (mmHg)	Recommence therapy BP level (mmHg) DBP	SBP	% (n) normotensive at 12 months
Myers et al [27]	Observational study of 21-80 year olds of subjects from family practice with ABPM*, family physician and nurse measurements.	246 (98)	NP	NP	<160/95*	≥160/95*		51% (50)
Stamler et al [36]	RCT with nutritional intervention. Age group NP.	189 (141)	>90	5	<90	1 visit >105 2 visits >99		Group 1 44% Group 2 15%
Takata et al [38]	Randomized comparison study 36-81 years old.	113 (72)	≥90	NP	<90	1 visit ≥105 2 visits >95		Diuretic 41% (12), ACEI 37% (11)
Thurm and Smith [39]	Observational: mild-moderate 20-65 year old hypertensives.	(69)	≥90	NP	<90	≥90		23% (16)
TONE [42][44]	RCT of 60-80 yo in 4 academic health centers.	(975)	NP	NP	< 85 on 1 drug (SBP <145)	1 visit ≥110 2 visits ≥100 3 visits ≥90	≥190 ≥170 ≥150	34% (Na ⇓) 37% (wt loss) 44% (both) 16% (control)

Table 2.1. Pivotal study design, sample population characteristics, criteria and success rates for maintenance of normotension post withdrawal of antihypertensive drugs (WAD) where predictors of success were investigated. NP = not provided. RCT = randomized controlled trial

Study	[38]	[39]	[6-8]	[36]	[3]	[24]	[22]	[26]	[25]	[19]	[42]
Blood pressure:											
Pre treatment level	-	↓	↓	+			-				
On treatment	-		-			+[1]			↓[2]		↓[3]
1 month post WAD	↓				↓						
Therapy:											
Duration	-	-					-		↑		↓
Type	-					+			-		-
Monotherapy			+	+							
Dose level				+					-		
Subject:											
Age at WAD	-		-			+[4]			-		-
Sex	-		-			-			-		
Race			-								-
Family history							-				
Body weight											
at WAD			-				-		-		-
after WAD			↓	↓			-				↓
Smoking			-								-
Alcohol				+							-
Vascular disease											+
Family history	-						-				
Exercise											-[8]
Organs:											
Heart											
LV mass	-							-			
Heart rate							-		-		
ECG				-							
Heart rate									-		
Kidneys											
Electrolytes							-				
Renin profile	-		↑				-				
Na/K excretion							-				
Proteinuria	-										
Interventions:											
Diet			↓	+[5]				-[6]			↓[7]
K supplements									-	-	
Stress tests									-		

Table 2.2. Pivotal studies that tested predictors of success. Statistically significant association: + = direction not specified or not relevant, ↓/↑ = direction of effect that predicted maintenance of normotension post WAD. No statistically significant association = -. (1) mea only, (2) standing DBP plus longer duration of normotension on drugs but not lying BP, (3) SBP only, (4) propanolol treated, (5) alcohol, weight and sodium reduction, (6) for increased potassium and decreased sodium, (7) Na reduction, (8) baseline.

months without individual data provided. The exceptions were for gender and those studies where an intervention was introduced.

Predictor	Study	Proportion*		RR	CI	p-value	Heterogeneity p-value
Sex	[4] [24-26][38] [39]	Male	280/595	0.96	0.85 – 1.08	0.51	0.54
		Female	266/513				
Body weight post WAD	[7][36][42]	Weight loss	274/475	1.31	1.16 – 1.48	<0.001	0.97
		No weight loss	291/66[illegible]				
Sodium restriction post WAD	[7][26][42]	Yes	353/699	1.30	1.17 – 1.45	<0.001	0.71
		No	329/857				

*Proportion with predictor who remained normotensive at 12 months post withdrawal of antihypertensive drug(s).

Table 2.3. A meta analyses of baseline characteristics as predictors of subjects who had antihypertensive drugs withdrawn and maintained normotension off medication at 12 months.

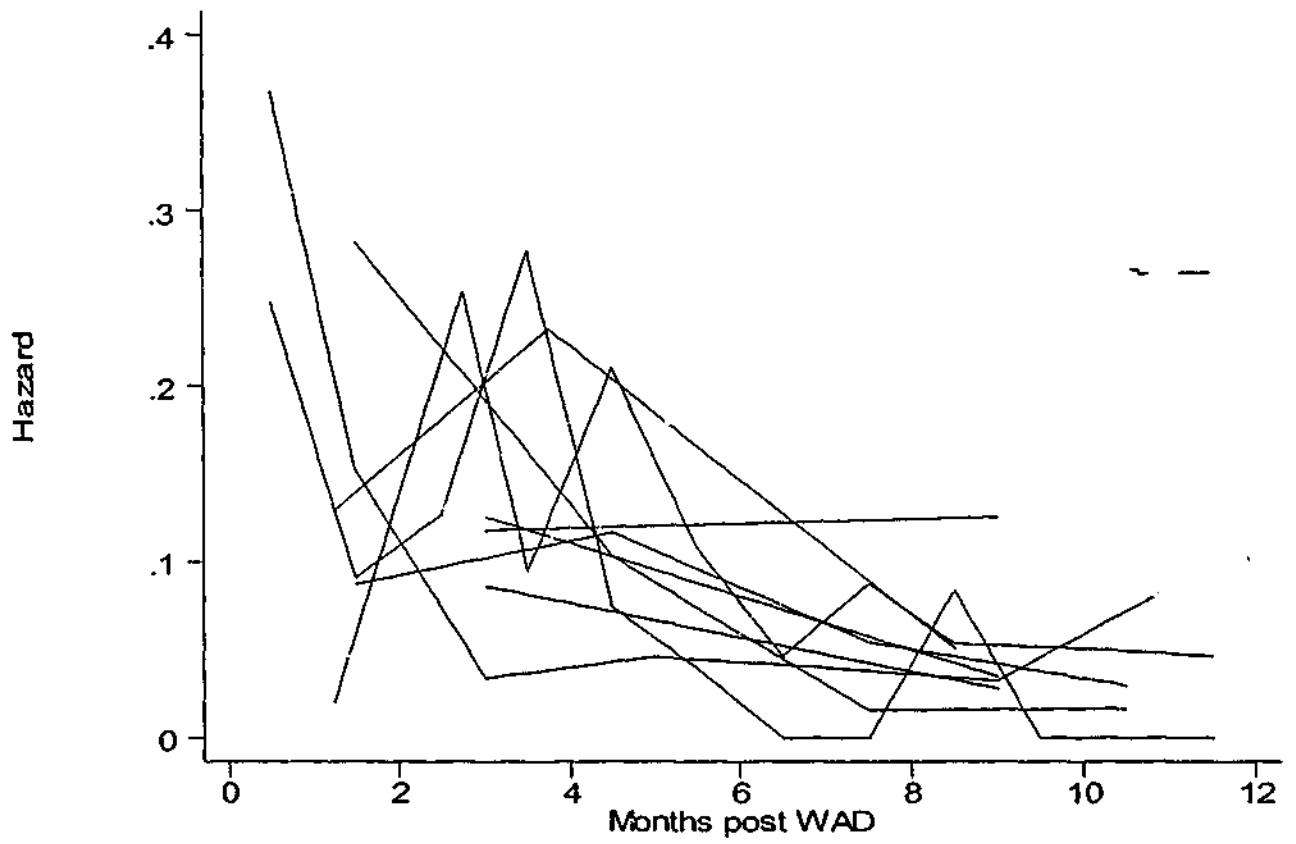


Figure 2.1. A multiple linear plot for studies with data of the 'natural history', i.e. without a lifestyle intervention or placebo, of withdrawal of antihypertensive drugs and subsequent risk of return to hypertension over 12 months (n = 9) [7][12][16][21][22][25][36][38][42]. The monthly hazard of returning to hypertension was produced by computing the risk within each reported time interval and averaging over the interval time span.

A simple meta-analysis for these characteristics is shown in Table 2.3. Weight reduction and salt restriction post WAD were both statistically significant predictors of maintenance of normotension. Gender was not a predictor.

Figure 2.1 shows the risk of patients returning to hypertension at varying times after drug withdrawal among groups not receiving lifestyle intervention. It shows that the risk of return to hypertension is greatest in the first six months. However the risk continues after this time. Similar results to the above can be found when one includes all studies (Table 1 appendix) where data is available in the analyses (Figure 2.2).

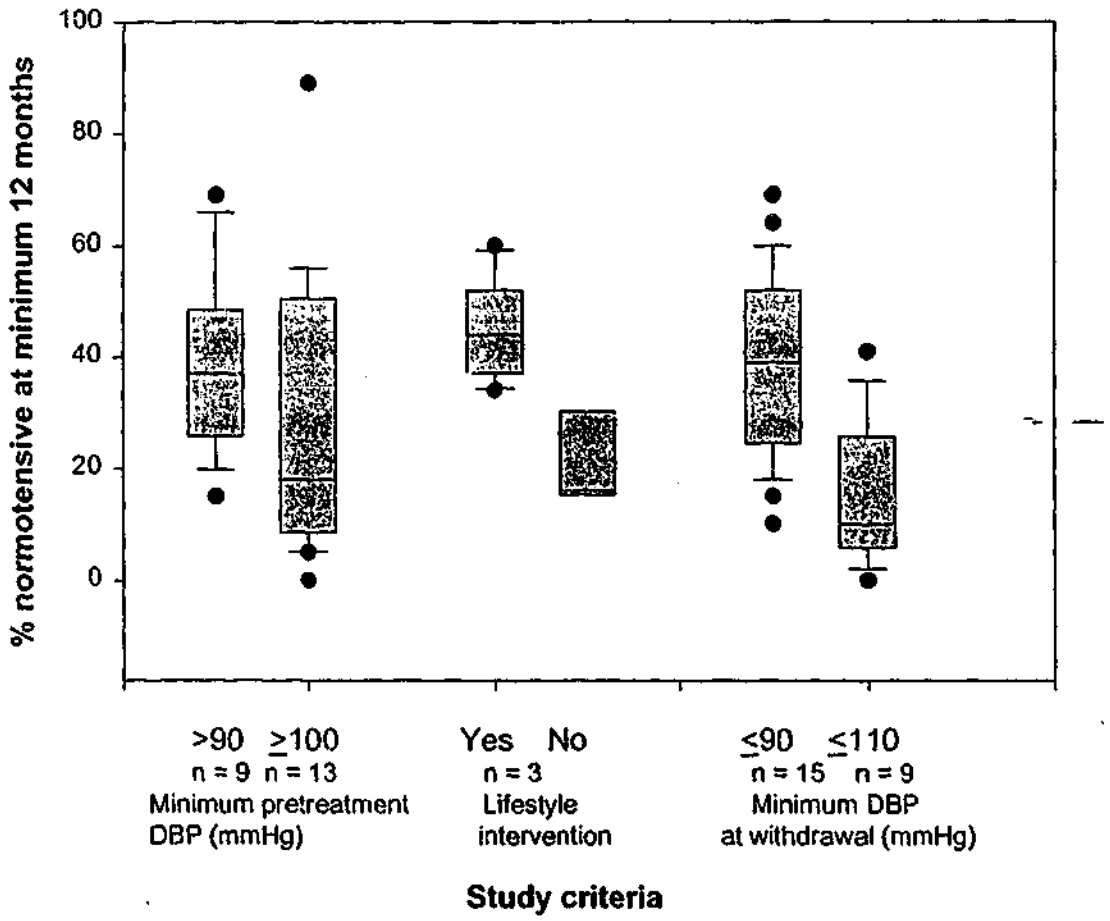


Figure 2.2. Comparisons of withdrawal of antihypertensive drugs study criteria and successful maintenance of normotension for 12 months or longer after withdrawal. Minimum pretreatment DBP is the recording made prior to the initiation of drug therapy. Lifestyle interventions were dietary advice, weight reduction and salt restriction. Minimum DBP at WAD is the recording made prior to cessation of antihypertensive medications.

Discussion

In the pivotal studies reviewed the most consistent predictors of successful antihypertensive drug withdrawal were relatively low levels of blood pressure, both before treatment was commenced and during therapy with a single drug. Adoption of lifestyle changes such as reduced body weight and reduced sodium intake after withdrawal were also useful predictors.

In a meta analysis reduced body weight and sodium restriction were also confirmed to be statistically significant predictors. These findings imply that a trial of drug withdrawal is most likely to be successful in patients with one or more of these characteristics especially if the latter lifestyle changes are adopted.

These conclusions are based on a review of information from 12 studies shown in Table 2.1. Most of these studies involved withdrawal of previous drug therapy as a prelude to participation in a clinical trial. The cohorts were then observed and the characteristics of those in whom hypertension recurred were compared with those in whom it remained low.

There are several limitations of the data from which the predictors are observed. The participants involved were not necessarily representative of hypertensive patients in general and the predictors examined varied from study to study and were not defined in a consistent fashion.

All studies however had at least 12 months of follow-up. In the absence of lifestyle interventions, success rates averaged approximately 42% over all studies with follow

up periods of this duration. With a single exception (Fagerberg *et al)*, the studies with follow-up periods between 2 and 5 years show similar rates of maintenance of normotension to those where the follow-up period was limited to twelve months [3][12][13][16][24][36][42][44]. The available information suggests that the rate of recurrence slows after six months (Figure 2.1).

Many studies have noted that several weeks or months commonly elapse between the cessation of drug treatment and the return of blood pressure to higher levels. This is believed to result from a reduction in hypertrophy in smaller arteries during treatment that reverses the elevated peripheral resistance [20]. A considerable period may elapse before such hypertrophy redevelops. This illustrates the need to institute long term monitoring of the blood pressure of patients withdrawn from antihypertensive therapy with the aim of detecting a return of hypertension. As seen in Figure 2.1 such monitoring needs to be most diligent in the first 6 months after withdrawal.

It may be that the majority of patients for whom drug withdrawal is appropriate are those whose therapy was commenced inappropriately. To avoid unnecessary drug therapy various national authorities have emphasized the importance of confirming the diagnosis repeatedly before starting treatment. For example the US Joint National Committee on the Detection, Evaluation and Treatment of High Blood Pressure has recommended that the decision to treat mild to moderate blood pressure elevation should be based on the results of at least two blood pressure readings on at least three separate occasions [46].

The importance of these recommendations was emphasized by the results of the Australian Therapeutic Trial in Mild Hypertension [47]. Despite entry criteria that required a mean diastolic blood pressure (from four recordings over two visits) in the range 95-110 mmHg, 48 percent of those randomized to placebo still fell below this level during the three years of follow-up.

The subsequent availability of 24-hour blood pressure monitoring has also revealed the presence of 'white coat' hypertension where blood pressure that becomes elevated during the stress of a medical encounter returns to normal levels at other times.

The percentage of patients who are correctly commenced on therapy but who subsequently become normotensive is likely to be much smaller than the percentage whose therapy was inappropriately commenced. However, it was notable in this review that adoption of appropriate lifestyle changes was identified as a consistent predictor of successful drug withdrawal. This is in keeping with the results of several major trials which have shown that a reduction in body weight, reduced salt and alcohol intake and an increase in physical activity may be sufficient to reduce marginal blood pressure elevations to normotensive levels [6][7][36][42]. Since long-term compliance with such interventions is low, continued monitoring of blood pressure is appropriate in these patients.

Few studies commented on the adverse effects of drug withdrawal, particularly rebound hypertension, that may accompany the sudden cessation of clonidine or the rebound hypersensitivity to adrenergic stimuli that accompanies sudden cessation of beta-adrenoreceptor blockers [48][49]. The latter is well characterized and may be

incorrectly attributed to a recurrence of elevated blood pressure. The symptoms, principally tachycardia in response to mild exertion, may lead to rebound angina and myocardial infarction and should be avoided by a slow and graded withdrawal of treatment. Programs that encourage drug withdrawal in selected patients should emphasize the importance of drug withdrawal symptoms and the strategy to avoid them.

Figure 2.3 presents an algorithm designed to assist primary care physicians. This algorithm is derived from this systematic review and is intended as a guide only. It has not been tested on a clinical population and therefore no formal estimates of success rates are provided. Patients who do not meet all of the criteria may still be suitable for drug withdrawal although success is likely to be lower. The need to continue to attend for regular blood pressure checks should be emphasized to all patients especially in the first 6 months. It is also recommended that behavioral modification is also encouraged as clinical trials have shown that such interventions

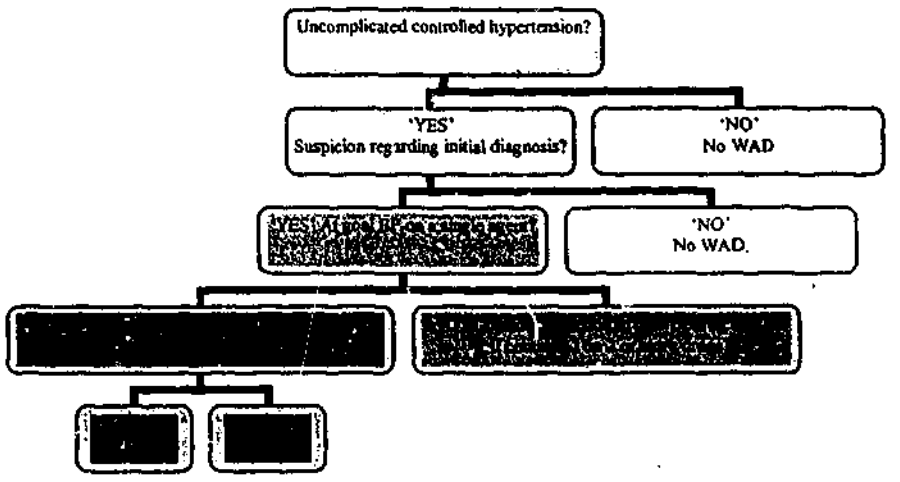


Figure 2.3. Algorithm demonstrating a proposed sequence of decisions for determining which patients should be considered for withdrawal of antihypertensive drugs. Depth of box shading represents increasing likelihood of successful maintenance of long term normotension. As lifestyle changes have been shown to double the rate of maintenance of normotension post withdrawal of antihypertensive drugs they should be offered to all patients in whom drug withdrawal or reduction is being contemplated.

roughly double the rate of successful maintenance of normotension post withdrawal of antihypertensive drugs [6-8][26][42]. Blood pressure measurements should also be taken at least twice on any one visit and at least on two occasions at least one week apart.

The current recommendations by expert committees support periodic reassessment of antihypertensive drug therapy for reduction in dosage and number of drug groups [50] as well as withdrawal of antihypertensive drugs in certain circumstances with adequate follow-up [46][51][52].

Conclusion

If antihypertensive medication is withdrawn from selected patients with mild to moderate hypertension, then approximately 42% of these patients are likely to remain normotensive for periods in excess of 12 months although success rates are likely to be half this where no behavioural intervention is pursued. The studies supporting this have had varying designs, patient populations and even definitions of hypertension. Predictors of success have been identified in a number of these studies and would suggest that the long-term well-controlled, mild hypertensive patient on single agent therapy is an appropriate candidate for a trial of withdrawal of antihypertensive medication, especially if they are willing to undertake lifestyle changes. None of the papers reviewed were Australian and general practice based. The following 2 chapters provide large scale prospective studies conducted that permit the identification of generalisable short and long term predictors of maintenance of normotension post withdrawal of all antihypertensive medication in such an environment.

Chapter 3

Short term predictors of maintenance of 'normotension' post withdrawal of antihypertensive drugs in the Second Australian National Blood Pressure Study (ANBP2).

Introduction

As outlined in the preceding chapters once initiated, antihypertensive drug therapy is most often considered life-long and cessation of therapy in order to determine the continuing need for therapy is rarely considered. Drug cessation may however be a useful strategy in ongoing patient management. It allows the doctor and patient the opportunity to focus on a condition which is predominantly poorly managed and complied with [1]. It also provides the patient with the opportunity to attempt non-pharmacological strategies for blood pressure control with a clear outcome (maintaining drug free status), and in many instances, it may identify for patients the continuing need for drug treatment in light of blood pressure elevation following cessation of therapy.

However, general practitioners, who are predominantly responsible for the management of primary hypertension in the community [2], have little or no experience with drug withdrawal as a patient management strategy for hypertension. Concerns in relation to sudden catastrophic events associated with cessation of therapy are predominantly unfounded [3] and the benefit of antihypertensive drug

therapy beyond that of blood pressure control is unfounded in primary hypertension in terms of improving cardiovascular outcomes.

This study examines the results of withdrawal of antihypertensive drug program conducted as part of the run-in phase of a large general practice based study of hypertension in the elderly [4]. It seeks to identify patient characteristics that may assist the general practitioner in targeting a withdrawal of antihypertensive therapy program as part of a patient management plan for hypertension control in general practice.

Methods

The Second Australian National Blood Pressure Study (ANBP2) was a randomised open label trial comparing two pharmacological strategies on morbidity and mortality outcomes in elderly patients with mild-moderate hypertension conducted entirely in Australian general practice [4]. Withdrawal of existing antihypertensive medication in currently treated patients to establish baseline blood pressure criteria was an entry requirement for the study. Initially all patients identified from practice records as aged 65-84 years and approved by their usual treating general practitioner were invited (by letter from their general practitioner) to attend the practice for a blood pressure screening program. Those attending who were already on pre-existing antihypertensive medication were asked to consider temporary withdrawal of their medication by their general practitioner in order to establish their eligibility for the study.

The general practitioner was provided with recommendations on the process of drug withdrawal. These recommendations included a stepwise withdrawal, i.e. one drug at a time, half doses at weekly intervals to the lowest usual therapeutic dose then cease, and withdrawal of beta-adrenoreceptor blockers or diuretics last if the patient was on more than one medication. For all patients commencing drug withdrawal, the study nurse monitored blood pressure on a weekly basis. If values exceeded 215 mmHg systolic or 115 mmHg diastolic, or a level that the general practitioner considered unacceptable or the patient expressed concern or hesitation, therapy was recommenced.

Hypertension was defined by research nurse recordings. The research nurse criterion was an average untreated (off antihypertensive medications for more than 2 weeks) sitting blood pressure of ≥160 mmHg systolic or ≥90 mmHg diastolic (if systolic blood pressure was > 140 mmHg) taken on the last consecutive visits at least one calender week apart by the following method. Blood pressure was taken in the seated position five minutes after the subject was seated. The upper arm was measured and an appropriate cuff size was chosen such that its bladder width was at least 80% of the circumference of the chosen arm. At least three recordings were made at least one minute apart with systolic Korotkoff phase 1 and diastolic Korotkoff phase 5 sounds recorded to the nearest 2 mmHg. Recordings were repeated until variation between the last two recordings was less than 10 mmHg systolic blood pressure and 6 mmHg diastolic blood pressure and these were then averaged. Nurse recordings showed excellent protocol adherence and little evidence of digit preference. For both systolic and diastolic blood pressure recording observed digit preference fell within 7

percentage points of the expected frequency although there was a slight zero digit preference (observed 22% systolic and 27% diastolic versus expected 20%).

Information was collected at baseline visit on all subjects identified as on antihypertensive medication and included age, gender and on treatment blood pressure. Additional information collected at subsequent visits for those who completed the antihypertensive drug withdrawal program included type and number of antihypertensive agents and post withdrawal blood pressure.

Complete drug withdrawal was defined as a subject ceasing all antihypertensive medication for at least one week. Blood pressure was measured according to a strict protocol by a study nurse [4]. Hypertension was defined as the average untreated sitting blood pressure at two subsequent visits at least one study week apart of ≥160 mmHg systolic or ≥90 mmHg diastolic (if systolic was >140 mmHg). 'normotension' was therefore defined as those subjects who did not meet these criteria. These criteria were also used for investigation of long-term predictors of maintenance of 'normotension' (Chapter 4). These criteria are by now historic as they were established prior to the first patient entering ANBP2 in early 1995. However previous studies suggest that the level of defined hypertension did not alter success of drug withdrawal (Chapter 2).

Final classification of treated subjects asked to consider the drug withdrawal program was as follows:

Group 1: Completed drug withdrawal (off all antihypertensive medication for 1 week) and remained 'normotensive' for at least 2 weeks (until last study nurse visit, range 2-18 visits post withdrawal).

Group 2: Completed drug withdrawal and returned to hypertension.

Group 3: Commenced but failed to complete drug withdrawal.

Data were analysed using SAS statistical software [SAS Version 8.2, (2001), SAS Institute Inc., Cary, NC, USA]. Group descriptive statistics are presented. Predictors of sustained 'normotension' and drug cessation were identified using Cox regression analysis in order to ascertain relative risks. The effect of clustering within doctor was adjusted for by using robust variance estimators. Only a priori predictors that had non-missing data were considered (e.g. gender, age, on treatment systolic and diastolic blood pressure, number antihypertensive agents). Those predictors that showed potential when looked at separately ($p<0.05$) were included in a model to test for independent predictors.

Results

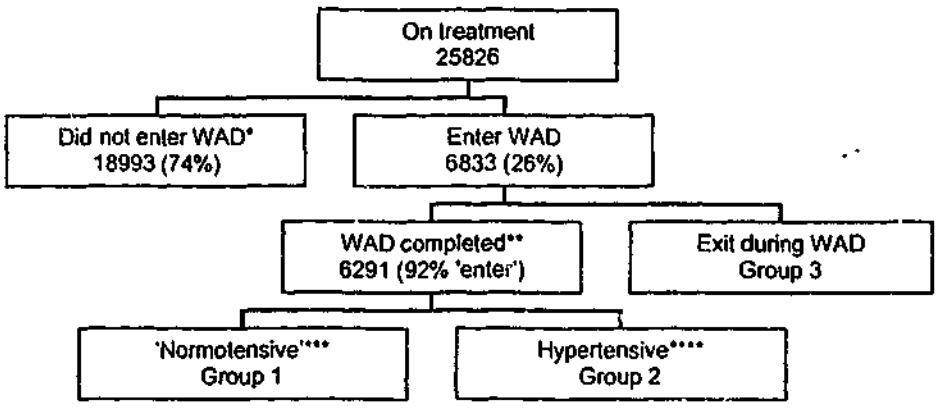
Fifty-four thousand two hundred and eighty-eight subjects attended the screening program of ANBP2, of whom 25,826 were identified as currently taking antihypertensive drugs (Table 3.1 overleaf). In comparison to those that entered the withdrawal program, the 18,933 patients who did not enter were older (mean 73.0 vs. 71.9 years) and more likely to be female (59% vs. 56%). Approximately one in four of these patients (26%) commenced the drug withdrawal program (Figure 3.1 overleaf). Patients not considered suitable for drug withdrawal were predominantly

those with pre-existing cardiovascular complications, difficult to manage patients or patients who on personal reflection or their family physician advice were not willing to consider drug cessation.

Of those subjects entering drug withdrawal, 6291 (92%) completed the program of whom 1229 'maintained normotension' (Group 1), and 5063 'returned to hypertension' (Group 2). Of the 542 subjects who did complete drug withdrawal (Group 3) all bar 59 were able to have their reason documented. The predominant reason for failing to complete drug withdrawal was either the family physician (60%) or the subject withdrawing consent (56%). Subjects could have more than one reason for exiting. Other reasons were withdrawal symptoms (43%), the rapid return to hypertension (25%), cardiac arrhythmia (2%), and cardiac failure (2%).

Characteristic		Entered antihypertensive drug withdrawal (N = 6833)	Did not enter antihypertensive drug withdrawal (N = 18993)
Age			
	Mean (years)	71.9	73.0
	65-69	2523 (36.9%)	5634 (29.7%)
	70-74	2238 (32.8%)	6139 (32.3%)
	75-79	1470 (21.5%)	4713 (24.8%)
	80-84	602 (8.8%)	2507 (13.2%)
Gender			
	M	3005 (44.0%)	7806 (41.1%)
	F	3828 (56.0%)	11187 (58.9%)
On drug therapy blood pressure. Mean (standard deviation) mmH	SBP	146.7 (16.9)	146.7 (19.6)
	DBP	80.6 (9.5)	79.2 (10.4)

Table 3.1. Baseline characteristics of subjects identified at screening as currently taking antihypertensive drugs who did or did not enter withdrawal of antihypertensive drugs (WAD).



*Unwilling to WAD or if willing, exited before withdrawal or failed to attend subsequent visits to initiate withdrawal.
**Off all antihypertensive medications for at least 1 week.
***At last study nurse visit (range 2-76 weeks post withdrawal).
****At last study nurse visit (range 0-108 weeks post withdrawal).

Figure 3.1. Flow chart of classification of subjects in ANBP2 who were offered withdrawal of antihypertensive drugs (WAD).

Characteristics of those subjects entering drug withdrawal are shown in Table 3.2. Cox regression analysis revealed that monotherapy and younger age were the strongest predictors of a subject being able to attempt and complete a drug withdrawal program (Table 3.3). Conversely the use of alpha- or beta-adrenoreceptor blockers predicted failure to complete the drug withdrawal program.

For the 6291 subjects completing the drug withdrawal program, 1228 (20%) subsequently remained 'normotensive' for 2-18 visits (2-76 weeks median 4) off all antihypertensive drugs. The most important factors predicting maintenance of 'normotension' were lower on treatment systolic and diastolic blood pressure and being on a single antihypertensive drug (Table 3.4). Treatment with an ACE-inhibitor predicted failure to maintain 'normotension'. Other predictors are also shown in Table 3.4.

Subjects were monitored during drug withdrawal by the study nurse, their usual treating general practitioner, or both. If they had an adverse event or a significant cardiovascular event during this period they were exited from the study. One hundred and fifty-nine subjects had such events including 7 acute myocardial infarctions (2 fatal), 2 coronary artery therapeutic procedures, and 2 strokes. The longest time for a patient to return to hypertension was 108 weeks. Serious adverse events that caused subjects to exit the program are shown on Table 3.5). It was not possible to establish the serious adverse event rate for all WAD subjects because the date of an event was rarely recorded on exit forms. The end-point rates for the ANBP2 cohort for the first 12 months post randomization were 36.0 events per 1000 person-years (excluding angina, arrythmia and non-vascular deaths) and 67.2 events per 1000 person-years (including angina, arrythmia and non-vascular deaths).

Characteristic			Group 1	Group 2	Group 3	Total
N			1229	5063	542	6834
Age		mean (sd)	71.5 (4.6)	72.0 (4.9)	72.5 (5.2)	
Antihypertensive drug(s)						
Number of agents	N (%)	1	874 (71.2)	2801 (55.4)	116 (21.4)	3791
		2	304 (24.8)	1743 (34.5)	255 (47.1)	2302
		3	41 (3.3)	404 (8.0)	117 (21.6)	562
		≥4	9 (0.7)	110 (2.2)	54 (10.0)	173
Type of agent	ACE inhibitor		372 (30.3)	2028 (40.1)	222 (41.0)	2622
	Calcium channel blocker		356 (29.0)	1722 (34.1)	183 (33.8)	2261
	Diuretic		378 (30.8)	1579 (31.2)	239 (44.1)	2196
	Beta blocker		273 (22.2)	1066 (21.1)	204 (37.6)	1543
	Alpha blocker		29 (2.4)	239 (4.7)	55 (10.2)	323
	Centrally acting		16 (1.3)	118 (2.3)	23 (4.2)	157
	Vasodilator		1 (0.1)	11 (0.2)	3 (0.6)	15
Gender						
		M	480 (39.1)	2311 (45.6)	214 (39.4)	3005
		F	749 (60.9)	2752 (54.4)	328 (60.5)	3829
Blood pressure mmHg on drug therapy		SBP μ (σ)	135.6 (13.3)	149.4 (16.4)	146.8 (18.8)	
		Range	94-179	94-234	101-250	
		DBP μ (σ)	75.4 (7.9)	81.6 (9.3)	80.0 (10.5)	
		Range	52-102	41-122	50-118	

Table 3.2. Characteristics of subjects identified as currently taking antihypertensive drugs who entered drug withdrawal.

	Univariate		Multivariate	
Predictor	**RR (95% CI)**	**p value**	**RR (95% CI)**	**p value**
Age				
65-69	1.05 (1.02-1.08)	0.002	1.05 (1.02-1.08)	0.002
70-74	1.05 (1.02-1.08)	0.003	1.05 (1.02-1.08)	0.003
75-79	1.04 (1.01-1.07)	0.02	1.04 (1.01-1.08)	0.02
80-84	1.00		1.00	
Drug therapy				
Monotherapy	1.13 (1.11-1.15)	<0.0001	1.10 (1.08-1.13)	<0.0001
Multitherapy	1.00		1.00	
On beta-blockers	0.93 (0.91-0.95)	<0.0001	0.95 (0.93-0.97)	<0.0001
Not on beta-blockers	1.00		1.00	
On alpha-blockers	0.90 (0.85-0.94)	<0.0001	0.93 (0.88-0.98)	0.004
Not on alpha-blockers	1.00		1.00	

Table 3.3. Patient characteristics that are independent predictors of being able to undertake and complete withdrawal of all antihypertensive drugs compared with patients who did not complete drug withdrawal. Multivariate analysis adjusting for age, gender, number and type of agent, and locality.

Predictor	RR	Lower CI	Upper CI	p value
Age				
65-69 vs 80-84	1.359	1.108	1.667	0.0033
70-74 vs 80-84	1.324	1.075	1.631	0.0082
Blood pressure (mmHg) on drug therapy				
Systolic<120 vs ≥170	36.171	13.466	97.157	<0.0001
120-139 vs ≥170	26.754	10.103	70.851	<0.0001
140-159 vs ≥170	14.899	5.646	39.314	<0.0001
160-169 vs ≥170	7.736	2.811	21 293	<0.0001
Diastolic<80 vs ≥90	4.152	3.033	5.684	<0.0001
80-89 vs ≥90	2.470	1.802	3 384	<0.0001
Drug therapy				
Monotherapy vs ≥2 drugs	1.971	1.711	2.271	<0.0001
On ACE-inhibitor vs not	0.714	0.643	0.793	<0.0001
On calcium channel blocker vs not	0.814	0.730	0.908	0.0002
On alpha-adrenoreceptor blocker vs not	0.653	0.456	0.937	0.0205

Table 3.4. Subject characteristics that are independent predictors by study criteria of maintenance of 'normotension' post withdrawal of all antihypertensive drugs (group 1 versus group 2).

Serious adverse events N (%)	Group 1 1229 (18.0)	Group 2 5063 (74.1)	Group 3 542 (7.9)	Total 6834
Any SAE	31 (2.5)	76 (1.5)	52 (9.6)	159 (2.3)
Myocardial infarction				
Non fatal	0 (0.0)	3 (0.1)	2 (0.4)	5 (0.1)
Fatal	1 (0.1)	1 (0.0)	0 (0.0)	2 (0.0)
Stroke				
Non fatal	1 (0.1)	1 (0.0)	0 (0.0)	2 (0.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non vascular death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Left ventricular or congestive cardiac failure	7 (0.6)	2 (0.0)	5 (0.9)	14 (0.2)
Coronary artery therapeutic procedures	1 (0.1)	1 (0.0)	0 (0.0)	2 (0.0)
Angina	12 (1.0)	20 (0.4)	11 (2.0)	43 (0.6)
Arrythmia	1 (0.1)	0 (0.0)	2 (0.4)	3 (0.0)
Other cardiovascular events	5 (0.4)	44 (0.9)	30 (5.5)	79 (1.2)
Transient ischaemic attacks	0 (0.0)	1 (0.0)	1 (0.2)	2 (0.0)
Cardiovascular hospitalization	6 (0.5)	11 (0.2)	3 (0.6)	20 (0.3)

Table 3.5. Serious adverse events occurring while in the drug withdrawal program by group classification.

Discussion

The major findings from this study are that in the general practice environment, one in four patients currently treated with antihypertensive drugs were willing and considered suitable by their general practitioner to commence a withdrawal of drug program to confirm the requirement for long-term antihypertensive therapy. In addition, of those that entered the program 18% remained 'normotensive' and drug free for two to seventy-six weeks (median four) following the cessation of therapy. Younger age, monotherapy, lower on treatment systolic and diastolic blood pressure, and type of agent were identified as factors that are readily assessed by the general

practitioner and are predictive of the likely successful outcome of a drug withdrawal program.

Previous studies in the area have identified a variety of factors which predict completed antihypertensive drug withdrawal and maintenance of 'normotension' [5-23]. Most of these studies have been laboratory based and identified factors that require detailed laboratory investigation and results that are not readily available to the general practitioner. However, it is questionable whether all patients on antihypertensive drugs should undergo these investigations for the purpose of identifying suitability of a drug withdrawal program. Also there is no indication as to how often these expensive investigations should be conducted in order to determine any change in the likely assessment of drug withdrawal. This study provides the general practitioner with easily available information that can help direct hypertension management plans for patients.

The proportion of subjects remaining 'normotensive' following treatment withdrawal is similar to that reported in previous studies [24]. It has been shown that structured non-pharmacological strategies to control blood pressure increases the chance of sustained normotension following withdrawal [8][9][14][18][23]. Such strategies were not offered in this study as patients were in the run-in phase of a trial seeking to maximize enrolments by blood pressure criteria.

The short-term duration of this current study only suggests that a drug withdrawal program is possible within a general practice environment with 92% of those entering the program following it to completion. For the 74% who completed and returned to

hypertension, the general practitioner is in the position of clearly identifying to patients the need for antihypertensive therapy for adequate blood pressure control. Further studies on the compliance to antihypertensive therapy in these patients are warranted. For those subjects who remained 'normotensive' at two weeks, long term follow-up has been undertaken in a subset of 503 subjects to determine long-term blood pressure control (Chapter 4).

The reason for the sustained 'normotension' is not clear. It may be related to poor initial diagnosis of hypertension due to inappropriate diagnostic methodology such as too few clinical recordings (up to 70% of general practitioners diagnose on 2 or 3 recordings [25]), or the unreliability of clinical recordings compounded by variability of the patient's blood pressure [26]. The patient may have 'white coat hypertension', where the circumstance of measuring the blood pressure leads to recordings that are elevated. However recent evidence has suggested that this may not be a benign condition as previously thought [27-29] and this is unlikely to be the sole reason for withdrawal of antihypertensive subjects remaining 'normotensive'.

Sustained normotension may also be explained by the effects of long-term drug treatment on vascular and cardiac hypertrophy [30] or the resetting of baroreceptors [7]. Repeat measurement of blood pressure itself may lead to resolution of the blood pressure elevation [12]. Alternatively it may be due to an alteration in the patients' lifestyle habits and behaviour affecting blood pressure since the initial diagnosis as previously reported (Chapter 2).

An important medico-legal aspect of antihypertensive withdrawal in general practice is patient safety and it is likely that general practitioners would have concerns that their patient may have a significant cardiovascular event during or after withdrawal. Alderman and Lamport report that "no studies of drug withdrawal in hypertension have reported any substantial adverse consequences" [3]. They identified three possible areas of concern for drug withdrawal, loss to follow up, a possible 'withdrawal syndrome' or an unanticipated loss of cardioprotective effect. No difference has been demonstrated between continued treatment and withdrawal of antihypertensive medications groups for loss to follow up but this does remain a real concern [12].

A 'withdrawal syndrome' is a cardiovascular event whether blood pressure remains normal, returns to pre-treatment levels or beyond (rebound phenomenon). Withdrawal with now infrequently used centrally acting agents such as clonidine and methyldopa has been associated with the rebound phenomenon. Withdrawal of beta-adrenoreceptor blocking agents is also associated with rebound tachycardia on mild exercise due to increased beta receptor sensitivity [31]. In this study these agents were found to be a negative predictor for success in drug withdrawal. An unanticipated loss of cardioprotective effect remains a theoretical risk for most agents although beta-adrenoreceptor blocking agents have a demonstrated benefit post acute myocardial infarction and therefore withdrawal should not be contemplated in such circumstances.

In this study subjects were monitored during drug withdrawal by the study nurse, their usual treating general practitioner, or both. If they had an adverse event or a

significant cardiovascular event during this period they were exited from the study. The result of such monitoring is presented in Table 3.5 (page 72). One hundred and fifty-nine subjects had such events including 7 acute myocardial infarctions (2 fatal), 2 coronary artery therapeutic procedures, and 2 strokes. Incomplete data meant that comparison of event rates was not possible. The overall events rate for ANBP2 in the first 12 months post randomisation was 67.2 events per 1000 person-years. It was however possible to compare rates in a subset of subjects and this is done in Chapter 4.

Conclusion

A strategy of drug withdrawal as part of patient management for hypertension may provide reinforcement for compliance to therapy in those subjects returning to hypertension and importantly, may provide the opportunity for 20% of the currently treated hypertensive population to avoid the costs and side effects of drug therapy. With sustained normotension, this could be done without increasing cardiovascular risk.

Chapter 4

Predictors of successful 'maintenance of normotension' on withdrawal of antihypertensive drugs in an elderly general practice population. 'WAD in ANBP2', a prospective study conducted in the ANBP2 cohort.

Introduction

ANBP2

The Second Australian Blood Pressure Study (ANBP2) was conducted in Australian general practice [1, 2]. ANBP2 was a prospective comparative outcome trial that had a withdrawal of antihypertensive drug arm within its subject recruitment strategy. Recruitment of subjects demonstrated that approximately 18% of patients withdrawn from medication remained 'normotensive' by study criteria at completion of the screening process (Chapter 3). ANBP2 provided an ideal opportunity to study these subjects to identify predictors of successful withdrawal of antihypertensive drug and develop clinical practice guidelines for general practitioners to implement withdrawal of antihypertensive drug as part of the normal management of his or her hypertensive patient. A subset of 503 patients in the run-in phase of ANBP2 in Victoria were enrolled in 'WAD in ANBP2' study.

ANBP2 was a cardiovascular outcome trial of the treatment of hypertension in the elderly. Six thousand and eighty-three patients in the 65-84 year age group were randomised to a diuretic or ACE-inhibitor based regimen and monitored for total cardiovascular events (fatal

and non-fatal) over a five year period. The aim of this study was to determine whether there were any differences in outcome as a result of treatment on a diuretic or ACE-inhibitor based regimen. Whilst a diuretic based regimen has been shown to improve cardiovascular outcome, there is as yet no evidence for the superiority of ACE-inhibitor based regimens in hypertensive patients despite their widespread use [3]. ANBP2 was conducted under the auspices of the High Blood Pressure Research Council of Australia and was conducted entirely in Australian general practice. It had ethical approval from the RACGP Ethics Committee. The pilot study was completed in South Australia and Victoria in 1995 and the full study thence expanded into Western Australia, Queensland and New South Wales [4].

ANBP2 involved the screening of the 65-84 year subjects deemed meeting the study protocol by their participating general practitioner. Screening took place in the general practitioners' rooms by study nurses and included a health and lifestyle questionnaire, blood pressure, body mass index (BMI) and waist-hip ratio. Subjects who met blood pressure criteria or who were taking antihypertensive medications were sent on to their general practitioner. Those on antihypertensive drugs were assessed for entry into the study on medical criteria and suitability for withdrawal of this medication. Subsequent repeat blood pressure measurements (off all antihypertensive medication for at least seven days) that satisfied criteria permitted randomisation into ANBP2. The predominant reasons for failing to complete drug cessation in ANBP2 were either the general practitioner exiting the subject (60%) or the subject withdrawing consent (56%). Other reasons were withdrawal symptoms (43%), the rapid return to hypertension (25%), cardiac arrhythmia (2%), and cardiac failure (2%).

Subjects were then followed with six monthly reviews of the general practitioner held medical record and were seen annually by study nurses to document major cardiovascular events and death. A blinded End-point Committee reviewed data to confirm end-points.

Background and rationale for Withdrawal of Antihypertensive Drugs in the Second Australian National Blood Pressure Study 'WAD in ANBP2'

Studies of the withdrawal of antihypertensive drugs consistently record a steady 20% or more of subjects remaining normotensive for extended periods after withdrawal (Chapter 2). Hence a current status of hypertension cannot be assumed just because a subject is receiving treatment. Conversely it can be argued that 20% of currently treated 'hypertensives' are in reality normotensive. Previous studies have also demonstrated that there are 'predictors of success' of withdrawal of antihypertensive drug and that there is benefit in lifestyle interventions such as dietary advice for this success in withdrawal of antihypertensive drug (Chapter 2). These studies have, in the main, been hospital or specialist clinic based and their recommendations may not necessarily be practical in a general practice management setting.

It is also known that all antihypertensive drug groups may have adverse effects on patients. These are well recognised such as poor exercise tolerance, exacerbation of asthma, electrolyte and lipid profile disturbance with potential deleterious cardiac effects, and postural hypotension. Such adverse events are associated with a particular class of drug. For the outcome offered by the treatment of their hypertension these side effects are warranted. However this cannot be argued for the individual who remains normotensive off their medication. Society and the individual have the cost of medication for individuals who don't

actually have the condition and the treatment of any resultant iatrogenic disease, for example a fall in elderly patient due to postural hypotension causing a fractured neck of femur.

The focus of this chapter is the identification of predictors that are suitable candidates in the general practice environment for successful withdrawal and maintenance of normotension.

Hypotheses

H_0 The hypothesis to be tested is that there are no baseline patient characteristics of elderly subjects treated for hypertension in Victorian general practice that predict which of them who have completed antihypertensive drug withdrawal and are 'normotensive' two weeks later will 'maintain normotension' off medication for twelve months.

H_1 The alternative hypothesis is that there are baseline patient characteristics of elderly Victorians who have completed antihypertensive drug withdrawal and are 'normotensive' two weeks later that predict which of them will 'maintain normotension' off medication at twelve months.

Aims and objectives

Aims

The aim of of this study is to identify predictors of 'maintenance of normotension' of all subjects selected for withdrawal of antihypertensive drug in the Victorian Region of ANBP2 from 28/11/96 to 30/6/98. Data collected will be used to develop recommendations for the withdrawal of antihypertensive drugs in the elderly in general practice.

In addition a secondary aim is to compare major cardiovascular outcomes and death of withdrawal of antihypertensive drug 'normotensives' with those who returned to treatment.

Primary objective

The primary objective will be the identification of predictors of 'maintenance of normotension' post withdrawal of antihypertensive drug in 65 to 84 year olds in the general practice setting.

Secondary objectives

Secondary objectives are to observe outcomes related to antihypertensive withdrawal in the elderly and to compare outcomes in the 'normotensive' and 'hypertensive' cohorts.

Method

Subject identification

Subjects of either sex from participating general practitioners' patient databases who were 65-84 years of age, who were receiving treatment for hypertension (who meet inclusion and exclusion criteria) and were considered suitable for withdrawal of antihypertensive drugs by their usual treating general practitioner were included in the study. Subjects were identified through their usual treating general practitioner.

The Senior Research Nurse visited the practice to initiate a review of all patient records to identify all patients aged 65-84. A practice computer or (as was usually the case) where this was unavailable, a manual record review, generated a patient list. In most cases a member of the reception staff did the record review although occasionally study nurses completed it.

These lists were scrutinised by registered general practitioners to exclude patients who may be deceased, incapable of informed consent, unable to attend the practice or who did not meet other inclusion or exclusion criteria. Additionally the general practitioners were asked to identify those patients they considered their usual patients. Once the list was reviewed it was entered in to a database. Patients who had not been identified as belonging to a general practitioner registered in the study were not entered into the database.

The patient databases were used to produce personalised letters to the patients with the practice address and signature of the participating practitioner on ANBP2 or practice letterhead. Those attending who were already on pre-existing antihypertensive medication were asked to consider temporary withdrawal of their medication by their general practitioner in order to establish their eligibility for the study.

Inclusion criteria

Subjects of either sex who:

1. Were 65-84 years of age.
2. Had confirmed hypertension, either untreated or previously treated, with average untreated sitting blood pressure on the 2nd and 3rd screening visits of the study ≥160 mmHg systolic or ≥90 mmHg diastolic (if systolic blood pressure was > 140 mmHg).
3. Had no history of recent cardiovascular morbidity (see under exclusion criteria), serious intercurrent illness or an absolute contraindication to an ACE inhibitor or diuretic. The latter criterion was necessitated by this study being conducted on subjects in the run-in phase of ANBP2.
4. Were capable of and willing to give informed consent.

5. Were ambulant and able to attend their general practitioner's practice throughout the study
6. Did not return to hypertension (definitions as above) at or before two weeks after cessation of all antihypertensive drugs.

Exclusion criteria

1. Presence of any previous non-fatal cardiovascular event which defines an end-point for the study in the past 6 months (Table 4.1).
2. Accelerated or malignant hypertension.
3. Dementia.
4. Plasma creatinine concentration >0.2 mmol/l.
5. Any life threatening illness considered to be likely to cause death within 5 years.
6. Presence of any absolute contraindication to or specific indication for an ACE-inhibitor or a diuretic.
7. Consideration by the subject's general practitioner that the subject was unsuitable for the study.

General practitioner recruitment

General practitioners were approached through their Division of General Practice. Divisions of General Practice are federally funded general practice organisations that are structured on a geographical basis. They were chosen for this reason as the clustering of practitioners makes it easier for the principal investigator to approach general practitioners in areas with suitable demographic profiles (i.e. >12% of population ≥65 years of age for a pragmatic enrollment) and for the study nurses to screen subjects in their practices. It was also thought

that they were more likely to contain committed general practitioners who would be more willing to participate in research activities. General practitioners were initially approached by letter from the principal investigator and the Division president with an invitation to attend a meeting at which the background to ANBP2 was outlined by a member of the main committee and the practical aspect of the study by the principal investigator (see Appendix). Aspects of substudies including 'WAD in ANBP2' were included in the discussions.

Those general practitioners who indicated a willingness to participate in the study but who could not attend the meeting were followed up by a visit from the principal investigator or the senior research nurse. Those who do not reply to the invitation were contacted by telephone by the principal investigator for similar follow up.

Sample size

The sample size calculations of ANBP2 were based on a five year follow-up period (on average), at the 5% level of significance and with a power of 90%, for a 25% difference in total cardiovascular events (including cardiovascular deaths) between the subjects treated with an ACE-inhibitor based regimen and the subjects treated with a diuretic based regimen [1]. It required a total of approximately 6000 subjects (3000 in each group) including an allowance of at least 700 subjects to account for dropouts and crossover to the alternative regimen. This sample size calculation has been based on the number of cardiovascular events (approximately 20 per 1000 patients per year) observed in the groups receiving active drug treatment in the SHEP [5] and MRC [6] studies. An approximate power calculation gives us ≥90% power to detect an odds ratio of 2 (after adjusting for other covariates) at a 5% significance level with a sample size of 454 (i.e. excluding 'Other' subjects).

Study conduct

Drug withdrawal was commenced under general practitioner supervision according to their instructions. The general practitioner was provided with recommendations on the process of drug withdrawal. These recommendations included a stepwise withdrawal, i.e. one drug at a time, half doses at weekly intervals to the lowest usual therapeutic dose then cease, and withdrawal of beta-adrenoreceptor blockers or diuretics last if the patient was on more than one medication. For all patients commencing drug withdrawal, the study nurse monitored blood pressure on a weekly basis. If values exceeded 215 mmHg systolic or 115 mmHg diastolic, or a level that the general practitioner considered unacceptable or the patient expressed concern or hesitation, therapy was recommenced. Subjects so selected returned to the study nurse for completion of withdrawal of antihypertensive drug. Those who remained 'normotensive' by study criteria two weeks after cessation of all antihypertensive medication entered 'WAD in ANBP2'.

As previously stated the entry criteria were selected due to the experience of drug withdrawal in ANBP2 prior to the commencement of the study (Chapter 3). Either the subject or general practitioner could elect to exit within the first 2 weeks without a clinical indication. These subjects are included in the analysis in Chapter 3.

The subjects were classified at a face to face meeting with the study nurse at 12 months. Where this was not possible subjects were classified by telephone or from the general practice held record.

'Maintained normotension' definition

Subjects of either sex who:

(a) Were 65-84 years of age at identification.

(b) Had confirmed previously treated hypertension.

(c) Had undergone withdrawal of antihypertensive drug and remained 'normotensive' by study criteria off antihypertensive medication at annual review. 'Normotension' was defined as a sitting blood pressure of <160 mmHg systolic or <90 mmHg diastolic (if systolic BP was > 140 mmHg) taken on the last consecutive visits at least one calender week apart.

'Return to hypertension' definition

Subjects of either sex who:

(a) Were 65-84 years of age at identification.

(b) Had confirmed previously treated hypertension.

(c) Had undergone withdrawal of antihypertensive drug, were 'normotensive' by study criteria at two weeks off all antihypertensive medication, and returned to hypertension by blood pressure criteria at or before 12 months. Blood pressure study criteria for 'return to hypertension' was study nurse measurement (seated mean systolic BP ≥160 mmHg or diastolic BP ≥90 mmHg on two occasions at least one calendar week apart), or a level that the individual's general practitioner considered justified reinstitution. This group was also analysed as 'return to hypertension early' (≤70 days post entry point into the study) and 'return to hypertension late' (>70 days post entry point into the study).

Study design

'WAD in ANBP2' was a prospective cohort study. Subjects were followed to end-points as defined in Table 4.1. Subjects who entered withdrawal of antihypertensive drug were followed weekly by the study nurse for at least six WAD visits (minimum five weeks post initiation of withdrawal of antihypertensive drug and two weeks cessation of all antihypertensive medication) and thereafter by their own treating general practitioner. Six monthly reviews of patient records for end-points and annual review for classification by the study nurse were then undertaken. End-points were then presented blinded to an independent End-point Committee.

Death Cardiovascular Coronary artery disease -myocardial infarction -sudden or rapid cardiac death Cerebrovascular disease -stroke Other cardiovascular deaths -cardiac failure -ruptured aortic or dissecting aneurism Non cardiovascular **Failure to maintain 'normotension'**	**Non fatal cardiovascular events** Cerebrovascular disease -stroke -reversible ischaemic neurological deficit (RIND) -transient cerebral ischaemic attack Coronary artery disease -myocardial infarction -unstable angina -intermediate coronary syndrome -coronary artery therapeutic procedures Cardiac failure (left ventricular or congestive) Other cardiovascular events -accelerated or malignant hypertension -ruptured aortic or dissecting aneurism -acute occlusion of a major feeding artery in any vascular bed other than cerebral or coronary

Table 4.1. 'WAD in ANBP2' end-points.

Hypertension was defined by research nurse recordings or a blood pressure level that the individual's general practitioner considered justified reinstituting therapy at or before the 12 month visit. The research nurse criterion was an average untreated (off antihypertensive medications for more than 2 weeks) sitting blood pressure of ≥160 mmHg systolic or ≥90

mmHg diastolic (if systolic blood pressure was > 140 mmHg) taken on the last consecutive visits at least one calender week apart by the following method.

Blood pressure was taken in the seated position five minutes after the subject was seated. The upper arm was measured and an appropriate cuff size was chosen such that its bladder width was at least 80% of the circumference of the chosen arm. At least three recordings were made at least one minute apart with systolic Korotkoff phase 1 and diastolic Korotkoff phase 5 sounds recorded to the nearest 2 mmHg. Recordings were repeated until variation between the last two recordings was less than 10 mmHg systolic blood pressure and 6 mmHg diastolic blood pressure and these were then averaged.

Data collection

Case record forms were collected by research nurses and processed by the Data Management Centre of ANBP2. Case record forms are provided in the Appendix.

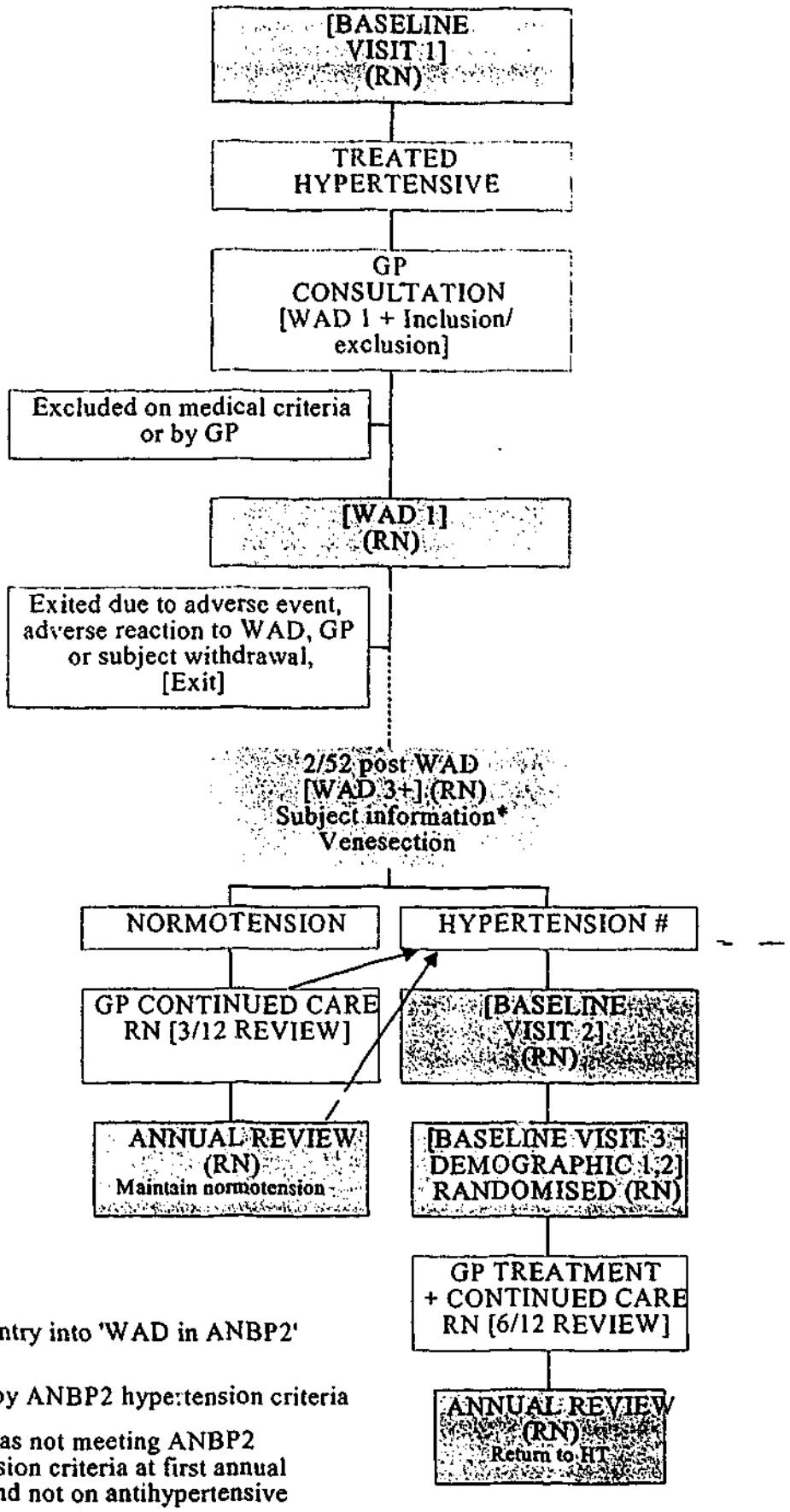
Candidate predictors

Baseline measurements that were available for investigation as predictors, were collected at baseline visit 1 (BV1), withdrawal of antihypertensive drug (WAD) visits, randomisation and yearly review (Figure 4.1 overleaf). Baseline measurements were as follows.

Baseline visit 1

Baseline visit 1 (BV1) recorded blood pressure, height (in centimetres) and weight (in

WAD in ANBP2 Flowchart



*Point of entry into 'WAD in ANBP2'

Defined by ANBP2 hypertension criteria

@ Defined as not meeting ANBP2 hypertension criteria at first annual review and not on antihypertensive medication

Figure 4.1 Flowchart of 'WAD in ANBP2'.

kilograms), body mass index (BMI kg/m^2), hip and waist circumference (hip/waist ratio), arm circumference, date of birth (age) and creatinine level.

Initial general practitioner consultation

Inclusion/Exclusion Criteria and Current Medication Form included a history of conditions that excluded the subject from the study and current chronic medication including dose, date commenced and primary reason for use. Antihypertensive Medication Withdrawal Entry Visit Form recorded duration of antihypertensive therapy, blood pressure prior to current course of therapy (pre-treatment blood pressure) and current antihypertensive medication (monotherapy vs. polypharmacy) and dose level.

Withdrawal Antihypertensive Drug visit

Random blood glucose, total cholesterol, HDL and serum potassium were recorded at this visit.

Baseline visit 3 ('return to hypertension') or Annual review ('maintain normotension')

Demographic and Risk Factor Information 1 form which included country of birth (if overseas born years in Australia), level of education, age at which left school, marital status, random blood glucose, total cholesterol, high density lipoprotein (HDL), serum potassium, history of hypercholesterolaemia or medication for said, history of diabetes (age of onset and management), smoking (year start and stop and number per day), alcohol intake (frequency, amount, type of beverage, bingeing and amount) or year ceased, exercise (walk/other and frequency) and family history of acute myocardial infarction (AMI) or cerebrovascular accident (CVA).

Demographic and Risk Factor Information 2 form which recorded history of hypertension (+/- treatment), angina (including duration), claudication, CVA, transient ischaemic attack (TIA), renal artery stenosis, AMI (definite/indeterminate or reinfarction), congestive cardiac failure (CCF), gout, coronary artery bypass grafting (CABG) including date, coronary angioplasty (and date), other diseases, occupation, duties and whether it was the subject's own business.

Candidate predictors analysed

Candidate predictors of maintenance of 'normotension' chosen for analysis from the above parameters were body mass index (BMI), waist-hip ratio, blood pressure (on treatment diastolic and systolic), heavy or higher weekend (binge) alcohol intake, exercise, number of antihypertensive drugs taken, and age. These potential predictors were identified by previous studies (Chapter 2) and their ready availability to a general practitioner.

End-point Assessment

End-point data were collected at six monthly research nurse case record review and subject visit at 12 months post withdrawal of antihypertensive drug with scrutiny of adverse event forms by the principal investigator for possible end-points. Cardiovascular morbidity and all cause mortality end-points were then presented blinded for subject identity to an End-point Committee.

Statistical Analysis

The relationship between potential predictors and 'normotensive' status at 12 months was assessed using generalized estimating equations (GEE) models to account for clustering within doctor [8]. The form of the model used was a log-binomial regression model and all results are expressed as relative risks (RR). Predictors of time to return to hypertension were ascertaincd using Cox's proportional hazards regression models, with robust variance estimation to account for clustering within doctor [9]. For both outcomes, a "multivariate" model was used to determine the independent predictors.

Classification of subjects at 12 months

Subjects were classified at 12 months post withdrawal of antihypertensive drug by the research nurse at a face to face meeting or where this was not possible, from the general practitioner held medical record or telephone contact with the subject. The medical record was scrutinised for evidence of subjects returning to hypertension by study criteria. If the subject was not on antihypertensive medication identified by a regularly updated list (see Appendix) they had their blood pressure measured by the standardised method previously mentioned. Subjects were then classified according to study criteria. Subjects who failed to meet these criteria were classified as 'Other'. This group included subjects of either sex who:

(a) Were 65-84 years of age at identification.

(b) Had confirmed previously treated hypertension.

(c) Had undergone withdrawal of antihypertensive drug and were 'normotensive' by study criteria at two weeks off all antihypertensive medication.

(d) Could not be classified at 12 months as they were dead or lost to follow-up.

or

(e) Had been returned to antihypertensive medication without meeting blood pressure criteria.

Members of this group were subjects who returned to medication for reasons other than hypertension, e.g. subject or general practitioner anxiety, angina, or peripheral oedema. Subjects who were in this group had their general practitioner record searched for preceding evidence of the condition that necessitated the return to medication. This was done to identify subjects who had unmasking, i.e. a covert condition becoming overt with the cessation of antihypertensive medication, versus protocol violation, i.e. the medication being inappropriately ceased as it had been prescribed for a condition other than hypertension.

Results

Frequency analysis

Subject classification at 12 months post study entry

The study population consisted of 503 subjects, all of who had remained 'normotensive' for at least two weeks after withdrawal of all antihypertensive drug therapy. All but five were followed according to the protocol and reviewed twelve months after study entry. At this time 37% remained 'normotensive', 53% were hypertensive and 10% had recommenced antihypertensive therapy for reasons unrelated to hypertension (Figures 4.2 and 4.3). Four subjects had died during the interim period, two of cancer and two with vascular events. The remaining unclassified subject was known to be alive and not taking antihypertensive

medication at 12 months. However she had not had her blood pressure recorded by her general practitioner and declined the classification visit at 12 months with the study nurse. Subjects who failed to meet study criteria were classified as 'Other'. In most instances 'Other' subjects treatment was restarted because of ankle swelling (n = 18) or heart failure (n = 8) (Figure 4.4).

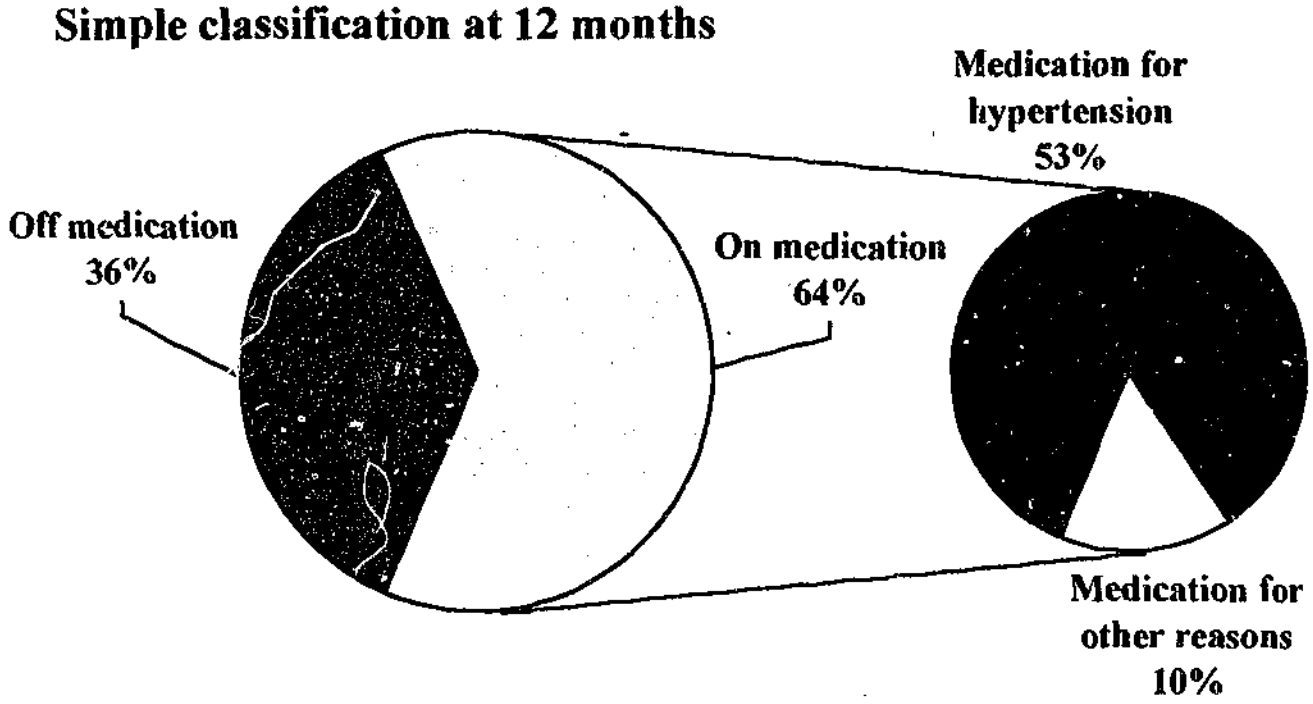


Figure 4.2. Classification of antihypertensive drug status 12 months after entry into 'WAD in ANBP2'.

There were two non-vascular deaths in the 'Other' group (carcinomas) and two vascular deaths in the cohort both of whom had returned to antihypertensive medication prior to death (Table 4.2). The other subject six subjects had unique reasons for censorship. They recommenced antihypertensive medication for prostatism, heartburn, headaches, glaucoma,

and due to being 'unwell'. One subject was identified as having never ceased his medication and hence was a protocol violation as he did not meet inclusion criteria.

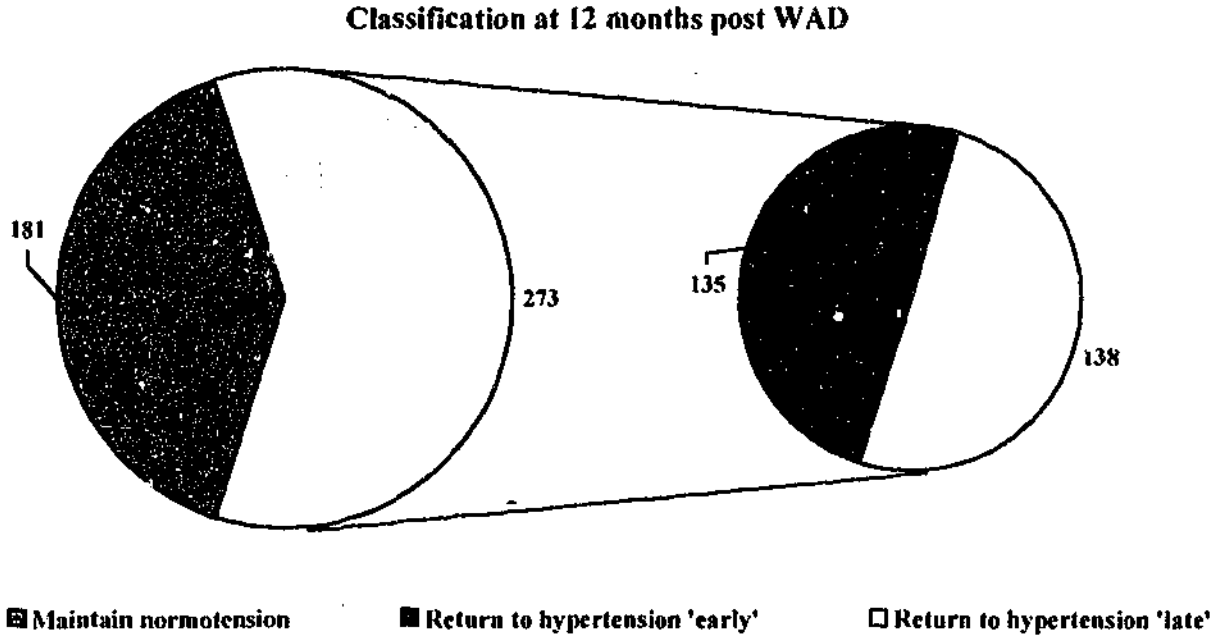
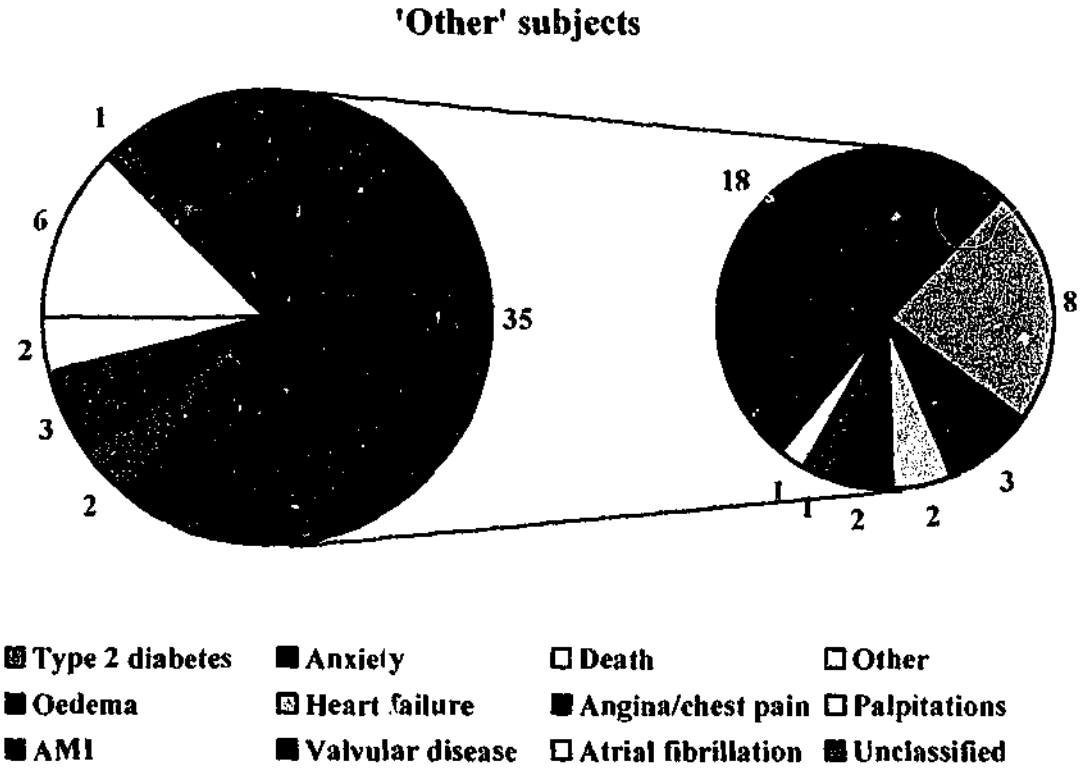


Figure 4.3. Classification of all subjects at 12 months post withdrawal of antihypertensive drug (n = 454). The left pie represents primary classification into subjects who successfully maintained 'normotension'



by study criteria and the right pie those who did not.

Figure 4.4. Subclassification of all and cardiovascular 'other' subjects from figure 5 at 12 months post entry into 'WAD in ANBP2' (n = 49).

Parameter	'Maintain normotension'	'Return to hypertension'	'Other'
Person years	196.9	297.4	51.0
		N (Rate per 1000 patient years)	
All non BP end-points	8 (40.6)	22 (74.0)	17 (333.6)
Nonfatal myocardial infarction	1 (5.1)	2 (6.7)	2 (39.2)
Left ventricular or congestive cardiac failure	0 (0.0)	1 (3.4)	4 (78.5)
Coronary artery therapeutic procedures	2 (10.2)	1 (3.4)	3 (58.9)
Angina	2 (10.2)	4 (13.4)	3 (58.9)
Arrythmia	0 (0.0)	6 (20.2)	1 (19.6)
Other coronary syndromes	2 (10.2)	1 (3.4)	1 (19.6)
Nonfatal stroke	1 (5.1)	4 (13.4)	0 (0.0)
Transient ischaemic attack	0 (0.0)	1 (3.4)	1 (19.6)
Heart failure or other coronary death	0 (0.0)	1 (3.4)	0 (0.0)
Fatal stroke	0 (0.0)	1 (3.4)	0 (0.0)
Non vascular death	0 (0.0)	0 (0.0)	2 (39.2)

Table 4.2 Non blood pressure end-points in 'WAD in ANBP2'.

All non blood pressure end-points (excluding angina and arrythmias) for the 'WAD in ANBP2' cohort was 60.5 events per 1000 patient years compared to the ANBP2 cohort rate of 51.0 events per 1000 patient years.

Multivariate analysis

Table 4.3 contrasts the characteristics of the 'maintain normotension' and 'return to hypertension' groups as classified at 12 months after study entry. Statistical significant differences between these groups are shown in Tables 4.4 and 4.5.

Characteristic			'Maintain normotension'	'Return to hypertension (all)'	'Return to hypertension (early)'	'Return to hypertension (late)'
			n=181	n=273	n=135	n=138
Gender	n (%)	F	95 (52.5)	161 (59.0)	72 (53.3)	89 (64.5)
		M	86 (47.5)	112 (41.0)	63 (46.7)	49 (35.5)
Age in years		median	70.0	71.0	72.0	71.0
		(range)	(65.0-84.0)	(65.0-84.0)	(65.0-84.0)	(65.0-82.0)
Blood pressure	(mmHg)	mean (sd)				
Pre-treatment		Systolic	169.8 (20.0)	169.4 (18.1)	171.6 (17.7)	167.5 (18.4)
		Diastolic	93.7 (10.2)	94.5 (9.6)	94.6 (9.7)	94.5 (9.6)
On treatment		Systolic	135.3 (13.0)	141.4 (13.6)	143.5 (13.4)	139.3 (13.5)
		Diastolic	76.0 (8.9)	77.0 (7.8)	77.5 (7.9)	76.5 (7.8)
		Mean Arterial	95.7 (8.9)	98.4 (8.3)	99.5 (8.0)	97.4 (8.6)
		Pulse Pressure	59.3 (11.6)	64.4 (12.1)	66.0 (12.8)	62.9 (11.2)
Other CVD risk factors						
BMI (kg/cm2): mean (sd)			26.9 (3.4)	27.3 (4.1)	27.0 (4.0)	27.5 (4.2)
Waist-Hip Ratio: mean (sd)			0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
Raised cholesterol: n (%)			102 (56.4)	118 (43.2)	49 (36.3)	69 (50.0)
Diabetes mellitus: n (%)			16 (8.8)	20 (7.3)	11 (8.1)	9 (6.5)
Smokers: n (%)			13 (7.2)	12 (4.4)	8 (5.9)	4 (2.9)
Family history heart disease: n (%).			99 (54.7)	145 (53.1)	67 (49.6)	78 (56.5)
Personal history cardiovascular disease*: n (%)			42 (23.2)	47 (17.2)	22 (16.3)	25(18.1)
Previous drug therapy Monotherapy: n (%)			141 (77.9)	173 (63.4)	84 (62.2)	89 (64.5)
Plasma creatinine umol/L		mean (sd)	86.1 (16.9)	88.5 (22.1)	89.4 (21.4)	87.7 (22.8)
Alcohol	n (%)	Heavy	64 (35.4)	81 (29.7)	41 (30.4)	40 (29.0)
		Moderate	83 (45.9)	95 (34.8)	49 (36.3)	46 (33.3)
		Never drink	28 (15.5)	78 (28.6)	36 (26.7)	42 (30.4)

*Angina, claudication, stroke, myocardial infarction, coronary artery bypass grafting, or coronary angioplasty.

Table 4.3. Baseline characteristics according to blood pressure classification group.

Table 4.4 shows the result of a stepwise multivariate analysis conducted to determine the most powerful independent predictors of maintenance of 'normotension'. These are expressed as risk ratios using return to hypertension 'all' and 'early' (≤70 days) as the comparison group. In both circumstances higher on treatment systolic blood pressure was the major predictor. Other predictors were younger age, lesser waist-hip ratio, and the use of a single antihypertensive drug.

	'All'				'Early'			
	RR	**Lower CL**	**Upper CL**	**p value**	**RR**	**Lower CI**	**Upper CI**	**p value**
Higher on treatment systolic blood pressure by 1 standard deviation increments	0.807	0.715	0.910	0.0005	0.808	0.732	0.892	<.0001
Age 65-74 versus 75-84	1.582	1.142	2.191	0.0058	1.442	1.095	1.899	0.0091
Greater waist-hip ratio by 1 standard deviation increments	1.167	1.022	1.332	0.0221	1.128	1.004	1.266	0.0423
On monotherapy versus two or more antihypertensive drugs	1.530	1.153	2.030	0.0032	1.410	1.102	1.805	0.0063

Table 4.4. Subject characteristics that are independent predictors by study criteria of maintenance of 'normotension' for 12 months after withdrawal of all antihypertensive medication versus return to hypertension ('All') and versus early return to hypertension ('Early' ≤70 days post study entry).

Table 4.5 (overleaf) shows the results of a multivariate analysis conducted to determine the most powerful predictors of time to return to hypertension. Those identified were a higher on treatment systolic blood pressure, being on two or more antihypertensive drugs, a lesser waist-hip ratio and an older age.

Figure 4.5 shows the proportion of the study population who was classified by blood pressure status who remained 'normotensive' at various times following drug withdrawal. It indicates that as many returned to hypertension in the first 70 days as the subsequent 330 days.

	Hazard ratio	Lower CI	Upper CI	p value
Higher on treatment systolic blood pressure by 1 standard deviation increments	1.281	1.127	1.457	0.0002
Greater waist-hip ratio by 1 standard deviation increments	0.833	0.703	0.987	0.0344
On monotherapy versus two or more antihypertensive drugs	0.743	0.580	0.952	0.0190
Age 65-74 versus 75-84	0.675	0.517	0.881	0.0039

Table 4.5. Subject characteristics that are independent predictors by study criteria by time of return to hypertension after withdrawal of all antihypertensive medication.

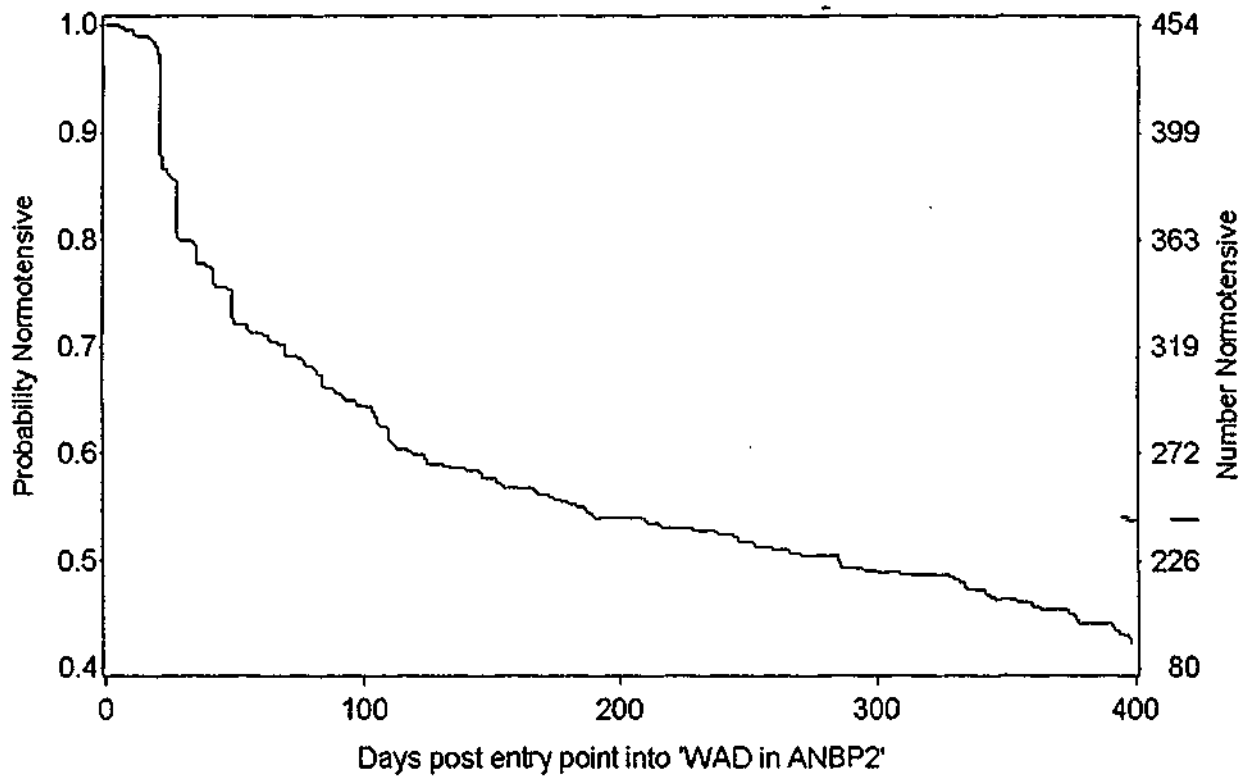


Figure 4.5. Survival plot of subjects classified by blood pressure status (n = 454) remaining 'normotensive' over a 12 month period after cessation of antihypertensive therapy. Subjects classified as 'Other' were excluded from this analysis (n = 49).

Discussion

A systematic review of predictors of maintenance of normotension after antihypertensive drug withdrawal suggested that if medication is withdrawn from selected patients with mild-

moderate hypertension then approximately 42% of these patients are likely to remain normotensive for 12 or more months [10]. Predictors of success for maintainence of normotension have been identified in these studies and would suggest the long-term well controlled mild hypertensive on single agent antihypertensive therapy is the optimal candidate for a trial of withdrawal of antihypertensive medication especially if they are also willing to undertake appropriate lifestyle changes.

'WAD in ANBP2' documents the experience of withdrawal of antihypertensive medication in 503 subjects aged 65-84 years in a cohort study conducted in a Victorian general practice setting and identifies patient characteristics that predict successful 'maintenance of normotension' over a 12 month period. The study is novel in prospectively investigating predictors of successful withdrawal for elderly patients that are likely to be useful to a general practitioner in routine clinical practice.

This study had a relatively high percentage (37%) of subjects who remained 'normotensive' one year after drug withdrawal. This finding has been replicated in other major studies and is similar to the 42% of the systematic review (Chapter 2) [10-19]. Figure 4.5 shows that while most return to hypertension in the first 70 days after entry into the study, the rate does not henceforth abate and therefore systematic follow-up is required for those patients who are offered this strategy in clinical practice.

This study has identified patient characteristics that predict the likelihood of successful antihypertensive drug withdrawal amongst patients treated in a general practice setting. The subjects selected were elderly (over 65 years) and had blood pressure levels judged safe to allow for a brief period of drug withdrawal prior to entry to the ANPB2 study. The

distribution of blood pressure levels is likely to have been similar to the typical mild-moderate hypertension patient encountered in general practice. This is reflected by the high number of patients on monotherapy prior to drug withdrawal (Table 4.3).

The study identified several predictors of sustained 'normotension' as well as early return to hypertension. All of these were amongst a series of simple clinical variables prospectively chosen as likely to be routinely available to guide a general practitioner's clinical management. To interpret the likely clinical values, certain limitations of the study design require comment.

In the first place the study was largely observational and relied on physician judgement both for commencing antihypertensive therapy and for determining whether it was appropriate to recommence treatment. Different practitioners vary in their thresholds for initiating treatment and are also encouraged to use different thresholds according to the level of integrated cardiovascular risk amongst individual patients [20]. However in all cases return to antihypertensive drug therapy was initiated by the patients' general practitioner as "the most appropriate" course of action for the individual patient.

Another limitation is the natural variability of blood pressure and its likelihood of being transiently elevated e.g. by alcohol intake, other drugs or fluctuations in body weight [21,22]. Predictors of successfully sustained 'normotension' may also bear a complex relationship to their outcome variable. For example they may:

(a) Reflect factors that have lead to more frequent than normal blood pressure measurement or a lower threshold for introduction of therapy, e.g. other illnesses or the presence of other cardiac risk factors.

(b) Reflect factors that have lead to a transient elevation of blood pressure that has subsequently resolved or exaggerated white coat effect, e.g. a transient period of excessive alcohol intake or body weight increase.

(c) Reflect factors associated with an increased likelihood of success of non-pharmacological blood pressure reduction [14, 19].

(d) Reflect inappropriate introduction of therapy because of poor measurement technique, too few blood pressure measurements, or a failure to initiate behaviour modification before introducing drug therapy [21, 22].

It is likely that the predictors identified in this study should fit several of these categories:

(a) On treatment systolic blood pressure is likely to correlate with the true pre-treatment blood pressure and is therefore a plausible predictor of successful withdrawal.

(b) Younger individuals may be more often commenced on therapy inappropriately because of an exaggerated white coat effect. Hence younger age is a plausible predictor of successful withdrawal.

(c) A low waist-hip ratio may predict earlier return to therapy because doctors have less option to encourage non-drug therapies in particular weight loss, or as a corollary those with a higher waist-hip ratio may lose weight and delay return to hypertension [10].

(d) Monotherapy reflects the mild nature of the blood pressure off treatment and therefore is a plausable predictor.

Considering the strength of the predictors and their plausible relationships to successful antihypertensive drug withdrawal it is likely that only a minority of the candidate predictors will be useful in a clinical setting. The most relevant predictors of successful withdrawal are

younger patients with relatively low 'on treatment' systolic pressures, and minimal drug therapy. Conversely those least likely to be successful are older subjects with higher pressures and two or more antihypertensive drugs. The systematic review had found the most consistent predictors identified amongst the identified studies were blood pressure (lower pretreatment, on treatment and post withdrawal), pharmacotherapy (fewer agents and lower dose) and dietary intervention (weight and sodium reduction) [10].

It should be noted that the predictive power each of the identified factors was relatively modest, ranging from 0.85 to 2.38. The ability of the model to predict 'maintenance of normotension' versus 'return to hypertension' was 41% of 'maintenance of normotension' correctly predicted, 83% of 'return to hypertension' correctly predicted, and 66% correct overall. The ability of the model to predict 'maintenance of normotension' versus 'early return to hypertension' was 90% of 'maintenance of normotension' correctly predicted, 38% of 'early return to hypertension' correctly predicted, and 68% correct overall. Thus identified predictors for maintenance of normotension are most useful for the first 70 days after drug withdrawal.

The ability of the model with on treatment systolic blood pressure only to predict 'maintenance of normotension' versus 'return to hypertension' was 16% of 'maintenance of normotension' correctly predicted, 91% of 'return to hypertension' correctly predicted, and 61% correct overall. Therefore 'on treatment' systolic blood pressure is the single most useful measure to exclude patients from a trial of antihypertensive drug withdrawal.

It is still quite possible however that other more powerful predictors may exist. Given the wide range of simple measurements in this study it would be of interest for future studies to

test physiological measures such as arterial compliance, pulse wave velocity, etc at baseline as clinical tests to predict maintenance of 'normotension'. Left ventricular hypertrophy for example, has been previously identified as such an important predictor [23]. However these are not readily available in the general practice environment and hence were not investigated in this study.

Conclusion

In view of the substantial cost of antihypertensive therapy, the findings in the present study emphasise the value of a trial of antihypertensive withdrawal therapy in patients fitting the profile of younger with blood pressure well controlled on relatively minimised therapy with systematic follow up.

Chapter 5

PBS/RPBS cost implications of trends and guideline recommendations in the pharmacological management of hypertension in Australia 1994-1998.

Introduction

The treatment of patients with mild-moderate hypertension is most commonly initiated with an agent from one of four major drug classes [1]. These are thiazide diuretics, beta-adrenoreceptor blocking drugs, calcium channel blockers or agents acting on the renin–angiotensin system (RAS). The blood pressure lowering efficacy of the members of these groups is similar and, while differences may be observed between agents in single symptoms, no major differences occur in their overall burden of adverse effects [2-5]. However, the calcium channel blockers and RAS agents are three to nine times more costly than beta-adrenoreceptor blockers and thiazide diuretics [6].

Until recently a reversal of the long term sequelae of hypertension (myocardial infarction and stroke) had been demonstrated only with thiazide diuretics and beta-adrenoreceptor blockers. Largely as a result of this, expert committees in several countries including Australia had recommended that drug therapy in uncomplicated mild-moderate hypertension should be commenced with either of these agents [7-10]. Over the past two years large-scale morbidity/mortality trials have been completed comparing these drugs with calcium channel blockers and RAS agents but these have not revealed any superiority of the more costly therapies [3-5][11].

Despite the consistency of the advice from various national committees, recommendations concerning initial antihypertensive therapy have not been widely accepted by prescribers who have generally chosen to initiate therapy with calcium channel blockers and RAS agents (Chapter 6) [6].

This study was intended to examine trends in the use of the major antihypertensive drug groups and to determine the cost implications resulting from these trends. Particular attention was directed to the additional costs resulting from the use of calcium channel blockers and RAS agents in the uncomplicated clinical setting where the less expensive drugs have been shown to have equivalent long-term efficacy.

Method

PBS/RPBS expenditure

Expenditure on specific classes of cardiovascular therapy through the Pharmaceutical Benefits Scheme (PBS) and the Repatriation Pharmaceutical Benefits Scheme (RPBS) from 1994 to 1998 was provided by Analysis Section, Pharmaceutical Benefits Branch of the Commonwealth Department of Health and Aged Care. This expenditure includes components for the professional services of the dispensing pharmacist as well as the cost of the drug(s) and patient contribution.

The patient co-payment for PBS/RPBS drugs is currently $3.30 for concession card holders and $20.00 for others unless a brand price premium and/or a therapeutic group premium is levied on a particular drug wherein there is additional cost to the consumer. If a 'safety net' of $631.20 spent on PBS drugs for the general category or $171.60 for the concession category is exceeded in a calendar year for an individual or family then further

out of pocket payments are at $3.30 or zero respectively. With some drugs the patient co-payment covers the total cost and in these instances the Commonwealth makes no contribution to the cost and these prescriptions are not recorded in the PBS/RPBS data. The PBS/RPBS data also omits the expenditure on medications provided directly from public hospital pharmacies.

Numbers receiving therapy

Total numbers of Australian patients receiving therapy with specific drug groups was determined using data from the Australian Pharmaceutical Index (API) and the Australian Medical Index (AMI). The API reports sales of specific drugs from wholesaler to community pharmacies but does not include drugs supplied to public hospitals. The AMI collects detailed prescribing information (including age, sex, and primary diagnoses) from a stratified sample of general practitioners. By dividing the total quantity of drugs (from the API) sold by the average daily dose (provided by the AMI) and assuming continuous therapy, an estimate can be made of the total number of individuals receiving a specific drug.

Proportion of hypertensives with specific comorbidities

An estimate of the distribution of comorbidity amongst mild-moderate hypertensive patients was made from data from the Second Australian National Blood Pressure Study (ANBP2) [12][13]. During the screening phase of this study 25,867 hypertensive patients were identified from general practices in all Australian mainland states, with 3,783 of these meeting the criteria for randomisation. For a pre-randomisation visit information was collected from these individuals about their comorbidity and prescribed medications. Using this data as a baseline, costs were estimated on 30, 40, and 50% absolute and

relative contraindications for older agents in order to provide a range of estimates for drug use related to contraindications.

Cost

Estimates were made of the differences in costs of antihypertensive drug therapy with prescribing patterns in 1998 and with prescribing strictly in accordance with then current published guidelines [7]. The estimate was confined to individuals free of significant comorbidity that would lead to a calcium channel blocker or a RAS agent being the preferred agent.

Results

Trends in the number of hypertensive patients prescribed the major classes of antihypertensive therapy from 1994-98 are shown in Figure 5.1. Over this time the estimated number of individuals receiving antihypertensive medication under the scheme increased by 27% (IMS data). Around 60% of these individuals were prescribed a single drug for their hypertension (IMS data). Actual percentages for each agent in 1998 were ACE-inhibitors 63.9%, calcium channel blockers 61.3%, diuretics 53.6%, and beta-blockers 60.0%.

Over the five-year time period examined approximately 80% of RAS active drugs were prescribed primarily for the treatment of hypertension and the number of prescriptions for this indication increased at a rate of 10% annually. A similar pattern was observed with calcium channel blockers, 75-80% of which were prescribed primarily for hypertension and which increased by an average of 7% per year. By contrast prescriptions of beta-adrenoreceptor drugs for hypertension increased by one percent while those of thiazide

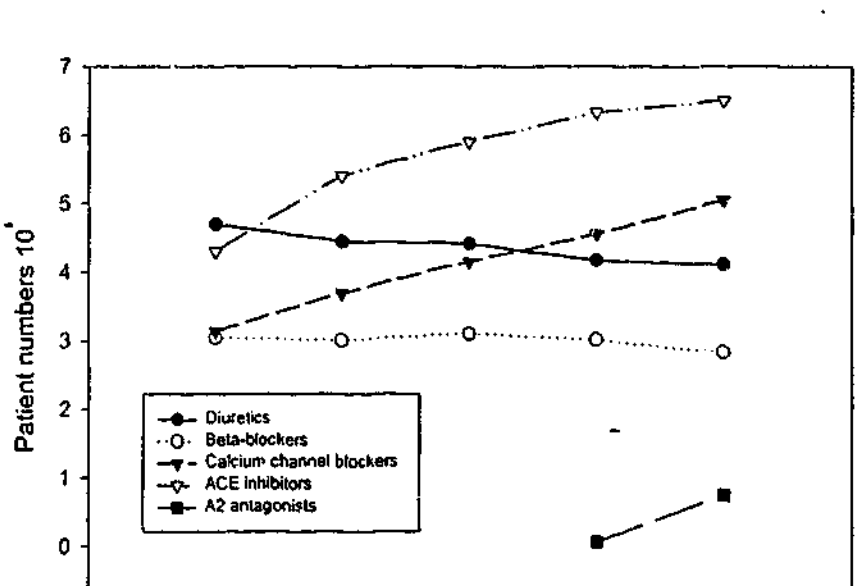


Figure 5.1. Patients receiving cardiovascular drugs for hypertension in Australia 1994-1998.

Source IMS data.

Comorbidity		On AD	ACE inhibitors	Diuretics	Beta-blockers	Calcium channel blockers	Alpha-blockers	Others
Total		3783	40.3	32.0	21.5	35.0	4.9	2.9
Coronary arterial disease	No	3410	40.1	32.4	21.0	34.5	4.8	3.1
	Yes	373	42.1	28.2	26.0*	39.9*	6.4	0.8*
Diabetes mellitus	No	3479	39.6	32.3	22.1	34.5	5.0	2.9
	Yes	304	49.3**	28.0	13.8**	40.8*	4.3	3.3
Raised cholesterol	No	2280	40.0	33.3	21.7	35.0	5.0	2.9
	Yes	1503	40.9	29.9*	21.2	34.9	4.7	3.0
Any of the above	No	1921	38.7	33.7	22.1	34.4	4.8	3.1
	Yes	1862	42.1*	30.1*	20.8	35.6	5.0	2.7

Table 5.1. Comorbidity data for subjects who entered the Second Australian National Blood Pressure Study (ANBP2) previously identified as taking antihypertensive drugs (On AD) at screening. The percentage of those taking each antihypertensive drug group who had a specified disease is shown. Statistically significant differences between those taking a specified agent who did or did not have each comorbidity are shown (*$p < 0.05$ **$p < 0.001$). Bold where a difference was expected by guidelines but was not observed.

diurectics decreased by one percent annually (hypertension was principal indicator of about 70% of beta-adrenoreceptor blocking drugs prescriptions and about 50% of diuretic prescriptions).

The proportion of mild-moderate hypertensives with comorbidity likely to influence prescribing of antihypertensive drugs was estimated from information supplied by entrants to ANBP2 (Table 5.1). Since entrants to this study were required to be 65-84 years this data provides a relatively imprecise indicator of comorbidity in the general population of hypertensives. Amongst these entrants, 10% have established coronary heart disease (angina or myocardial infarction) and 8% were diabetic. Sixteen percent of those on monotherapy had identified comorbidity. A comparison of the ANBP2 treated hypertensive subject age and gender distribution with a general hypertensive population is provided in Table 5.2 (overleaf). It can be seen that there is a relative excess of 'older' females and fewer 'younger' males. Given the limitations of this dataset the proportion of comorbidity was modeled on 30, 40 or 50% clinical indication / contraindication for newer over older agents.

The cost of each class of medication was determined assuming 1998 prices quoted in the PBS/RPBS and converted to a daily cost (Table 5.3 overleaf). From Table 5.4 an estimated reduction in PBS/RPBS government expenditure of $43-92 million would have been made in 1998 if patients on monotherapy without comorbidities were prescribed according to the Australian guidelines.

	Age					
Database	ANBP2	ABS	ANBP2	ABS	ANBP2	ABS
Age group	65-74	65-74	75-84	75+	65-84	65+
Gender n						
%						
Females	1320	336,584	691	278,145	2011	614,729
	34.89	*32.47*	*18.26*	*26.84*	*53.16*	*59.31*
Males	1299	280,375	473	141,354	1772	421,729
	34.34	*27.05*	*12.51*	*13.64*	*46.84*	*40.69*

Table 5.2. A comparison of ANBP2 subject age and sex distribution and the general hypertensive population. This later group was identified from the ABS analysis of the 1995 Australian Nutrition Survey [14]. The groups have different age group classifications for the >74 years of age.

Drug		Cost of agent PBS / RPBS $m per annum	% agent use for hypertension	Cost for hypertension $m per annum	Hypertension patient numbers '000s	Cost per patient Cents per day
RAS agents	Government	256.3	81.5	208.9	723.0	79.2
	Consumer	79.7		64.9		24.6
	Total	336.0		273.8		103.8
Calcium channel blockers	Government	155.5	78.2	121.6	504.3	66.0
	Consumer	44.4		34.7		18.9
	Total	199.9		156.3		84.9
Diuretics	Government	24.8	52.4	13.0	410.4	8.7
	Consumer	7.4		3.9		2.6
	Total	32.2		16.9		11.3
Beta-adrenoreceptor blockers	Government	33.3	65.5	21.8	282.2	21.2
	Consumer	11.3		7.4		7.2
	Total	44.6		29.2		28.4

Table 5.3. Per patient daily cost in 1998 of each class of commonly prescribed antihypertensive drug. Column 1 data derived from Pharmaceutical Benefits Branch, column 2 AMI, and column 4 API / AMI

Drug agent	Estimated patients on monotherapy '000s	Redistributed to guideline recommendations and assuming the underlying rates of adverse event or relative or absolute indication / contraindication. '000s (change)		
		30%	*40%*	*50%*
RAS agents	462	174 (-288)	232 (-230)	290 (-172)
Calcium channel blockers	309	174 (-135)	232 (-77)	290 (-19)
Diuretics	220	406 (+186)	348 (+128)	290 (+70)
Beta-adrenoreceptor blockers	169	406 (+237)	348 (+179)	290 (+121)
All agents cost $m per annum				
Government	228.1	136.5	160.9	185.4
Consumer	69.3	42.0	49.2	56.3
Total	297.3	178.5	210.1	241.7
Change		(-118.8)	(-87.2)	(-55.6)

Table 5.4. Estimated cost of single agent therapy for uncomplicated hypertension in 1998. Column 1 estimated actual costs. Columns 2-4 estimated costs if all patient regimens were based on a diuretic (50%) or beta-adrenoreceptor blocker (50%) but had 30, 40 or 50% indications for other agents or contraindications to these agents.

Discussion

This analysis indicates that the Australian government spends a minimum of $43 million annually (50% model total less consumer savings of $13 million) as a result of Australian doctors non-adherance with established guidelines for the management of mild to moderate hypertension. This is the difference between current expenditure on first-line therapy for mild-moderate hypertension without comorbitity and the expenditure that would be incurred if diuretics or beta-adrenoceptor blocking agents were routinely prescribed as the initial therapy for such individuals. The figure is likely to be a

substantial underestimation because it is based on a number of conservative assumptions and does not take into account Commonwealth expenditure through public hospitals. This is however offset by the PBS/RPBS capturing much more of the cost of the newer more expensive agents than thiazide diuretics or beta-adrenoreceptor blockers.

The practice of using angiotensin converting enzyme inhibitors or calcium channel blockers for the initial management of mild-moderate hypertension runs counter to the Australian and international guidelines established in recent years for the management of this condition. In 1992 an Australian consensus conference recommended that unless clinical reasons existed for choosing an alternative agent, the first drug to be used should be a thiazide diuretic or a beta-adrenoceptor blocking drug [7]. Where comorbidity exists specific advice is given (Table 5.5). Since that time several other bodies, including the US National Institutes of Health, the British Hypertension Society and the Australian National Heart Foundation have released guidelines with similar recommendations [8-10]. The major exception was the WHO/ ISH 1999 guidelines which expressed no preference for any of the four principal classes of antihypertensive drug [15].

The rationale for recommending a thiazide diuretic or a beta-adrenoceptor blocking drug stemmed principally from the lack of large scale morbidity-mortality trials confirming a favourable risk-benefit ratio with ACE-inhibitor or calcium channel blocking drug. More recently such data has become available for ACE-inhibitor and calcium channel blocking drugs through large-scale trials comparing these agents with thiazide diuretic and/or beta-adrenoceptor blocking drug. Of the four such studies presently available, (CAPPP, STOP-2, INSIGHT, NORDIL) none have yet demonstrated that neither ACE -inhibitor nor calcium channel blocking drugs are more effective than thiazide diuretic or

	Australian guideline 1994 [7].	BHS 1999 [9].	JNC-VI 1997 [8].	WHO/ISH 1999 [15].
BP criteria for initiation of drug therapy (no. measurements x no. occasions)	≥2 x ≥4	NS	≥2 x ≥3	NS
❖ No other risk factors DBP	≥90	≥100	≥100	≥90
SBP	≥160	≥160	≥160	≥140
❖ With other risk factors DBP	≥90	≥90	≥90	≥90
SBP	≥140	≥140	≥140	≥140
Recommended first line drug*				
❖ Uncomplicated	2, 4	2, 4	2, 4	NS
❖ LV dysfunction	1 > 2, 3, 4, 5, 6	1	NS	1
❖ AMI	1, 2	2 > 3	1[ii], 2[iii] > 3[iv]	1, 2
❖ Heart failure	1 > 4	1 > 2, 7	1, 4 > 2[v], 7[vi]	1, 4 > 2, 7[xiii]
❖ Angina	2	2, 3	2, 3	2, 3
❖ Tachyarrythmias	2		2, 3[vii]	2
❖ Diabetes (type 1)	1	1	1[viii] > 3[viii]	1[xiv] > 2, 4
❖ Diabetes (type 2)	1	NS	1[viii] > 3[viii], 4	1[xiv] > 2, 4
❖ Lipid disorders*	5 > 1,3	5	5	5
❖ Renal disease	1[i]	1	1[i]	NS
❖ Elderly / systolic hypertension	4	4 > 3[ix]	4 > 3[ix]	3, 4
❖ Prostatic hypertrophy*	NS	5	5	5
❖ Pregnancy	NS	NS	6[x]	2
❖ PVD / atherosclerosis	3?	NS	NS	3
❖ Osteoporosis	NS	3?	4[xi]	NS
❖ Migraine	NS	NS	2[xii], 3[vii]	NS
❖ Hyperthyroidism	NS	NS	2	NS
❖ Essential tremor	NS	NS	2[xii]	NS
Goal BP criteria	≤140/90	<140/85	<140/90	
❖ Younger	120-130/80	NS	<140/90	<130/85
❖ Older	140-160/90	NS	<140/90[xvi]	<140/90
❖ Diabetes		<140/80[xv]	<140/90[xv]	<130/85

Key. 1 = ACE Inhibitor, 2 = beta-blocker, 3 = calcium channel blocker, 4 = diuretic, 5 = alpha-blocker, 6 = central acting agent, 7 = AII antagonist. NS = not specified. *The higher risk of combined CVD events (particularly congestive heart failure) demonstrated recently with doxazosin versus chlorthalidone has raised questions as to the safety of α-blockers which should no longer be seen as appropriate first line agents [16].

Table 5.5. Current recommendations for initiation of drug therapy for mild hypertension. This table does not include relative and absolute contraindications.

[i] With caution can lead to deterioration and contraindicated in bilateral renal artery stenosis.
[ii] With systolic dysfunction
[iii] Non-intrinsic sympathetic activity
[iv] Diltiazem, verapamil.
[v] Carvedilol.
[vi] Losartan
[vii] Non-dihydropyridine (Non-DHP)
[viii] With proteinuria
[ix] DHP
[x] Methyldopa
[xi] Thiazide
[xii] Non cardioselective
[xiii] And for ACE inhibitor cough where I indicated
[xiv] Nephropathy
[xv] Renal disease ≤130/85 (≤125/75 with proteinuria >1 g per 24 hours).
[xvi] SBP <160 with marked systolic hypertension

Study (design)	Subject characteristics				Drugs	CVD endpoints	
	N	*Age*	*Gender M (F)*	*Blood pressure mmHg*		*Event rate 1000 patient years*$^{-1}$	*RR (95% CI)*
STOP-2	6614	70-84	2196	SBP ≥180	ACE I / CCB	43.6	0.96
[4]			(4418)	DBP ≥105	β-blocker /diuretic	44.9	(0.86-1.08)
(PROBE)							
CAPPP	10985	25-66	5864	DBP ≥110	Captopril	11.1	1.05
[11]			(5111)		β-blocker /diuretic	10.2	(0.90-1.22)
(PROBE)							
INSIGHT	6321	55-80	3929	≥150/95	Nifidipine	18.2	1.10
[3]			(3392)	SBP ≥160	Co-amilozide	16.5	(0.91-1.34)
(RDBCT)							
NORDIL	10881	50-74	5290	DBP ≥100	Diltiazem	16.6	1.00
[5]			(5591)		β-blocker /diuretic	16.2	(0.87-1.15)
(PROBE)							

Study design PROBE – prospective randomised open-labelled with blinded endpoints.
RDBCT – randomised double-blind comparative trial.

Table 5.6. Large-scale comparative outcome trials for older and newer antihypertensive agents.

beta-adrenoceptor blocking drug in preventing coronary events or prolonging survival (Table 5.6) [3-5][11]. Other similar studies including ANBP2 are ongoing and will report their results in coming years.

In the absence of proven additional benefit on medium to longer term cardiovascular outcomes, the choice of ACE-inhibitor or calcium channel blocking drugs could be justified if they were better tolerated by the majority of patients or had a lower incidence of serious adverse effects. However the few published studies comparing these agents have found that most patients tolerate these agents with no major differences existing in the proportions that must cease treatment because of adverse effects. In the INSIGHT study for example, 129 of the calcium channel blocker group (N = 3157) compared to 1048 of the diuretic group (N = 3164) withdrew because of adverse events [3]. Although there are a variety of specific adverse effects

associated with the specific drug groups, no studies have yet demonstrated a difference in the overall burden of adverse effects between these drugs [2].

Despite the results of these studies it is well recognised that thiazide diuretic and beta-adrenoceptor blocking drug are not appropriate initial therapies for all patients. For example a percentage of patients will be unsuited to either of these agents because of comorbidity e.g. a combination of type 2 diabetes and asthma that form contraindications to both drugs. Comorbidity may also provide an indication for other agents (Table 5.5). A further percentage will have tried one or other of these agents and been intolerant to them. In the present study it was assumed that up to 50% of individuals would fit into one of these categories and would be more appropriately treated with an ACE-inhibitor or calcium channel blocker (Table 5.4).

Without evidence of clinical superiority in the majority of patients, the relative cost of drug therapy becomes a major factor in determining the appropriate choice of therapy. Comparisons of costs are complicated by the system where Australian medication costs are shared between government and private individuals. In 1998, when this costing was undertaken, Australian pensioners and other 'concession card' holders paid the first $3.20 of each medication prescribed with the Commonwealth Government (through the PBS/RPBS) bearing the remaining cost. Others paid the first $20.00 of each item until their out of pocket expenses reached $612.60 after which they reverted to the same payment scheme as pensioners.

The analysis did not take into account any difference in cost that might come about because of a difference in monitoring requirements or in the costs of managing

adverse effects. There are no specific recommendations for electrolyte monitoring in the product information sheets, commercial drug compendia or the Australian Medicines Handbook and no apparent reason why any specific drug would require more intensive clinical monitoring [17]. On the other hand it is conceivable that the costs associated with the clinical management of adverse effects might be greater with one or other agent but there is presently insufficient information to quantify these differences.

The reasons why prescribers prefer the more expensive antihypertensive drugs are likely to involve a combination of factors. There is a perception that these agents are more 'modern', more potent and better tolerated (see Chapter 6). These perceptions have been enhanced by widespread reference in advertising material to surrogate measures (e.g. effect on lipids) with an expectation of improved cardiovascular outcomes. The pharmaceutical industry, which is largely responsible for creating these perceptions through their extensive advertising of these drugs, would argue that unless newer agents are continually introduced to supplant older agents the process of pharmaceutical innovation will be threatened.

There are few worthwhile price signals that provide an incentive to cost-effective prescribing. However it is worth noting that price differences to consumers are around the same as they are to government. It is also possible that studies soon to be reported will provide the evidence of superiority of ACE-inhibitors or calcium channel blockers. However the experience with antihypertensive agents should help guide future policy in relation to drug reimbursement. In particular:

1. The failure of Australian drug regulatory authorities to reflect the consensus conference guidelines raises questions about the appropriate link between evidence-based medicine and the regulatory process.

2. The lack of a mechanism to support 'public good' research to fill gaps in knowledge should be addressed. For example if a properly conducted study had been available comparing the adverse effect burden of the major antihypertensive drug classes it may well have countered the notion that the newer agents are better tolerated before this concept became entrenched. It was clearly not in the interests of the pharmaceutical industry to sponsor such research but the results could have been vital to the PBS. Several reports have commented that an ability to commission such research is a vital part of the research and development that should accompany any large enterprise. The present case is an example where such research could have saved many times what it cost.

3. The example of antihypertensive drugs provides an excellent example of the need for academic detailing or a similar form of advertising to prescribers to counter when appropriate the advertising of the pharmaceutical industry.

Conclusion

The trend evident in Figure 5.1 would seem to indicate that clinical practice has pre-empted the newer clinical trials and, contrary to evidence to date, have assumed superiority of newer over older agents. Thus while comorbidity does appropriately influence prescribing patterns, clinicians are not prescribing according to current

recommendations. Possible reasons why this is occurring are that clinicians are unaware of the guidelines or find them impractical, or they are influenced by personal or patient preference, or because drug marketing selectively promotes newer agents. There is therefore a need for the production of a simplified, pragmatic standardized paper and web-based clinical guidelines and further investigation of pharmaceutical industry influence on compliance to them.

The implications of this study for withdrawal of antihypertensive medication in the general practice environment are twofold.

1. The lack of conformity to clinical practice guideline recommendations on the agent of choice for initiation of pharmacotherapy may be reflected in diagnostic criteria and therefore the inappropriate initiation of such drug therapy.
2. The preference for the more expensive agents would increase the cost saving of successful cessation of antihypertensive medication.

Chapter 6

Factors influencing general practitioner adherence to hypertension guidelines: questionnaire survey.

Introduction

Because of the high prevalence of mild-moderate hypertension, the choice of initial therapy may have substantial cost implications for drug reimbursement agencies. National guidelines developed during the 1990s have generally recommended the relatively inexpensive thiazide diuretics and beta-adrenoreceptor blockers as the most appropriate agents to use as first line therapy for this condition [1-5]. Several new large-scale trials of more expensive antihypertensive therapy have been published but none have yet provided evidence that their efficacy, tolerability or long term satety is significantly better than these cheaper agents [6-9].

Despite the advice provided in the guidelines, prescribing surveys have shown a progressive decline in the use of diuretics and beta-adrenoreceptor blockers with a commensurate rise in the prescribing of calcium channel blockers and ACE-inhibitors (Chapter 5). Although this trend has been observed in both Australia and the United Kingdom there is little information about why doctors reject the use of thiazide diuretics and beta-adrenoreceptor blockers as initial therapy in uncomplicated mild-moderate hypertensive patients [10-12]. Cabana *et al* in a systematic review identified 7 basic

barriers to clinicians following clinical practice guidelines [13]. They are related to knowledge (lack of awareness or familiarity), attitude (lack of agreement with or belief in self-efficacy, or the inertia of current practice), and behaviour (difficulty in use, patient and environmental barriers).

Patient characteristics have been demonstrated as statistically significant predictors of non-adherence to guidelines. These include age, gender and race in the lower use of thiazide diuretics in the elderly (older, female, and black) [14]. The cut off points for diagnosis and treatment of hypertension in patients has also been shown to rise with age despite the absence of guideline differentiation [15, 16]. These studies found a good knowledge of guidelines suggesting it is intent rather than ignorance of guidelines that explains the non-adherence.

General practitioner characteristics have also been studied. Yap *et al* found no significant difference for goal blood pressure between urban and rural general practitioners [17]. They found longer time to follow up in rural general practitioners (72+/-13 and 36+/-5 days respectively) and a clear preference for newer agents (ACE-inhibitors 46%, diuretics 18.5%, beta-adrenoreceptor blockers 18.5%, calcium channel blockers 16%, alpha-adrenoreceptor blockers 1%). Agent preference however may vary from country to country as found in a survey conducted in Sweden and Minnesota in the early 1990s where despite near identical recommendations for all comparison items, the former preferred beta-adrenoreceptor blockers to the latter's ACE-inhibitors [16]. This survey also demonstrated a variation in lifestyle advice between countries with significantly

more Swedish family physicians recommending decreased alcohol and fat intake and stress management and Minnesota family physicians weight reduction and salt restriction.

The present study was designed to investigate the approach taken by general practitioners to the use of various antihypertensive drugs as monotherapy. It focussed on the reasons used by doctors for choosing one antihypertensive drug rather than another and examined the characteristics of doctors associated with particular prescribing patterns. The study tested the hypothesis that doctors choose the more expensive forms of therapy because they believe that these drugs are more efficacious, are associated with fewer side effects and have better long-term safety.

Method

Sample

General practitioners were recruited through a commercial database of Victorian general practitioners compiled by AMCo Publishing, the publishing arm of the Australian Medical Association (AMA). The database supplied contained over 800 randomly selected names from which a random sample was selected by sequentially deleting every third name until as near to 400 names remained without further culling (n = 419).

The AMA identified medical practitioners on this database as general practitioners. Subjects were excluded who on mail out reported they were no longer in general practice either because they were retired or considered themselves a special interest practitioner.

This latter group includes for example non-specialists who are doing counseling full-time and hence no longer manage hypertension. A number of specialists were also erroneously identified as general practitioners in the database.

Questionnaire

The survey instrument was a single page postal questionnaire of general practitioner characteristics, attitudes towards antihypertensive drug groups, knowledge of guidelines and preference for initiation of drug therapy in an uncomplicated moderate hypertensive case vignette (see Appendix).

General practitioner demographic data consisted of age, sex, vocational registration status, and whether they were in full or part-time practice. Preference for initiation of drug therapy was sought by rank order of the major antihypertensive drug groups, ACE-inhibitors, dihydropyrodine calcium channel blockers (DCCB), beta-adrenoreceptor blockers, non dihydropyrodine calcium channel blockers (NDCCB), angiotensin-II (AII) blockers and diuretics. Trade names were given as examples of each to ensure that respondents recognized which group corresponded with the agents they prescribe. Attitudes towards these antihypertensive drug groups were measured on a 5 point Likert scale (1 = poor to 5 = excellent) for blood pressure lowering efficacy, short-term side-effects (i.e. adverse reactions) and long-term side-effects (i.e. safety), and cost to government (1 = low to 5 = high). Knowledge of guidelines was measured by correct

identification of the recommended first line drug agents for uncomplicated primary hypertension, a diuretic or beta-adrenoreceptor blocking agent [4].

Three mailings occurred at 2 week and 3 week intervals between June and October 1999 with a retest mail out one further week later. Thence a telephone plus or minus facsimile contact was made to those who did not return a questionnaire.

Data Analysis

The questionnaire was validated by test-retest of 32 (11%) of respondents with a McNemar χ^2 Test for instrument reliability. Simple frequency analysis and a one-sample χ^2 Test comparing general practitioner characteristics and responses were conducted with computer software (SPSS for Windows 10; SPSS, Inc; Chicago, IL). A statistically significant result was accepted as clinically significant at a p value < 0.005.

Ethics approval

The Alfred Hospital Ethics Committee granted ethics approval.

Guidelines

Current recommended management for the initiation of antihypertensive drug therapy in uncomplicated mild-moderate hypertension was taken from 'The management of hypertension: a consensus statement' published in the Medical Journal of Australia in

1994 [4]. More recent publications, JNC VI (1997), BHS, the National Heart Foundation Guide, and WHO/ISH guidelines (1999) with the exception of the last, which has no preference, all agree with the Australian consensus guideline that the drug groups of choice are a diuretic or a beta-adrenoreceptor blocker [1-3][5].

Results

Response

Four hundred and nineteen letters were mailed out of whom 26 were identified as not in active general practice. One hundred and seventy responded to the first mail out, 51 to the second, 12 to the third, and 21 to facsimile and telephone follow-up. A total of 283 replies were received giving a response rate of 72% (283 of 393).

General practitioner demographics

A comparison with national data for general practitioner demographics, in parentheses, would suggest that the sampling method was valid and the results therefore generalisable to Australian general practice (Figure 6.1) [18]. The sample was predominantly male 70% (67%), vocationally registered 92.7%, and in full-time practice 71% (75%).

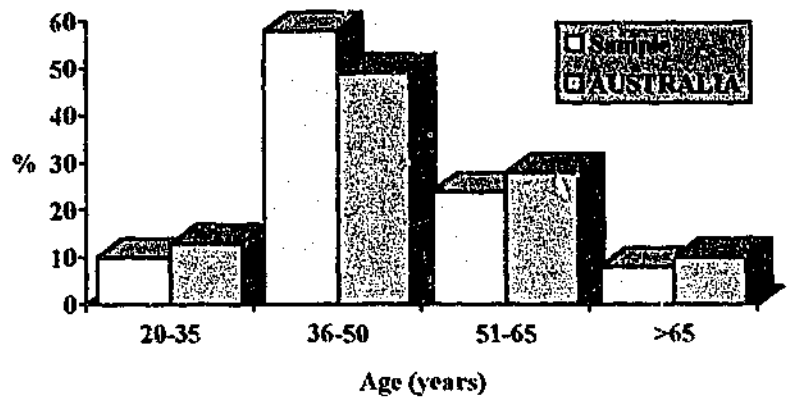


Figure 6.1. A comparison of sample Victorian general practitioner age demographics with national statistics [18].

Case vignette

The general practitioner preference for a first line agent in the case vignette is shown in Figure 6.2. ACE-inhibitors or AII blockers were ranked first choice by 75% of respondents. The second choice agent selected by those favouring an ACE-inhibitor as initial therapy was a dihydropyridine calcium channel blocker in 45% and an AII blocker in 18% . Of note was the relatively high percentage (27% diuretics, 15% beta-adrenoreceptor blockers) of respondents who indicated that they would use these agents only as a last resort.

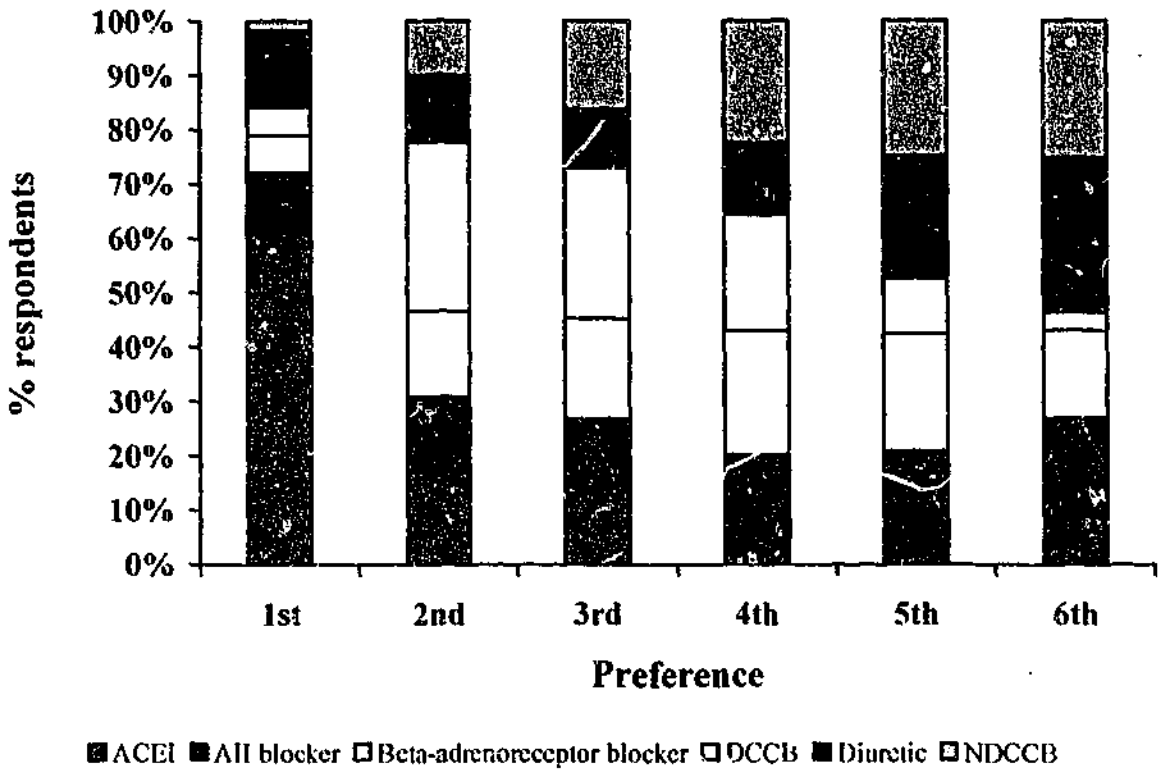


Figure 6.2. General practitioner preference expressed as a percentage of respondents who ranked each of the major antihypertensive drug agents for first line treatment in a 50-year-old male with a blood pressure of 180/100 mmHg, no other cardiovascular disease risk factors and who had not responded to advice on lifestyle changes.

Attitudes towards drug agents

General practitioner perceptions of efficacy, tolerability and long term safety of the major classes of antihypertensive drugs are shown in Figures 6.3-6.6 and are summarised in Table 6.1. In general, prescribers considered ACE-inhibitors, AII blockers and dihydropyridine calcium channel blockers to be more efficacious than beta-adrenoreceptor blockers and diuretics. ACE-inhibitors and AII blockers were also perceived as being associated with a lesser burden of adverse events and have better long term safety compared with other agents.

Newer agents were generally recognized as being more expensive than older. Twice as many rated AII blockers as being high cost than ACE-inhibitors despite the marketing of these agents at similar costs in the Federal pharmaceutical schemes. This response was most marked in the 20-35 age group. Conversely diuretics (70%) and beta-adrenoreceptor blockers (28%) were ranked correctly as cheapest with the respective average daily cost being $0.11 and $0.28 respectively (Chapter 5).

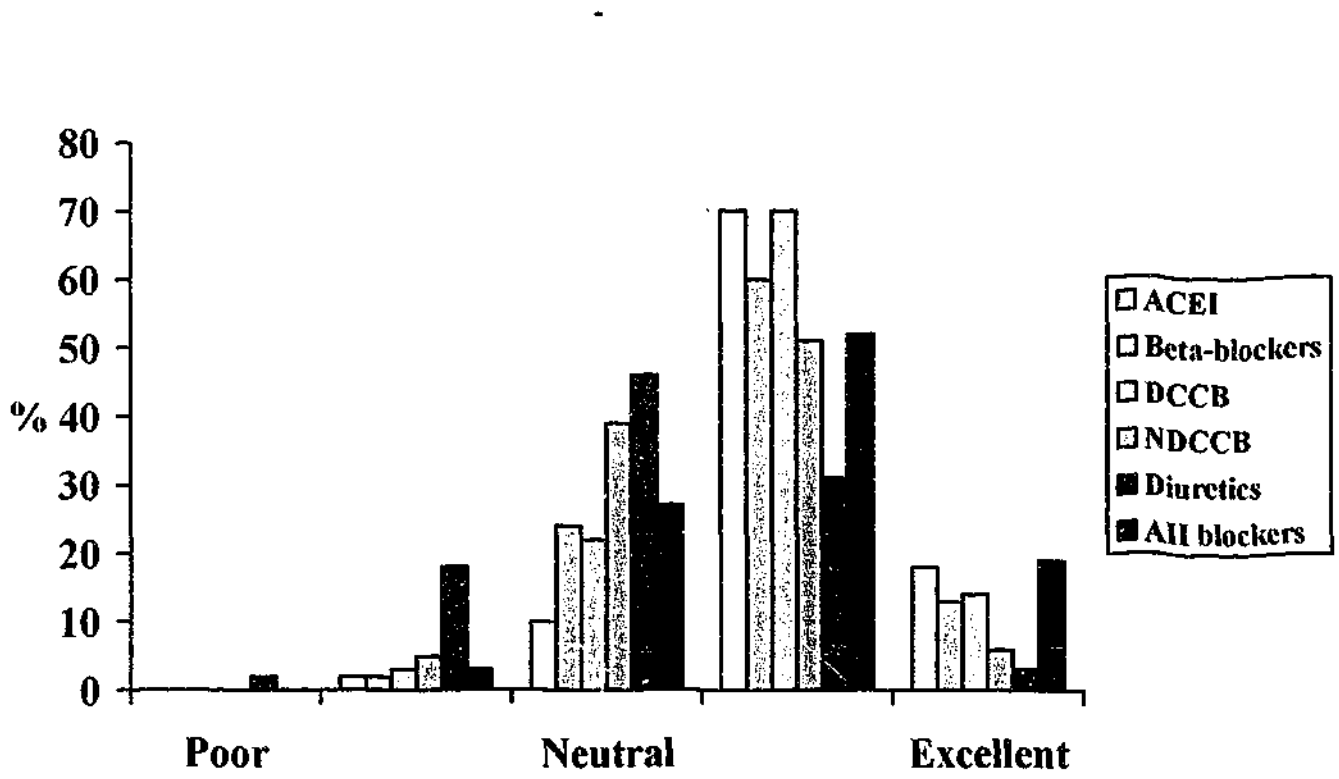


Figure 6.3. General practitioner attitudes towards drug groups' efficacy (blood pressure lowering).

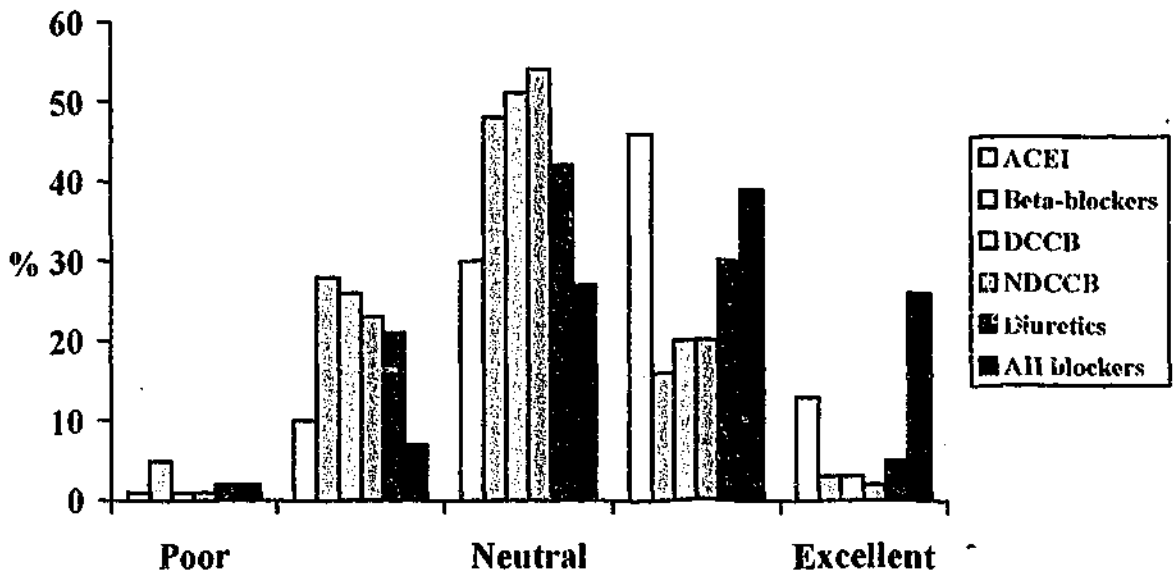


Figure 6.4. General practitioner attitudes towards drug groups' side effects (short-term).

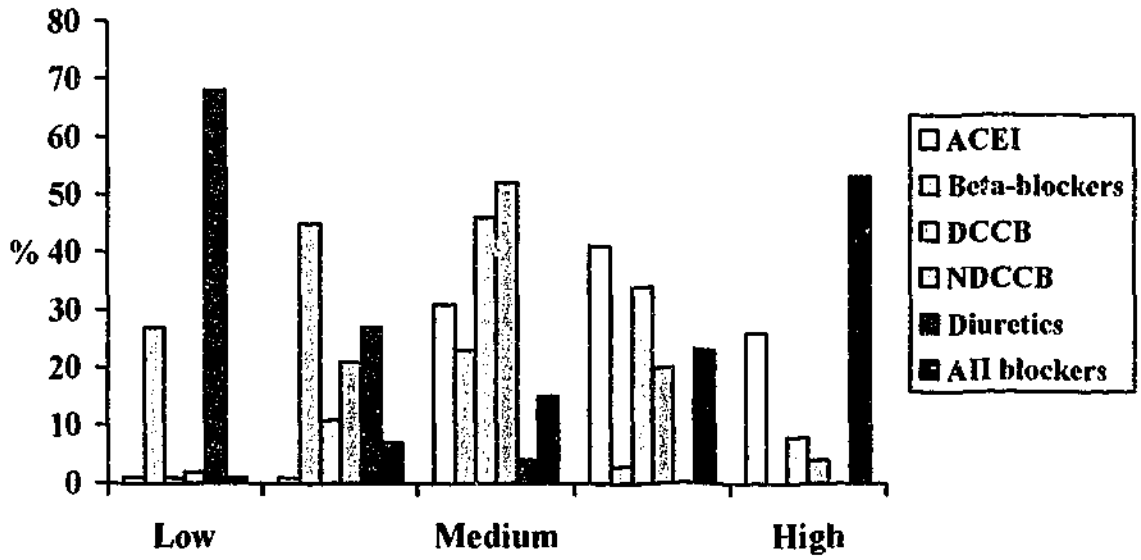


Figure 6.5. General practitioner attitudes towards drug groups' long-term safety.

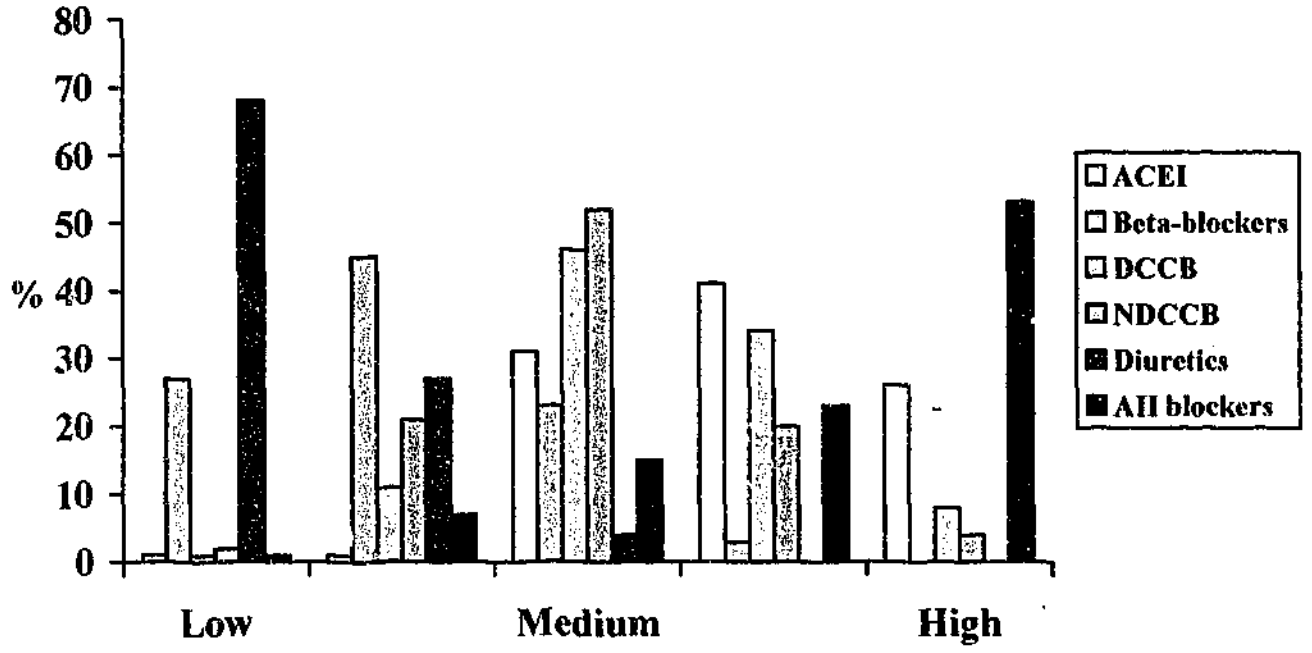


Figure 6.6. General practitioner attitudes towards cost to government.

Factor / Agent	Efficacy	Short term side-effects	Long term safety	Cost to government
	Scale			
	1 = poor to 5 = excellent			1 = low to 5 = high
ACE-inhibitor	4.04	3.59	4.17	3.91
Beta-blocker	3.83	2.82	3.73	2.24
DCCB	3.87	2.98	3.71	3.37
NDCCB	3.59	3.00	3.66	3.03
Diuretic	3.16	3.13	3.30	1.38
AII antagonist	3.86	3.80	3.76	4.20

Table 6.1. Mean scores on a Likert scale (1 to 5) of general practitioner perceptions of efficacy, side-effects, safety, and cost to government of antihypertensive drug agents.

Knowledge of guidelines

General practitioners nominated the following agents as those recommended by current consensus guidelines for first line treatment of uncomplicated primary hypertension. ACE-inhibitors 38.5%, beta-adrenoreceptor blockers 48.8%, dihydropyrodine calcium channel blockers 21.6%, non-dihydropyrodine calcium channel blockers 12.7%, diuretics 58.0% and AII blockers 4.9%. As previously reported current recommendations are a thiazide diuretic or a beta-adrenoreceptor blocker [4, 5]. Only 36.7% of respondents correctly identified one or both of the current recommended drug agents and no other agent.

The relationship of general practitioner characteristics to questionnaire responses

Age was a major determinant of general practitioner attitudes towards drug properties. In general younger prescribers were less likely to follow recommended guidelines and were most likely to hold optomistic views of the efficacy and safety of the newer agents (Figures 6.8-6.14 pages 133-136).

Guideline knowledge was a statistically significant ($p < 0.005$) determinant of drug agent preference in the case vignette (Figure 6.7 overleaf) and also as a determinant of general practitioner attitutdes towards drug properties (Figures 6.15-6.17 pages 136-137).

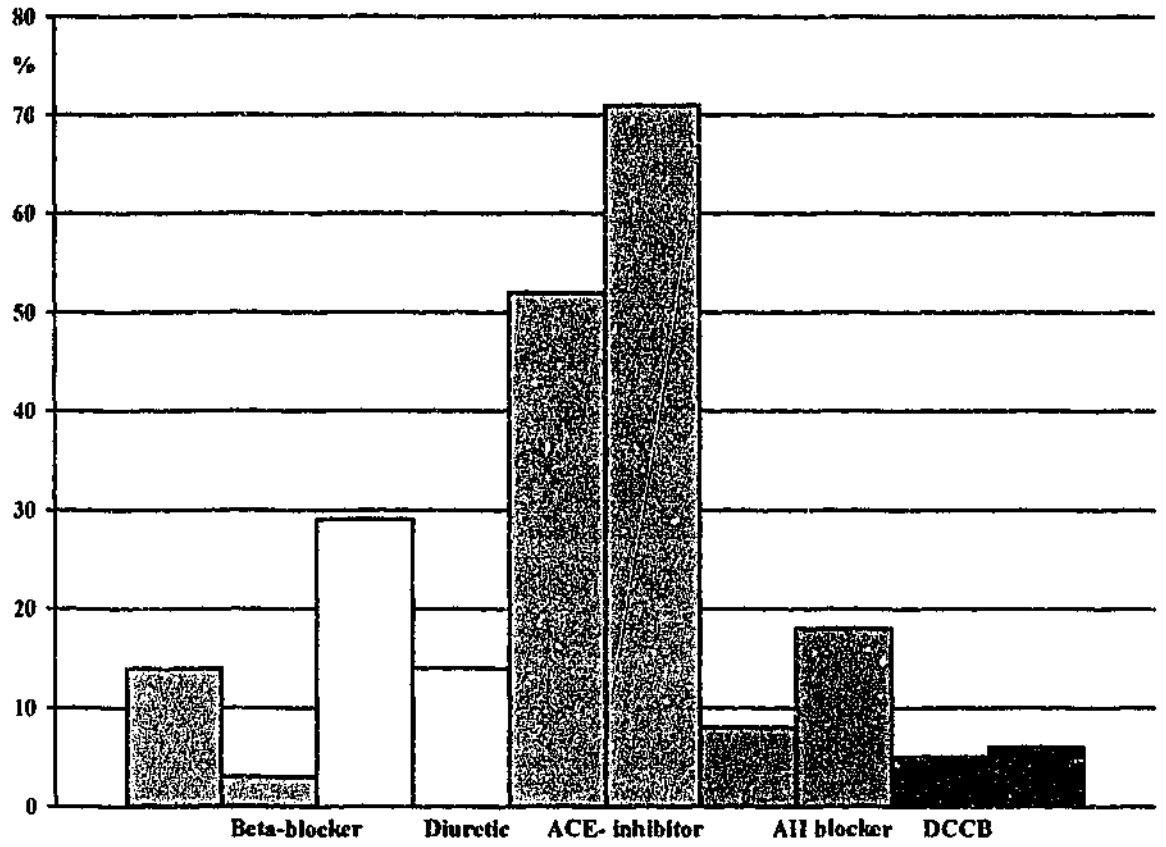


Figure 6.7. Drug agent first preference by antihypertensive drug agent in the case vignette compared with knowledge of the appropriate first line agent in the guidelines. Left column for each agent are general practitioners who had correct guideline knowledge and right for those who did not. All differences between these groups were statistically significant.

Comparison of respondent characteristic to drug agent properties demonstrated that younger general practitioners believed that blood pressure lowering was greater for AII blockers and dihydropyridine calcium channel blockers and these agents had additional benefits for cost to government and fewer long-term side-effects respectively. Older general practitioners believed that older agents had better blood pressure lowering than their younger colleagues did (beta-adrenoreceptor blockers) and short-term side-effects (beta-adrenoreceptor blockers and diuretics).

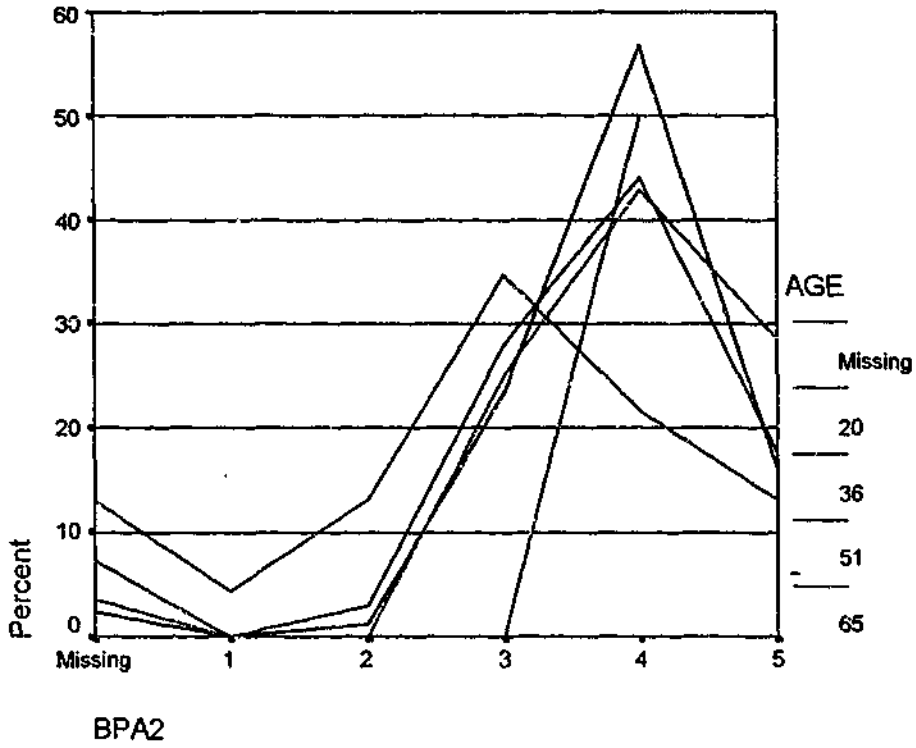


Figure 6.8. General practitioner attitude by age group towards the blood pressure lowering efficacy of AII antagonists (BPA2). 1 (poor) – 5 (excellent). Age groups are 20 = aged 20-35 years, 36 = aged 36-50 years, 51 = aged 51-65 years, and 65 = aged over 65 years.

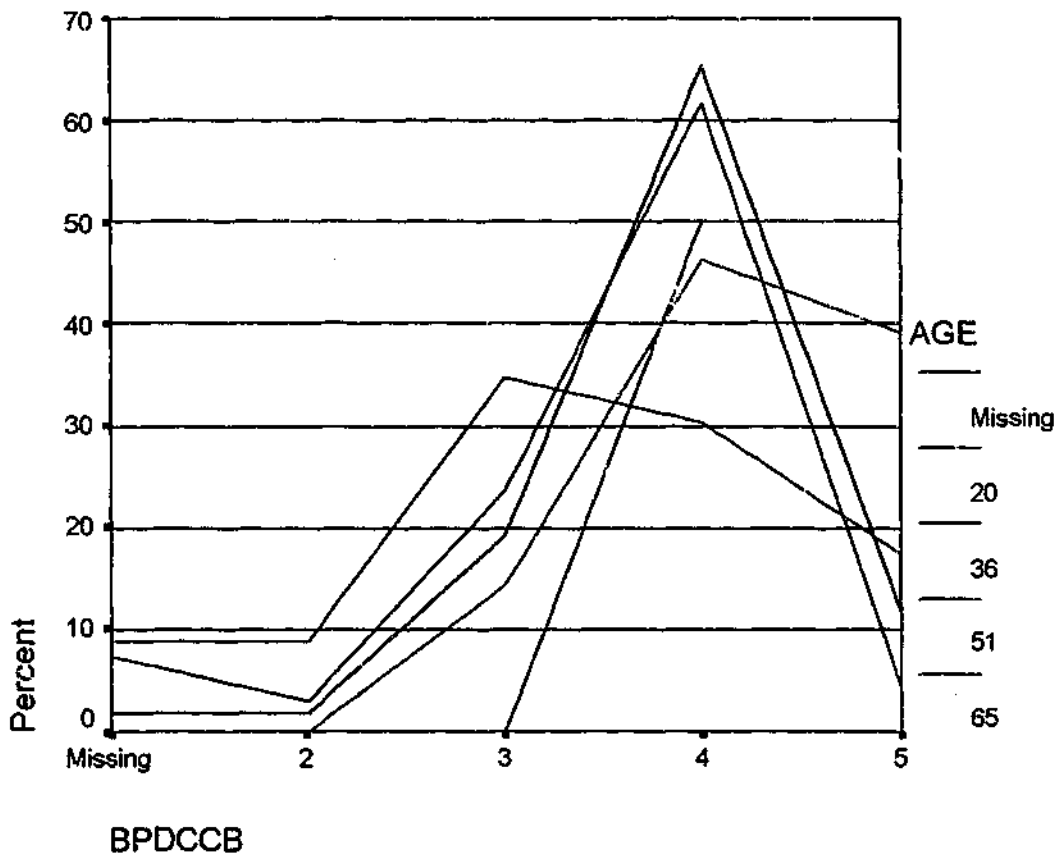


Figure 6.9. General practitioner attitude by age group towards the blood pressure lowering efficacy of dihydropyridine calcium channel blockers (BPDCCB). 1 (poor) – 5 (excellent). Age groups are 20 = aged 20-35 years, 36 = aged 36-50 years, 51 = aged 51-65 years, and 65 = aged over 65 years.

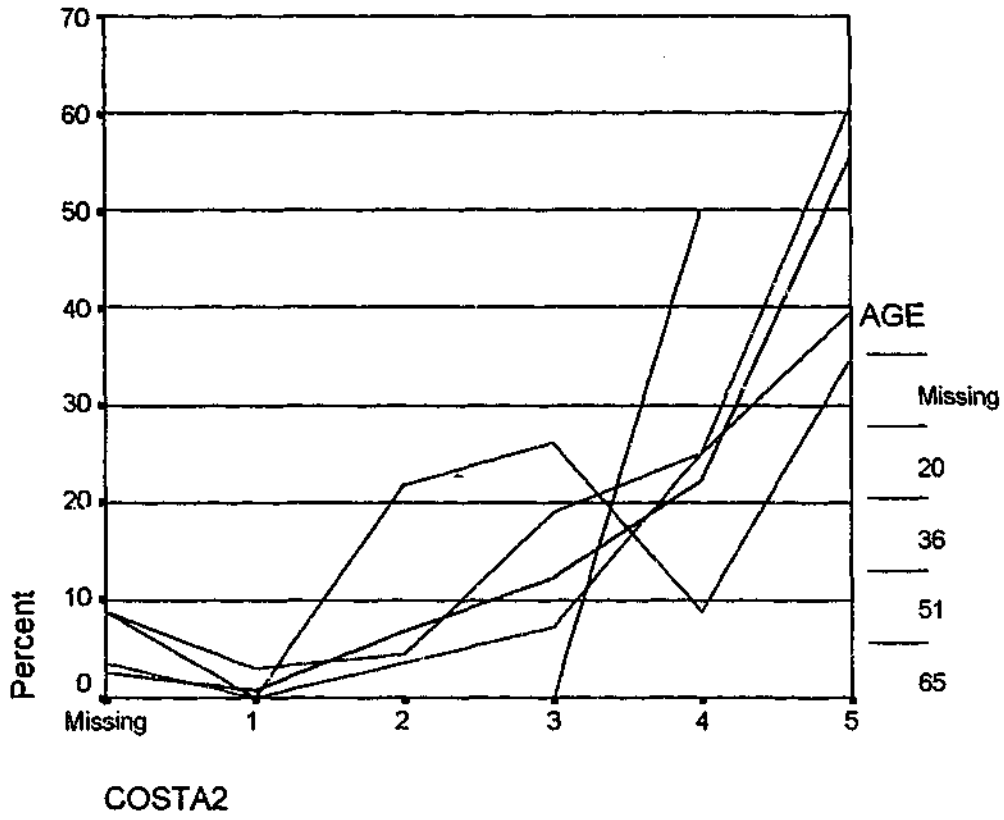


Figure 6.10. General practitioner attitude by age group towards the cost to government of A2 antagonists (COSTA2). 1 (low) – 5 (high). Age groups are 20 = aged 20-35 years, 36 = aged 36-50 years, 51 = aged 51-65 years, and 65 = aged over 65 years.

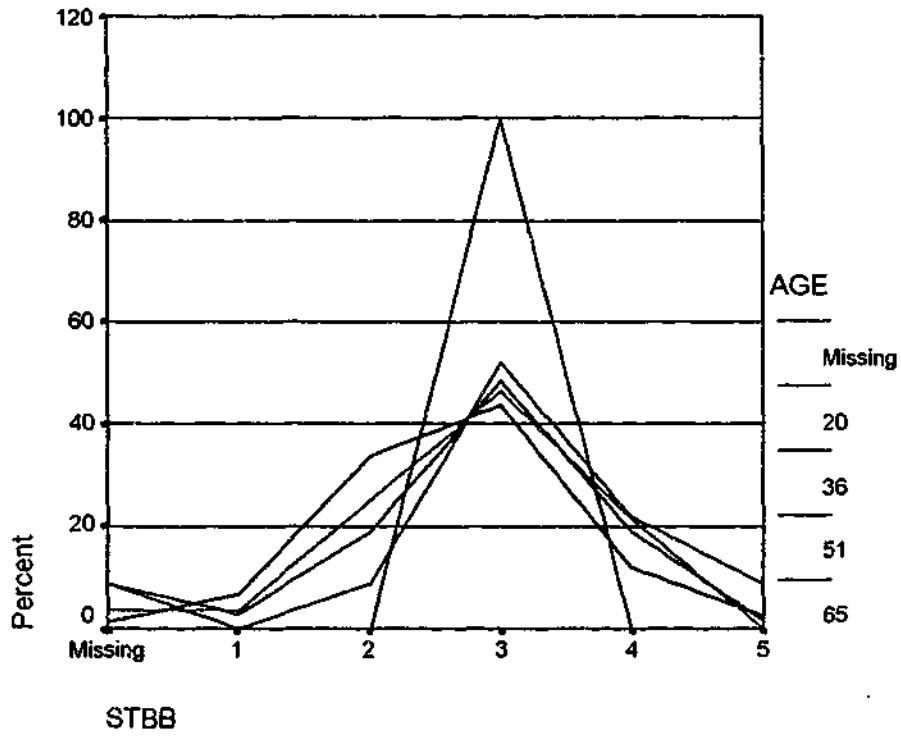


Figure 6.11. General practitioner attitude by age group towards the short term side-effects of beta-adrenoreceptor blockers (STBB). 1 (poor) – 5 (excellent). Age groups are 20 = aged 20-35 years, 36 = aged 36-50 years, 51 = aged 51-65 years, and 65 = aged over 65 years.

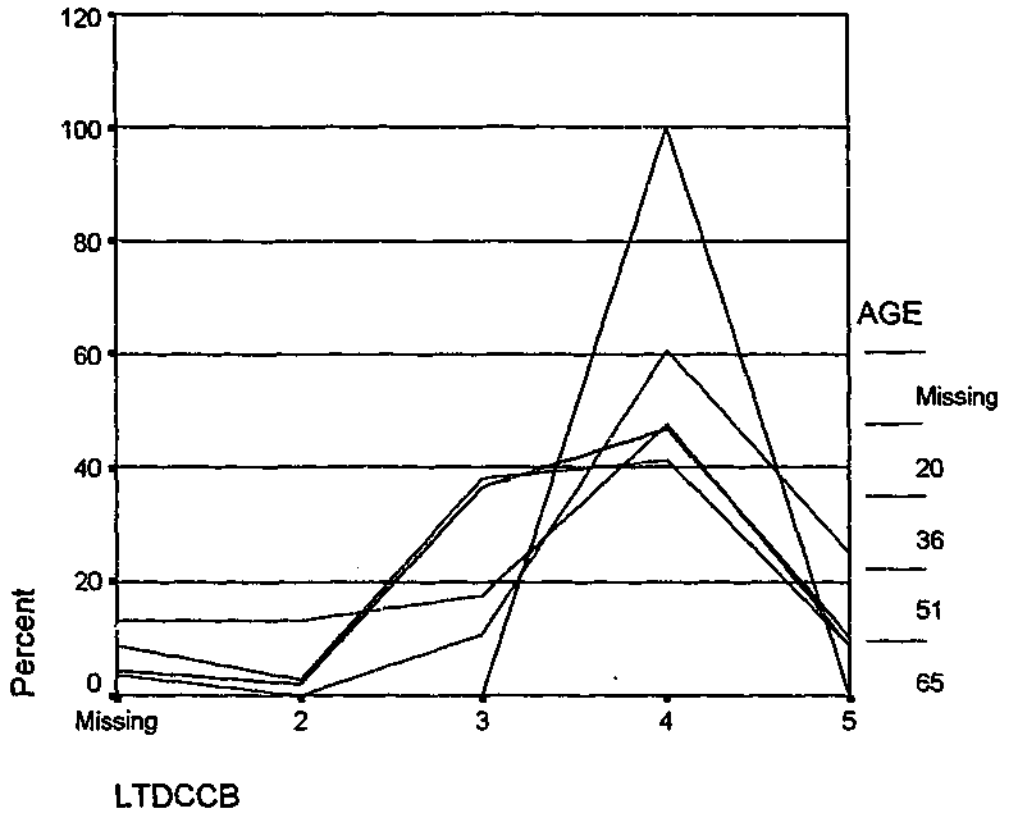


Figure 6.12. General practitioner attitude by age group towards the long term side-effects of dihydropyridine calcium channel blockers (LTDCCB). 1 (poor) – 5 (excellent). Age groups are 20 = aged 20-35 years, 36 = aged 36-50 years, 51 = aged 51-65 years, and 65 = aged over 65 years.

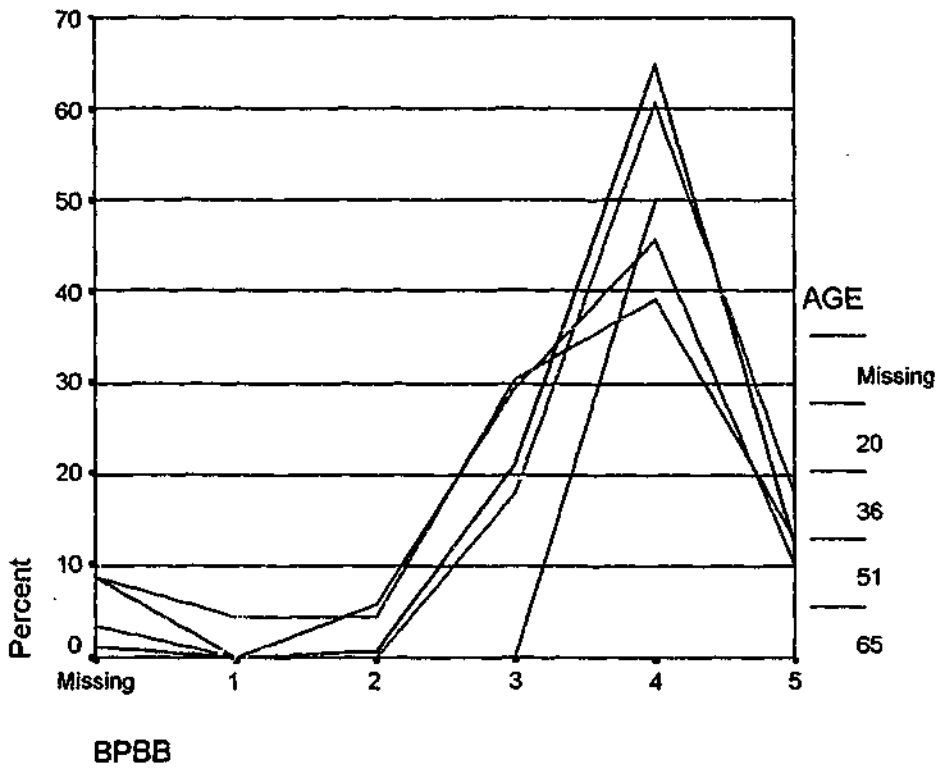


Figure 6.13. General practitioner attitude by age group towards the blood pressure lowering efficacy of beta-adrenoreceptor blockers (BPBB). 1 (poor) – 5 (excellent). Age groups are 20 = aged 20-35 years, 36 = aged 36-50 years, 51 = aged 51-65 years, and 65 = aged over 65 years.

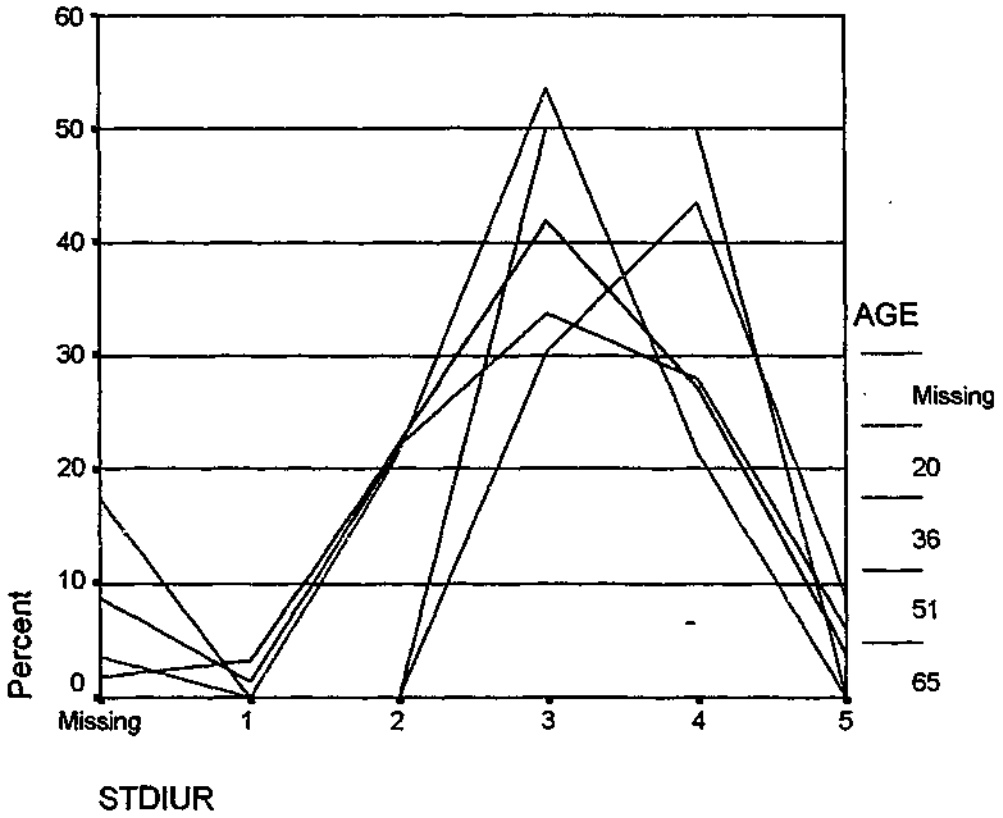


Figure 6.14. General practitioner attitude by age group towards the blood pressure short-term side effects of diuretics (STDIUR). 1 (poor) – 5 (excellent). Age groups are 20 = aged 20-35 years, 36 = aged 36-50 years, 51 = aged 51-65 years, and 65 = aged over 65 years.

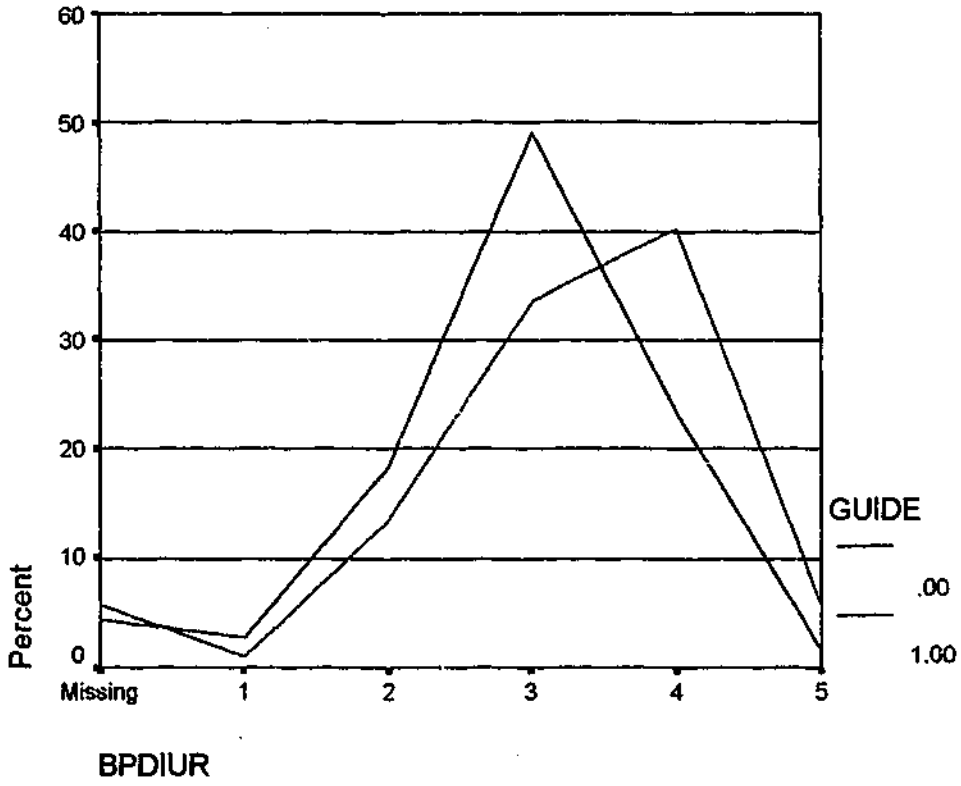


Figure 6.15. General practitioner attitude by knowledge of guidelines towards the blood pressure lowering efficacy of diuretics (BPDIUR). 1 (poor) – 5 (excellent). 0 = no knowledge, 1 = correct knowledge of guidelines.

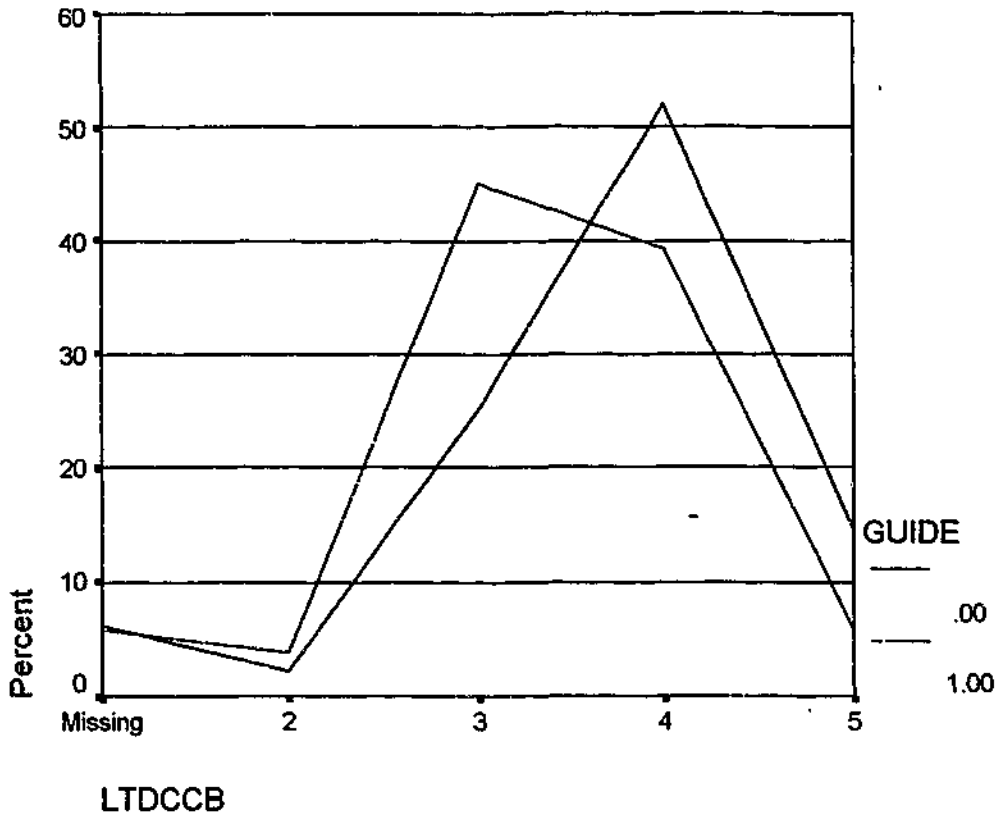


Figure 6.16. General practitioner attitude by knowledge of guidelines towards the long term side effects of dihydropyridine calcium channel blockers (LTDCCB). 1 (poor) – 5 (excellent). 0 = no knowledge, 1 = correct knowledge of guidelines.

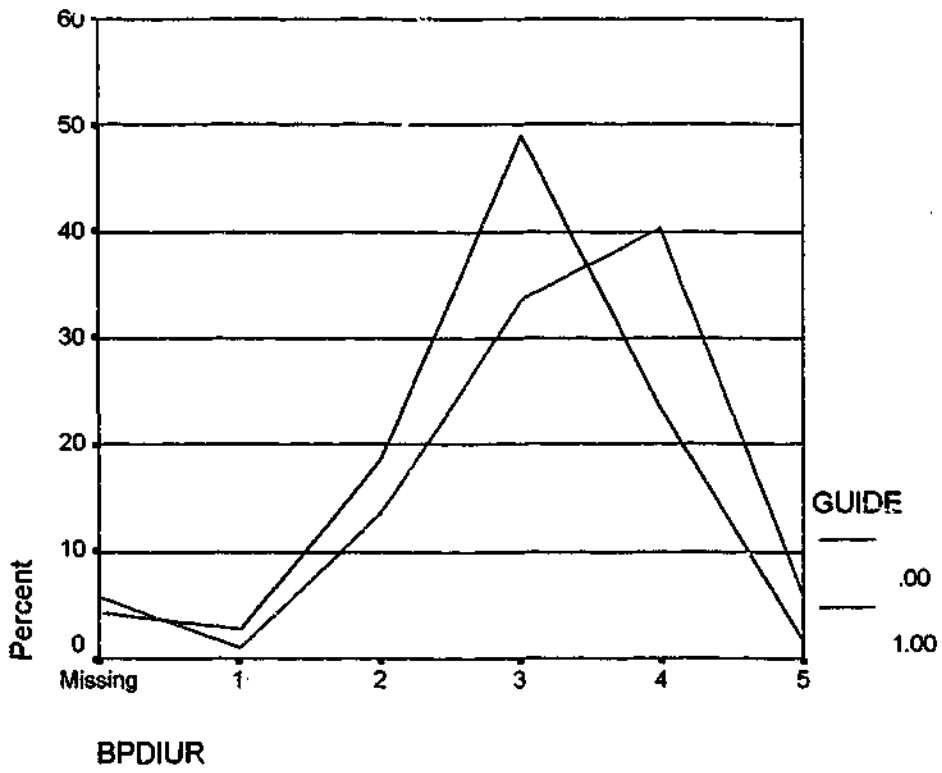


Figure 6.17. General practitioner attitude by knowledge of guidelines towards the blood pressure lowering of diuretics (BPDIUR). 1 (poor) – 5 (excellent). 0 = no knowledge, 1 = correct knowledge of guidelines.

Discussion

The reliability of the sampling instrument and the generalisability of the results are assisted by the high response rate, test-retest analysis and the similarity of general practitioner demographic data to that of national figures for registered doctors. The results may be influenced by non-responders being less interested in issues related to hypertension but it is unlikely that their inclusion would substantially alter the findings reported.

Simple frequency analysis revealed that general practitioners preferred newer agents to older in the case vignette. The high percentage choosing ACE-inhibitors or dihydropyridine calcium channel blockers is in keeping with the trends in antihypertensive drug therapy observed in government prescribing surveys (Figure 6.2) [19]. The highest ranking of these agents was by respondents who were unaware of guideline recommendations.

There was a trend of respondents believing newer agents to be more efficacious in blood pressure lowering. This trend was most evident in younger respondents. These beliefs are held despite that "there is no reliable or consistent evidence that indicates substantive differences between drug classes in their effect on blood pressure" [3]. There is evidence however that patients of black African descent do respond differently to these classes but these patients are not commonly encountered in an Australian general practice setting [20].

Respondents also considered newer agents to have superior short-term side-effect profiles with most ranking agents operating on the renin-angiotensin system as superior to other agents. Differences in the incidence of specific symptoms are known to occur among different antihypertensive drug classes but differences in the overall burden of adverse effects is small [21]. Large-scale trials have reported no significant differences in adverse events and quality of life scales [8, 9, 20, 22]. Age appears to be a key factor influencing opinion about the side effect profile of older agents, with older general practitioners having fewer concerns regarding an adverse side-effect profile.

The present study suggested that, despite the lack of evidence, general practitioners considered that agents operating on the renin-angiotensin system had superior long-term safety. Furthermore younger doctors and those without guideline knowledge believe AII blockers and dihydropyradine calcium channel blockers were superior to other agents.

Conclusion

A random sample of Australian general practitioners indicated a strong preference for initial treatment of uncomplicated mild-moderate hypertension with a renin-angiotensin system active drug, or in cases where these agents were contraindicated, with a dihydropyridine calcium channel blocker.

General practitioners generally believe that newer antihypertensive agents are more efficacious, have better short and long-term side-effect profiles, and are more expensive.

Those that know current guideline recommendations are influenced significantly in their decision making but, like their compatriots who are ignorant of the guidelines, still have a preference for newer agents. Amongst the Victorian general practitioners sampled ACE-inhibitors were the drug agent of choice. While other important influences on the choice of agent for the pharmacotherapy of hypertension such as co-morbidity and patient preference has not been investigated, it would appear from the responses that irrespective of the level of evidence newer agents are considered superior to older agents.

Although knowledge of guidelines had a significant influence on adherence to guidelines in the stated practice of general practitioners in the initiation of antihypertensive medication it did not have much effect on the attitudes to various agents. Age (experience) seems to be the determining factor here. This study therefore suggests that adherence to guidelines could be improved by the specific promotion of older agents to younger doctors as well as of the guidelines *per se* to all. There is also demonstrable need for government to invest in the promotion of accurate information on drugs through continuing education of prescribers and facilitating the production of a standardized paper and web-based clinical guidelines.

The findings of this survey have significance for antihypertensive drug withdrawal in general practice. It suggests that lack of knowledge of guidelines by the majority of general practitioners and subsequent non adherence may lead to inappropriate prescribing and management of blood pressure and hence influence success rates for drug withdrawal.

Chapter 7

Conclusions

Aims revisited

In Chapter 1 we saw that hypertension and its management must not be considered in isolation from other factors that delineate absolute risk of a cardiovascular event. The change of emphasis to absolute risk classification and the management of hypertension within the umbrella of cardiovascular disease prevention therefore has implications for withdrawal of antihypertensive drugs. Thus those who may be offered a trial of withdrawal of antihypertensive drugs are limited to uncomplicated mild-moderate hypertension preferably willing to adopt lifestyle changes as outlined in Chapter 2. The population studied in Chapters 3 and 4 were elderly and therefore by definition at least medium absolute risk *should they redevelop hypertension* (Table 1 page 4). An increase in blood pressure would place them at adverse risk therefore there is a need for systematic surveillance and reinstatement of drug therapy if and when hypertension returns.

In Chapter 2 the aim was to identify subject characteristics reported in the literature that predict maintenance of normotension for a period of 12 months after all antihypertensive drugs have been withdrawn. The systematic review of the literature and a meta-analysis of predictors of maintenance of normotension post withdrawal of antihypertensive drugs suggested that withdrawal of antihypertensive drugs may be offered to both sexes but that

success rates are improved by salt restriction and loss of body mass. It also suggested that long-term well controlled patient on monotherapy is best suited to withdrawal of antihypertensive drugs. From Chapter 2 it was also seen that the rate of return to hypertension is not related to the criteria established for hypertension *per se*.

The aim of Chapter 3 was to identify subject characteristics in a large comparative outcome study that predict successful drug withdrawal and 'maintenance of normotension' for a period of 2-76 weeks. Subject characteristics that predicted successful drug cessation were younger age and monotherapy for hypertension. Characteristics that predicted 'maintenance of normotension' for the specified period were monotherapy again, and lower on treatment systolic and diastolic blood pressure.

Chapter 3 also demonstrated that antihypertensive drug withdrawal could be successfully completed in a large cohort throughout mainland Australian in a variety of general practice settings (metropolitan, provincial city, town, rural and remote, corporate and doctor owned practices, solo and group practices). Approximately one in four subjects (26%) commenced the drug withdrawal program. Patients not considered suitable for drug withdrawal were predominantly those with pre-existing cardiovascular complications, difficult to manage patients or patients who on personal reflection or their general practitioner advice were not willing to consider drug cessation. Of those subjects entering drug withdrawal, 6291 (92%) completed the program defined as off all antihypertensive medication for one week. Of those who did not complete drug

withdrawal the majority did so because they or their general practitioner did not wish to continue rather than adverse events associated with withdrawal.

Therefore a strategy of drug withdrawal as part of patient management for hypertension may provide reinforcement for compliance to therapy in those subjects returning to hypertension and importantly, may provide the opportunity for 20% of the currently treated hypertensive population to avoid the costs and side effects of drug therapy. With sustained 'normotension', this could be done without increasing cardiovascular risk.

Chapter 4 aimed to identify subject baseline characteristics that are predictors of maintenance of normotension at 12 months and time to return to hypertension in an elderly hypertensive general practice based cohort. The pragmatic predictors of successful withdrawal are 'younger' age with low on treatment systolic pressures, greater waist-hip ratio, and minimal drug therapy. Conversely those least likely to be successful are older subjects with higher pressures, lesser waist-hip ratio and two or more antihypertensive drugs.

An additional aim was to compare major cardiovascular outcomes and death of those who maintain normotension with those who returned to hypertension. In the 'Withdrawal of Antihypertensive Drugs in ANBP2' cohort there were 8 non blood pressure end-points in the 'maintain normotension' group, 22 in the 'return to hypertension' group, and 17 in the 'other' group. The respective rate per 1000 patient years was 40.6, 74.0, and 333.6. The overall rate of all non blood pressure end-points (excluding angina and arrythmias)

for the 'WAD in ANBP2' cohort was 60.5 events per 1000 patient years compared to the ANBP2 cohort rate of 51.0 events per 1000 patient years. There were four deaths, two non-vascular deaths (neoplasias) and two vascular deaths both of whom had returned to hypertension and medication prior to their fatal events. In the ANBP2 cohort who entered drug withdrawal there were 31 serious adverse events in the 'maintain normotension' group (2.5% of that group), 76 in the 'return to hypertension' group (1.5%), and 52 in the group who exited during withdrawal (9.6%). There were two deaths, both fatal acute myocardial infarctions, one each in the maintain normotension, and return to hypertension groups. While the study had insufficient power to prove statistical significance the higher rate reinforces the need to utilize predictors and offer lifestyle changes to all who are offered drug withdrawal.

In view of the substantial cost of antihypertensive therapy, these findings emphasise the value of a trial of antihypertensive drug withdrawal in patients without overt vascular disease or target organ damage, fitting the profile of younger age with blood pressure well controlled on minimal drug therapy. Systematic long-term follow up and reinstatement of drug therapy is mandatory if this strategy is followed.

In Chapter 5 the aim was to examine trends in the use of the major antihypertensive drug groups and to determine the cost implications resulting from these trends. The trend evident indicated that clinicians had assumed superiority of newer over older agents despite the lack of empirical evidence to support this. Although comorbidity did appropriately influence prescribing patterns, clinicians were not prescribing according to

current recommendations. Possible reasons why this is occurring are that clinicians were unaware of the guidelines (Chapter 6) or found them impractical, or they were influenced by personal or patient preference, or because drug marketing selectively promotes newer agents.

In Chapter 5 it was also stated that the rationale for the choice of a particular agent for each individual patient should ideally be based on clinical rather than economic grounds provided there is additional clinical benefit to offset the increased cost to the individual and community. However when no clinical advantage exists, as was the case here, the potential savings to the Federal Government if prescribing followed the guidelines extant in 1998 were in the vicinity of $43 million in that year alone.

The implications of these findings for withdrawal of antihypertensive medication in the general practice environment are twofold. Firstly the lack of conformity to guideline recommendations on the agent of choice for initiation of pharmacotherapy may be reflected in diagnostic criteria and therefore the inappropriate initiation of such drug therapy. Secondly the preference for the more expensive agents would increase the cost saving of successful cessation of antihypertensive medication.

In Chapter 6 the aim was to investigate the approach taken by general practitioners to the use of various antihypertensive drugs as monotherapy for mild to moderate hypertension, to identify reasons used by doctors for choosing one antihypertensive drug rather than another and to examine the characteristics of doctors associated with particular

prescribing patterns. The postal survey reported in Chapter 6 supported the findings in Chapter 5 that general practitioners do not prescribe antihypertensive medication according to current guidelines. A random sample of Victorian general practitioners indicated a strong preference for initial treatment of uncomplicated mild-moderate hypertension with a renin-angiotensin system active drug, or in cases where these agents were contraindicated, with a dihydropyridine calcium channel blocker.

General practitioners generally believed that newer antihypertensive agents were more efficacious, had better short and long-term side-effect profiles, and were more expensive. Those that knew current guideline recommendations were influenced significantly in their decision making but still had a preference for newer agents. In Victorian general practice ACE-inhibitors were the drug agent of choice. While other important influences on the choice of agent for the pharmacotherapy of hypertension such as co-morbidity and patient preference had not been investigated, it would appear from the responses that irrespective of the level of evidence newer agents were considered superior to older agents.

Key points from this chapter are that a minority of doctors were aware of antihypertensive guideline contents and that knowledge of guidelines had a statistically significant influence on adherence to guidelines although not on the attitudes toward various agents. It was also found that age/exposure to drug agents influences attitudes toward the common antihypertensive drug agents. Adherence to guidelines could be improved by the specific promotion of older agents to younger doctors as well as of the

guidelines *per se* to all. There was also a demonstrable need for government to invest in continuing medical education and in studies to establish justification for more expensive forms of treatment.

These findings suggest that lack of knowledge of guidelines by the majority of general practitioners and subsequent non adherence may lead to inappropriate prescribing and management of blood pressure and hence influence success rates for drug withdrawal.

Future investigation

Like 'Withdrawal of Antihypertensive Drugs in the Second Australian National Blood Pressure Study' none of the studies identified in the literature review have been sufficiently powered to demonstrate the safety or otherwise of withdrawal of antihypertensive drugs. The issue of safety was dealt with by surrogate measures or inference. The majority of studies were opportunistic and observational and were constrained by the needs of other studies. However the gold standard of a randomised double blinded clinical trial is very unlikely to occur because of pragmatic aspects of the conduct of such trials. The first of these is cost. The stakeholders in such a study would be the Federal Government and the drug companies. The Federal Government has shown a willingness to participate cooperatively with industry in research that has potential benefits for patients and their own bottom line. ANBP2 is such an endeavour. However core funding is unlikely to come from an industry that would potentially lose custom should it be successful.

Double blinding also assumes the use of a placebo. Use of a placebo is not the same as non-medication due to the placebo effect and would therefore not reflect real practice. The sample size would also need to be enormous given the cardiovascular endpoints rate seen even in the elderly. ANBP2 will collect data for 25,000-30,000 patient years. This has major cost and practical implications.

There is also the problem of therapeutic inertia. Given the extensive evidence of the benefits of treating hypertension and the recognition that the prevailing problems are the large number of undiagnosed, under treated, and non-compliant individuals, general practitioners are resistant to ceasing medication.

Given these difficulties a meta-analysis of withdrawal of antihypertensive drugs studies is the approach required to establish beyond surrogate measures the safety of withdrawal of antihypertensive drugs. It is likely to be a difficult task given the varying study designs, criteria and reporting of adverse events.

Final recommendations

Suitable candidates for withdrawal of antihypertensive drugs in the elderly in a general practice setting are:

1. Not at high absolute risk for a cardiovascular event, i.e. no associated clinical conditions, target organ damage or other adverse cardiovascular disease risk factors.
2. In the goal range for blood pressure.
3. Preferably have the following characteristics:
   a) Younger age.
   b) Single antihypertensive drug therapy.
4. Be willing to accept lifestyle changes such as salt restriction and loss of weight (where indicated).
5. Must have a reminder/recall system in operation. The systematic review and 'WAD in ANBP2' demonstrated no abatement in subjects returning to hypertension after an initial higher rate of return as shown by the similarity of Figure 1.1 (page 10), Figure 2.1 (page 56), and Figure 4.5 (page 99). The swale shape of Figure 1.1 is almost certainly due to more frequent subject review in the first six months compared to the second rather than a real effect.

To address concerns of possible adverse risk of cardiovascular events related to withdrawal of antihypertensive medication all of the above should be followed but specifically predictors considered and lifestyle interventions implemented or adverse risk may entail.

In the busy general practice environment the likely candidate for withdrawal of antihypertensive drugs is the mild-moderate hypertensive patient, especially if there are doubts regarding the diagnosis, with the above characteristics who is being rewarded for

compliance to drug therapy and or lifestyle changes, and who has reached goal blood pressures. Such a patient must be willing to accept or continue behavioral change, blood pressure monitoring, and restart drug therapy as blood pressure levels dictate.

It is worth revisiting the algorithm produced in Chapter 2 to review its contents (Figure 7.1). It would essentially remain unchanged except for the addition of the recommendation of lifestyle change to all.

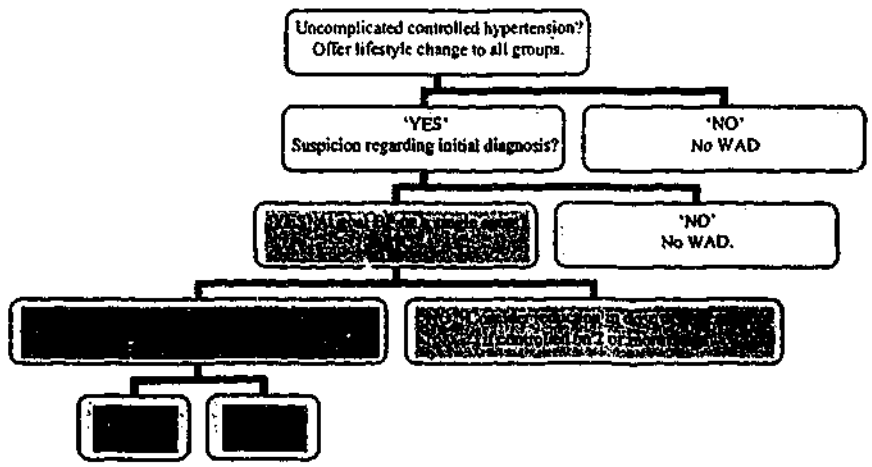


Figure 7.1. Algorithm demonstrating a proposed sequence of decisions for determining which patients should be considered for withdrawal of antihypertensive drugs. Depth of box shading represents increasing likelihood of successful maintenance of long term normotension. As lifestyle changes have been shown to double the rate of maintenance of normotension post withdrawal of antihypertensive drugs they should be offered to all patients in whom drug withdrawal or reduction is being contemplated.

Promotion of guideline adherence with subsequent government and community cost savings in the pharmacological management of hypertension can be enhanced by:

1. Guidelines being evidence based, offering consistent recommendations and regularly updated. It would be preferable that they also be web based or compiled into a single tome for ease of access.

2. Acceptance and promotion of the guidelines by peak bodies (NHMRC, NHF, HBRCA etc), professional bodies (RACP, RACGP, ACRRM etc), government (DHAC etc), QANGOs (NPS etc), and consumer groups.
3. Academic detailing especially of older agents to younger doctors.
4. Continuing medical education in the rational use of medicines.
5. Ensuring that quality data is available through continuing research. This research must also include investigating how to change clinical behaviour to improve the adoption of evidence based health care.

Summary

This thesis has investigated the pharmacological management of hypertension in the elderly in Australia. It has done so at a community level through a cost analysis of pharmacological management at odds with guideline recommendations that identified potential savings to Federal Government schemes of approximately $43-92 million per annum. It has done so at a general practice management level through identifying poor guidelines adherence through lack of knowledge of such guidelines and a belief that newer drug agents are superior to older despite the lack of empirical evidence. It has also done so at a patient level through the identification of readily available predictors that permit drug withdrawal to be part of a management plan for hypertension in the elderly.

It has demonstrated that many elderly patients can be successfully withdrawn from therapy and remain normotensive. It has identified simple predictors for those for whom withdrawal of antihypertensive drugs is likely to be worthwhile. Lastly it has identified

gaps in the uptake of evidence based medicine in general practice that lead to excess costs associated with non adherence to the principles of evidence based care.

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Appendix

Contents

Authors	Study type and sample population	N (N WAD)	Pre-treatment DBP (mmHg)	Duration of treatment (years)	DBP at withdrawal (mmHg)	Recommence therapy BP level (mmHg)	Follow-up (months)	% normotensive at follow-up (n)
Alderman *et al* [Alderman, 1986 #182]	Observational. Unselected union members (mean age 55.7).	157 (88)	≥95 on 2 visits	≥ 0.5	<85 (<65y) <90 (≥65y)	1 visit ≥110 ≥200 2 visits ≥95 ≥160(<65) ≥95 ≥165 (≥65)	≥12	28% (44)
Aylett and Ketchin [Aylett, 1991 #214]	Observational study of GP patients aged 40-64 years.	(9)	>100 on 3 visits	≥ 2	NP	>100 on 3 visits	12	89% (8)
Aylett *et al* [Aylett, 1999 #336]	Longitudinal observational study in 18 UK general practices. Patients 40-69 years.	723 (224)	NS	≥ 2	Mean <90 on 3 visits SBP <160	NS	3	(88 not on medication)
Beltman [Beltman, 1996 #199]	Observational study comparing ABPM and clinical seated measurements on 25-75 year olds in general practice.	34 (29)	≥95 on 3 visits	1	≤90	≥85	14	48% (14)
Boyle *et al*[Boyle, 1979 #212]	Observational study of 34-68 year olds.	(20)	>100	≥ 2	<100	>100 on repeat visits.	up to 31	10% (2)
Dannenberg & Kannel[Dannenberg, 1987 #194]	Framingham Heart Study. Retrospective case-control of previously treated hypertensives. Cohorts of no medication normotensive no medication hypertensive medication till censored	1138 (95) (242) 801	> 95 and/or SBP ≥160	NS	<140/90	NS	24 for (95) 48 72 96 120 144 168	28% (95) (25) (11) (4) (2) (1) (1) (0)

Authors	Study type and sample population	N (N WAD)	Pre-treatment DBP (mmHg)	Duration of treatment (years)	DBP at withdrawal (mmHg)	Recommence therapy BP level (mmHg)	Follow-up (months)	% normotensive at follow-up (n)
DISH [Blaufox, 1984 #188] [Langford, 1985 #193] [Ho, 1994 #33]	Multi-center RCT in 30-69 yo with dietary intervention (Na/K or wt reduction).	496 (415)	1st visit ≥95 2nd visit ≥90	≥5	<95 SBP <180	1 visit ≥105 2 visits ≥100 3 visits ≥95	≥12	Placebo 35% Wt loss 60% Salt restrict 52%
Dustan *et al*.[Dustan, 1968 #184]	Observational study of essential and secondary hypertension in 15-60 year olds on placebo or no treatment.	(65) -26 malignant/ secondary -39 essential	> 120	0.5-25	≤ 95	NP	96	6%
Ekbom *et al* [Ekbom, 1994 #47]	Prospective observational study of 70-84 year olds in the STOP-Hypertension pilot study	(333)	NP	NP	NP	≥105 or ≥90 + ≥180	60	20%
Fernandez *et al* [Fernandez, 1982 #219]	Prospective observational study of 27 - 65 yo. Placebo 4/52 of whom no therapy thereafter.	(36) (24)	>95 + SBP >140 at three consequetive visits	0.16 - 2	<95 with SBP <140	DBP >95 SBP >140	11 14	75% (24) 50% (18)
Finnerty [Finnerty, 1984 #189]	Observational study: mild hypertensives controlled on low dose monotherapy aged 31-63. Nine month step down period.	67 (59)	92-104	0.5	<85	>85	24 30 48	56% (38) 54% (36) 54% (36)

Authors	Study type and sample population	N (N WAD)	Pre-treatment DBP (mmHg)	Duration of treatment (years)	DBP at withdrawal (mmHg)	Recommence therapy BP level (mmHg)	Follow-up (months)	% normotensive at follow-up (n)
Fotherby & Potter [Fotherby, 1994 #26]	Pilot study 65-84 years in family practice and hospital inpatient and outpatient clinics.	105 (78)	NP	>1	<100 with SBP <175	2 visits ≥ 90 +/or ≥160	12	25% (20 of 74)
Grimm *et al* [Grimm, 1990 #161]	RCT, placebo-controlled with double blinding. Males aged 45-68 given KCl or placebo post WAD plus low sodium diet.	(287 - 145 placebo)	NP	≥3.5	<90	1 visit ≥115 2 visits ≥95 3 visits ≥90	≥12	56% (160) 57% (81) KCl 54% (79) Placebo
Hansen *et al* [Hansen, 1983 #187]	Observational study on > 60 yo who had WAD as entry into a prevalence study of secondary hypertension.	466 > 50 (169 of whom 105 >60 & <110 at 3/52)	NP	NP	< 105 50-59 < 110 ≥ 60	≥110 DBP	12	41% (43) of those normotensive 3/52 post WAD
Imataka *et al* [Imataka, 1988 #172]	Retrospective study in hypertension clinic of subjects aged 30-69 at commencement of treatment.	282 (NP)	90-119 on 2 visits.	≥ 5	NP	NP	12	(33)
Jennings *et al* [Jennings, 1995 #8]	Observational, no age range given.	(83)	>95 on 3 visits	1-22	<95 for 1 year	2 visits >95	12	28%
Jennings *et al.* [Jennings, 1984 #197]	Observational 29-64 yo.	(11)	Mean = 118	1.5-27	<90	>170/100	2.5	36% (4)
Levinson *et al* [Levinson, 1982 #181]	Observational placebo controlled: mild controlled on diuretics alone. No age given.	(24)	90-109	≥1	≤90	1 visit >114 2 visits >99 3 visits >94	≥12	21% (5)

Authors	Study type and sample population	N (N WAD)	Pre-treatment DBP (mmHg)	Duration of treatment (years)	DBP at withdrawal (mmHg)	Recommence therapy BP level (mmHg)	Follow-up (months)	% normotensive at follow-up (n)
						6 month av >90		
Maland *et al.* [Maland, 1983 #186]	Double-blind placebo controlled aged 30-70+	62	mean 90	1 year diuretic alone	<90 mean 78	DBP 1 visit >105 2 visits >95 3 visits >90	12	64% (20)
Medical Research Council [Hypertension, 1986 #195]	Randomised controlled study on 35-64 year olds at entry.	2765 (783)	90-109	6	<90	> 90	≥12	Diuretic M 44% F 54% β-blocker M 47% F 28%
Mitchell *et al* [Mitchell, 1989 #168]	Longitudinal descriptive study of 30-70 yo in a family practice and a work site.	125 (107)	NP	10.5 (average)	NP	>90	≥12	37% (38)
Morgan *et al* [Morgan, 1994 #223]	Placebo controlled randomized double blind trial on 60-79 years with dietary advice intervention.	(102)	>100	≥ 2	<90	2 visits >90	≥12	10%
Myers *et al* [Myers, 1996 #242]	Observational study of 21-80 year olds of subjects from family practice with ABPM*, family physician and nurse measurements.	246 (98)	NP	NP	<160/95*	≥160/95*	≥12	51% (50)
Page and Dunstan [Page, 1962 #192]	Observational study: no age group given.	27 severe: 19 essential, 7 renal, 4 malignant	NP	0.5-25	NP	DBP > 95?	6-60	33% (9)

Authors	Study type and sample population	N (N WAD)	Pre-treatment DBP (mmHg)	Duration of treatment (years)	DBP at withdrawal (mmHg)	Recommence therapy BP level (mmHg)	Follow-up (months)	% normotensive at follow-up (n)
Perry and Schroeder [Perry, 1956 #232]	Prospective observational study of 24-65 outpatients on hexamethnium and hydralazine therapy.	114 40 <115 41 <130 33 ≥130	>100	NP	<100	NP	36	7% (10)
Perry *et al* [Perry, 1966 #233]	As above.	316	≥110	>7	<100	NP	84-144	5% (15)
Prasad *et al* [Prasad, 1997 #277]	Observational study conducted in 2 general practices in UK. ABPM, echocardiograms and clinical measurements.	126 (25)	NP	NP	ABPM ≤ 150/90	ABPM >150/90	12	24% (6)
Reid *et al* [Reid, 1994 #203]	Randomised parallel group design study with lifestyle intervention in general practice.	44 (20)	NP	≥ 0.5	NP	NP	9	75% (15)
Ruoff *et al* [Ruoff, 1986 #231]	Randomised placebo controlled double blind study of subjects aged 18-72 on terazosin therapy.	104 (54)	95-119	0.6-1 or 0.1 arms current therapy	<95 3 visits + 10 below pretreatment level	DBP >90	1.5-2	(18) though all bar 2 lost to follow-up eventually returned to hypertension, last day 439.
Schmieder *et al* [Schmieder, 1997 #243]	Open prospective study. Males (47 +/- 7 yrs), managed in general practice.	158 with 64 loss to follow up 88 (51)	≥95	0.5	<140/90	SBP ≥160 DBP ≥95	72	25% (22)
Schmieder *et al.*	Observational. Middle aged	47 (30)	≥95	0.5	NP	SBP ≥160	5	26%

Authors	Study type and sample population	N (N WAD)	Pre-treatment DBP (mmHg)	Duration of treatment (years)	DBP at withdrawal (mmHg)	Recommence therapy BP level (mmHg)	Follow-up (months)	% normotensive at follow-up (n)
[Schmieder, 1985 #66]	males with essential hypertension on monotherapy.					DBP ≥95		
Stamler *et al* [Stamler, 1984 #198]	RCT with nutritional intervention. Age group NP.	189 (141)	>90	5	<90	1 visit >105 2 visits >99	≥12	Group 1 44% Group 2 15%
Straand, Fugelli and Laake [Straand, 1993 #222]	Observational study conducted in general practice on >75 yo on diuretics[1] for hypertension, heart failure peripheral oedema unknown indication	65 (33) (12) (6) (5) (10)	NP	Mean 10	≤110 and/or ≤220 SBP	NP	6	55%[2] (18)
Takata *et al* [Takata, 1992 #127]	Randomized comparison study 36-81 yo.	113 (72)	≥90	NP	<90	1 visit ≥105 2 visits >95	≥12	Diuretic 41% (12), ACEI 37% (11)
Thurm and Smith [Thurm, 1967 #185]	Observational: mild-moderate 20-65 yo hypertensives.	(69)	≥90	NP	<90	≥90	≥12	23% (16)
TONE [Whelton, 1998 #292; Whelton, 1998 #292]	RCT of 60-80 yo in 4 academic health centers.	(975)	NP	NP	< 85 on 1 drug (SBP <145)	1 visit ≥110 ≥190 2 visits ≥100 ≥170 3 visits ≥90 ≥150	≥12	34% (Na ⇓) 37% (wt loss) 44% (both) 16% (control)
van den Bosch *et al* [van den	Retrospective.	2143 (25)	>100 for three visits	NP	<85 for three visits	DBP ≥100 three visits	60	56% (14)

[1] loop, potassium sparing and thiazide.
[2] whole group, no figure available for hypertension alone.

Authors	Study type and sample population	N (N WAD)	Pre-treatment DBP (mmHg)	Duration of treatment (years)	DBP at withdrawal (mmHg)	Recommence therapy BP level (mmHg)	Follow-up (months)	% normotensive at follow-up (n)
Bosch, 1994 #50] van Kraaij *et al* [van Kraaij, 1997 #281]	Audit of medical records and 1 year follow-up of ≥75	144 (51)[3].	NS	NS	NS	NS	12	52%
Veteran Administration [Veterans Administration Cooperative Study Group on Antihypertensive Drugs, 1975 #183]	Randomised double-blind placebo controlled on veterans (mean age 52).	86 (60)	>110	5	≤95	DBP 1 visit >129 2 visits >99 3 visits >94	18	15% (9)

Table 1 Trials of antihypertensive medication withdrawal.

[3] This study included all clinical indications for diuretic usage N = 593 (218).

Study (see end of table)	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	BB
Blood pressure;																												
Pre treatment level	-		+		+	+	+			+	-	-[7]			-		+		+	-			+[14]	+[15]			-	
Pre treatment # of recordings												-																
On treatment BP	-					-				+		+[8]					+[11]	+				+[13]					-	+
Post WAD BP	+												+[9]	+				[12]										
Cold pressor test[4]	[5]		+[6]											[10]														
Therapy;																												
Duration	-				-				+	+		-			+			-		-		+					+	
Type	-		-[17]														+											
Monotherapy	[16]					+	+					+						-										
Dose level							+					+										-[18]						
Subject;																												
Age at treatment												-															-	
Age at WAD	-		+[19]			-					-[20]	-					+[22]	-				-		-[23]	+[24]		-	
Sex	-					-						-						-										
Race						-					?[21]																	

[4] Immersion of hands into a bucket of iced water!
[5] SBP and DBP at one month.
[6] rise in SBP or DBP.
[7] DBP and SBP
[8] DBP and SBP
[9] mean BP from one month.
[10] vs seated BP measurement.
[11] men
[12] SBP only
[13] standing DBP plus longer duration of normotension on drugs but not lying BP.
[14] SBP
[15] SBP and DBP
[16] ACE inhibitor and non-thizide diuretics. Return to hypertension was quicker with the former.
[17] oxprenolol and nitrendipine.
[18] vs 2 drugs.
[19] older have quicker return to hypertension.
[20] younger more likely to return to hypertension.
[21] statistically significant at 3 weeks only but but confounded by higher pretreatment DBP.

Study (see end of table)	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	BB
Family history																				-								
Body weight																												
at WAD						-	+											+		-		-		-			-	
after WAD						+														-							-	
Smoking						-												-						-			-	
Total cholesterol																								+			-	
Alcohol							+											-									-	
Vascular disease																		-										
Organs																												
Heart LV mass																												
Heart rate				+				+	+	+[25]								-									+	
Cardiac output																				-		-						
Total peripheral									+																		+	
resistance																											+	
Stress test																												
ECG							-											+					+				
Kidneys																												
Electrolytes																				-								
Renin profile									-							+				-								
24/24 Na/K excretion									-											-							-	
Interventions																												
Diet		+				+	+														-[26]							+
K supplementation		+																								-		
Exercise																												
Other																												
Psychophsiological testing			-																									

[22] propanolol treated
[23] statistically significant difference though for subjects who were WAD normotensives at 2 years but eventually returned to hypertension or died of cardiovascular disease. Relapse group were younger.
[24] >85 higher failure.
[25] on echocardiography
[26] for increase potassium and decrease sodium.

Table 2 WAD studies that tested predictors of success of WAD. + = statistically significant association, - no statistically significant association, ? possibly significant but the design of the study did not allow this to be demonstrated. Bold no statistical test.

KEY TO STUDIES

A Takata *et al* [Takata, 1992 #127]
B Reid *et al* [Reid, 1994 #203]
C Schmieder *et al* [Schmieder, 1985 #66]
D Fagerberg *et al* [Fagerberg, 1992 #190]
E Thurm and Smith [Thurm, 1967 #185]
F Blaufox *et al* [Blaufox, 1984 #188]
G Stamler *et al* [Stamler, 1984 #198]
H Jennings *et al* [Jennings, 1984 #197]
I Jennings *et al* [Jennings, 1991 #218]
J Jennings *et al* [Jennings, 1995 #8]
K Veteran Administration [Veterans Administration Cooperative Study Group on Antihypertensive Drugs, 1975 #183]
L Ekbom *et al* [Ekbom, 1994 #47]
M Alderman *et al* [Alderman, 1986 #182]
N Beltman *et al* [Beltman, 1996 #199]
O Page and Dunstan [Page, 1962 #192]
P Ho *et al* [Ho, 1994 #33]
Q MRC [Hypertension, 1986 #195]
R Fotherby and Potter [Fotherby, 1994 #26]
S Dustan *et al* [Dustan, 1968 #184]
T Levinson *et al* [Levinson, 1982 #181]
U Morgan *et al* [Morgan, 1994 #223]
V Mitchell *et al*[Mitchell, 1989 #168]
W Imataka *et al*[Imataka, 1988 #172]
X Dannenberg and Kannel[Dannenberg, 1987 #194]
Y Strand, Fugelli and Laake[Straand, 1993 #222]
Z Grimm *et al*[Grimm, 1990 #161]
AA Schmieder *et al*[Schmieder, 1997 #243]
BB Whelton *et al*[Whelton, 1998 #292]

Research materials
26th September 1996

«address»

Dear Dr «name»

We are writing to invite you to participate in a research project being conducted by the High Blood Pressure Research Council of Australia and based in the Baker Medical Research Institute at the Alfred Hospital (the Second Australian National Blood Pressure Study - ANBP2). The study is being conducted through Divisions of General Practice throughout Australia. It is being conducted in general practice to produce results relevant to you. Your participation in the project will qualify for 20 points PA points which is your minimum triennial requirement. *All consultations generated from the study attract Medicare payments plus an administration fee of $100.00 per patient randomised.* The project will be a prospective open drug trial comparing mortality and major cardiovascular and non-cardiovascular events between two groups of hypertensives, one treated with diuretics (the current 'gold standard') and the other ACE inhibitors (as yet no outcome research). One of us (MN) will give a talk explaining the study and the other (PH) will speak on a lifestyle intervention developed by the Ballarat Heart Health Consortium which will be integrated into the main study in our Division. A dinner sponsored by MSD will follow.

Venue
TBA
Wednesday November 6th
at 7:00 pm with dinner to follow at 7:30 pm.

Participation in the project would involve an invitation by letter to your patients aged 65 - 84 years for a blood pressure check by an ANBP2 SRN in your clinic. New hypertensives identified would be referred to you for your management. Established hypertensives on medication would, under your supervision and approval, have their medication withdrawn according to a strict protocol before entering the study proper. Studies have shown no

adverse morbidity or mortality to short-term antihypertensive drug withdrawal.

It is rare that such research is conducted in general practice and this is an excellent way for your Division to be involved in research of such national and international importance.

Please complete, detach and return the form below in the reply paid envelope provided or fax the whole page to us on (03) 9521 1837 before the 1st of November.

[redacted]

Dr Mark Nelson
Victorian Regional
Medical Co-ordinator,
ANBP2.

Dr Paul Hemming
Executive director,
Ballarat & District Division
of General Practice.

I «name»

- ☐ Wish to participate in the Second Australian National Blood Pressure Study and will be attending the dinner.
- ☐ Wish to participate in the Second Australian National Blood Pressure Study but cannot attend the dinner.
- ☐ Would like to be sent more information.
- ☐ DO NOT wish to participate in the Second Australian National Blood Pressure Study.

☑ Please tick the appropriate squares and return before the 1st of November.

Withdrawal of Antihypertensive Drugs in the

☑ WAD in ANBP2

Second Australian National Blood Pressure Study

Subject Information Sheet

BLOOD PRESSURE SCREENING

Participants who have withdrawn from medication and remain normotensive.

We are seeking your participation in this research study because you have had your high blood pressure medication withdrawn and your blood pressure has remained normal. We are interested in finding out what may prevent your blood pressure from rising when you are off your medication.

What are we asking you to do?

If you do not redevelop high blood pressure you will be followed up by your own doctor. Before the study nurse hands you back to your doctor's care he/she will collect a blood sample from a vein in your arm which may cause mild pain and may result in bruising. We will also ask you some questions about your background.

The study nurse would wish to see you again if your doctor finds that your blood pressure rises again to high levels or in twelve months time, whichever is the sooner.

We will monitor your progress by looking at your medical history held by your doctor. You may leave the study at any time by expressing that wish to your doctor without prejudicing your care in any way. Records will be kept in confidentiality for seven years and will then be destroyed.

If you need any more information

If you need any more information please contact your doctor or the study nurse who has been looking after you up to this time.

You should know that this study has been approved by the Alfred Healthcare Group Ethics Committee and the RACGP Research and Evaluation Ethics Committee. Should you wish to speak to someone not involved in the study you can contact the Secretary of the Alfred Healthcare Group Ethics Committee.

Alfred Healthcare Group Ethics Committee

Alfred Hospital
Commercial Rd
Prahran, Vic 3181
Telephone (03) 9276 2000

Second Australian
ANBP2
National Blood Pressure Study

Information Sheet

BLOOD PRESSURE SCREENING

Participants currently receiving treatment for High Blood Pressure

Why you are being given this information sheet

You have been identified from your treating doctor's practice list as being in the age range 65-84 years. We are interested in identifying people in this age group from your doctor's practice who have high blood pressure which is either being treated or is currently not being treated. You have been identified as currently receiving treatment for high blood pressure.

What we are asking you to do

We will ask you to come and discuss your blood pressure treatment with your doctor. Your doctor will ask you whether you would be prepared to take part in a study to compare the long-term outcome with two different treatments which are used to treat high blood pressure. This study is described for you on a separate information sheet.

If you do agree to take part in the blood pressure treatment study, we will first ask you to reduce the dose(s) of and then stop the medication(s) which you are currently taking for your high blood pressure. This will be done under the supervision of a registered nurse and your doctor. During this period of time we will ask you to come to your doctor's clinic every week for blood pressure measurements by the nurse to make sure that your blood pressure is not getting too high and that you are not suffering from any symptoms produced by withdrawing your blood pressure medication.

If at any time your doctor considers that it is unwise for you to continue with drug withdrawal, this will be stopped and you will be returned to your previous treatment.

Also if at any time you do not feel comfortable with having your medication reduced, you are at liberty to cease treatment withdrawal and continue to be treated as you have been previously by your doctor.

Once you have stopped taking your medication we will need to keep you off medication for at least 2 weeks until we have taken measurements of your blood pressure on at least 2 occasions at least one week apart. Depending on your blood pressure readings you may need to come to the clinic on at least one more occasion making a total of three.

Is there any problem being without your blood pressure medication?

There is usually little risk of you being without your blood pressure medication for periods of 2-3 weeks as long as your blood pressure is being carefully followed and your medication is restarted if your blood pressure becomes too high. As you know we intend to see you every week in the clinic while you are not taking your medication and will also make sure that you know how to get into contact with your doctor at any other times if you are feeling unwell.

In some people there is no increase in blood pressure when medications are stopped. If this happens in your case your doctor may decide just to watch your blood pressure and not restart treatment unless your blood pressure rises again to levels which require treatment.

About the Blood Pressure Measurements

You are probably very familiar with blood pressure measurements but we would like everyone to receive the same information so that you will know exactly what will happen when you come to the clinic.

When you come to your doctor's clinic the nurse will first ask you to remove any clothing from your upper arm which is likely to interfere with the blood pressure measurements. You will then be asked to sit quietly on a chair for at least 5 minutes before the measurements are taken.

The nurse will wrap a cuff around your upper arm. Once the cuff has been positioned the nurse will blow up the bag in the cuff using a rubber bulb. You will feel the cuff tightening around your upper arm – this may be mildly painful. As soon as the nurse has blown up the cuff so that the pressure in the cuff is higher than your blood pressure, the pressure in the cuff will be gradually reduced while the nurse listens to your pulse sounds at your elbow with a stethoscope.

When the nurse has finished making each reading the pressure in the cuff will be completely removed. On each occasion you come to the clinic the nurse will need to make at least 3 blood pressure measurements in a similar manner. Each reading will take 30-60 seconds.

If a routine blood test has not been taken over the past 12 months a small 10ml blood sample will be required. The sample will be taken by inserting a needle into a small blood vessel in the arm. This may cause mild pain and may result in bruising.

If you are found to have high blood pressure when not taking medication

If you are still found to have a high blood pressure after either 2 or 3 visits you will be asked to see your doctor again. Your doctor will ask you whether you would be willing to take part in the blood pressure treatment study which was previously mentioned. If so you will be given further information about the treat-ment study and your doctor will discuss it with you before you make any decision to take part.

If you are found to have high blood pressure but you do not want to take part in the treatment study, this will have no adverse influence on your subsequent medical care. Your doctor will discuss with you the appropriate options for treatment of your high blood pressure, which may include restarting your previous treatment.

If you need any more information

If you need any more information about either stopping your medication of the blood pressur measurements you may either contact your doctor or the nurse who will be looking after you.

You should know that this study has been approved by the Ethics Committee of the Royal Australian College of General Practitioners. Should you want to speak to someone not involved with the study about either the blood pressure measurements or the proposed blood pressure treatment study you can contact the Secretary of the Ethics Committee at the Royal Australian College of General Practitioners.

RACGP Ethics Committee

39 Terry Street
Rozelle NSW 2039
Telephone (02) 555 8177

Second Australian
ANBP2
National Blood Pressure Study

Consent Form

Reference No: 917513

BLOOD PRESSURE SCREENING

Participants currently receiving treatment for High Blood Pressure

I, ... have had explained to me

by ..... the nature and effects of the Research Study:

Blood Pressure Screening for the Second Australian National Blood Pressure Study.

I have been provided with a *Subject Information Sheet* about the study, which I have read and understood.

I understand that the study involves the following procedures:

- Reduce the dose(s) and then stop the medication which I am currently taking for my high blood pressure.
- Come to my doctor's consulting rooms each week for blood pressure measurements while my drug treatment is being reduced by my doctor and the study nurse.
- After treatment for my high blood pressure has been stopped, remain off treatment for at least a further 2 weeks for more blood pressure measurements to be taken by the nurse.
- To have a small blood sample taken if required.
- Provide information to the nurse about my medical history and my general health.

I have understood and am satisfied with the explanations that I have been given and hereby consent to participation in the above study.

I understand that the study has been reviewed and approved by the Ethics Committee of the Royal Australian College of General Practitioners (RACGP).

I understand that the results of this study may be published in summary form, but my identity will be kept confidential.

I understand that I may withdraw my consent at any stage without affecting my rights or the responsibilities of the study investigators or my doctor in any respect.

I understand that staff employed by the study or representatives of the RACGP Ethics Committee may need to access my medical record held by my doctor for information related to the study. I am happy to authorise access to my medical record for this purpose.

Signature: _____ Signature of Witness: _____

Date: _____ Print Name of Witness: _____

Date: _____

Second Australian
ANBP2
National Blood Pressure Study

Result Sheet

BLOOD PRESSURE SCREENiNG

Thank you for attending the Second Australian National Blood Pressure Study Screening Program at your General Practitioner's surgery.

Your results today were:

BLOOD PRESSURE / ***mmHg***

BODY WEIGHT ***Kg***

Your blood pressure is within / above a desirable range for your age.

Your body weight is below / within / above a desirable range for your height.

It is very important to have your doctor measure your blood pressure on a regular basis to ensure that it is at the appropriate level.

Remember:

- ***Moderate regular exercise helps to keep blood pressure under control***
- ***Reduce excess alcohol intake***
- ***Reduce excess salt intake***
- ***Maintain a desirable body weight***
- ***Quit smoking***

Thank you for attending the ANBP2 Blood Pressure Screening Program.

Nurse Signature Date

Second Australian
ANBP2
National Blood Pressure Study

Regional Centre ☐☐☐ Patient ID ☐☐☐☐☐☐

Baseline Visit 1 – Patient Registration Form

To be completed by the Research Nurse. Send original to the Data Management Centre and retain a copy for the patient file.
Please complete **ALL** questions. **Record visit in patient case notes.**

Initials (FML) ☐☐☐ **Sex** ☐

Visit Date: ☐☐ ☐☐ ☐☐

Practice ID: ☐☐☐☐

GP ID: ☐☐☐☐

Date of Birth: ☐☐ ☐☐ ☐☐ **Date of Discovery:** ☐☐ ☐☐ ☐☐

Plasma Creatinine Record from history if result available (within past 12 months) ☐☐☐ µmol/L (Limit ≤ 200 µmol/L)

Arm circumference ☐☐☐ (cm) **Right** ☐ Left ☐ **Cuff size** Standard (>33 cm) ☐ Alternate (33-45 cm) ☐ Obese (>45 cm) ☐

Height ☐☐☐ cm **Weight** ☐☐☐ ☐ kg **Waist** ☐☐☐ cm **Hip** ☐☐☐ cm

Blood Pressure
If BP measurements 2 & 3 differ by 10 mmHg systolic or by 6 mmHg diastolic take further measurements until two consecutive measurements are within these limits.
(DBP = Korotkoff Phase V)

Systolic	Diastolic
☐☐☐	☐☐☐
☐☐☐	☐☐☐
☐☐☐	☐☐☐
☐☐☐	☐☐☐
☐☐☐	☐☐☐
☐☐☐	☐☐☐

Average of last 2 measures ☐☐☐ ☐☐☐

For untreated subjects, study BP criteria:
SBP ≥160 mmHg **OR**
DBP ≥90 (if SBP ≥140mmHg)

Checklist
(Tick YES or NO for each question)

	Yes (✓)	No
1. Is the subject aged 65 - 84 years at the Date of Discovery?	☐	☐
2. Has a blood sample been taken for Plasma Creatinine?	☐	☐
3. Has the subject signed the Baseline Consent Form?	☐	☐
4. Is the subject receiving antihypertensive drug treatment?	☐	☐

For subjects receiving antihypertensive drugs

	Yes (✓)	No
5. Is the subject willing to consider drug withdrawal? *If NO, provide subject with a RESULT SHEET and go to 8.*	☐	☐

For subjects NOT receiving antihypertensive drugs

	Yes (✓)	No
6. Is the subject willing to continue in the study?	☐	☐
7. Are blood pressure criteria satisfied for Visit 2 *If NO, provide subject with a RESULT SHEET and go to 8*	☐	☐

Follow - up Action

	Yes (✓)	No
8. Has an appointment been made for the next visit? If YES, date of next appointment: ☐☐ ☐☐ ☐☐	☐	☐
9. Has the subject exited from the study?	☐	☐

***White copy:** Data Management Centre **Pink copy:** Regional Centre **Blue copy:** Patient File*

DMC Date: ☐☐ ☐☐ ☐☐ DMC Signature: _____

RN ID: ☐☐☐☐ RN Signature: _____

Second Australian
ANBP2
National Blood Pressure Study

Regional Centre ☐☐☐ Patient ID ☐☐☐☐☐☐

Baseline Visit 2 – Blood Pressure and Clinical Assessment

To be completed by the Research Nurse. Send original to the Data Management Centre and retain a copy for the patient file. Please complete **ALL** questions. **Record visit in patient case notes.**

Subject Initials ☐☐☐ **Date of visit** ☐☐ ☐☐ ☐☐ **Practice ID** ☐☐☐☐ **GP ID** ☐☐☐☐

Plasma Creatinine Enter result if available ☐☐☐ µmol/L (Limit ≤ 200 µmol/L)

Blood Pressure *Arm:* Right ☐ Left ☐

Cuff size: Standard (>33 cm) ☐ Alternate (33-45 cm) ☐ Obese (>45 cm) ☐

If BP measurements 2 & 3 differ by 10 mmHg systolic or by 6 mmHg diastolic take further measurements until two consecutive measurements are within these limits.
(DBP = Korotkoff Phase V)

Systolic	Diastolic
☐☐☐	☐☐☐
☐☐☐	☐☐☐
☐☐☐	☐☐☐
☐☐☐	☐☐☐
☐☐☐	☐☐☐

Average of last 2 measures ☐☐☐ ☐☐☐

Study BP criteria:
SBP ≥160 mmHg **OR**
DBP ≥90 (if SBP ≥140mmHg)

Checklist
(Tick YES or NO for each question)

	Yes (✓)	No
1. Has a blood sample been taken for Plasma Creatinine?	☐	☐
2. Has the Inclusion / Exclusion Form been completed?	☐	☐
3. Is the subject willing to continue in the study?	☐	☐
4. Has the subject been through the drug withdrawal phase? *If NO to 4, go to 6* *If YES to 4, go to 5*	☐	☐
5. Is the SBP ≥ 250 mmHg or DBP ≥ 115 mmHg? *If YES, Inform GP, document in patient case-notes and go to 6* *If NO, go to 6*	☐	☐

Follow - up Action

	Yes (✓)	No
6. Has a randomisation appointment been made?	☐	☐
If YES, date of next appointment: ☐☐ ☐☐ ☐☐		
7. Has the subject exited from the study? *If YES, Complete PATIENT EXIT FORM*	☐	☐

White copy: *Data Management Centre* ***Pink copy:*** *Regional Centre* ***Blue copy:*** *Patient File*

☐☐ ☐☐ ☐☐ DMC Date: _____ DMC Signature:

☐☐☐☐ RN ID: _____ RN Signature:

Second Australian
ANBP2
National Blood Pressure Study

Regional Centre ☐☐☐ Patient ID ☐☐☐☐☐☐

Baseline Visit 3 – Randomisation Visit

To be completed by the Research Nurse. Send original to the Data Management Centre and retain a copy for the patient file. Please complete **ALL** questions. **Record visit in patient case notes.**

Subject Initials ☐☐☐ **Date of visit** ☐☐ ☐☐ ☐☐ **Practice ID** ☐☐☐☐ **GP ID** ☐☐☐☐

Plasma Creatinine Enter result if not previously entered ☐☐☐ µmol/L (Limit ≤ 200 µmol/L)

Blood Pressure *Arm:* Right ☐ Left ☐

Cuff size: Standard (>33 cm) ☐ Alternate (33-45 cm) ☐ Obese (>45 cm) ☐

If BP measurements 2 & 3 differ by 10 mmHg systolic or by 6 mmHg diastolic take further measurements until two consecutive measurements are within these limits. (DBP = Korotkoff Phase V)

Systolic	Diastolic
☐☐☐	☐☐☐
☐☐☐	☐☐☐
☐☐☐	☐☐☐
☐☐☐	☐☐☐
☐☐☐	☐☐☐
☐☐☐	☐☐☐

Average of last 2 measures ☐☐☐ ☐☐☐

Study BP criteria:
SBP ≥160 mmHg **OR** DBP ≥90 (if SBP ≥140mmHg)

CALL DATA MANAGEMENT CENTRE ON 1800-655391 NOW

Checklist
(Tick YES or NO)

	Yes (✓)	No
1. Does Plasma Creatinine satisfy entry criteria?	☐	☐
2. Has Main Study Consent Form been signed?	☐	☐
3. Is the subject willing to continue in the study?	☐	☐
4. Are all Inclusion / Exclusion criteria satisfied?	☐	☐
5. Are entry blood pressure criteria satisfied?	☐	☐

(From discussion with DMC Av BP BV2 & BV3____/____)

Follow - up Action

		Yes (✓)	No
Treatment Group	ACE Inhibitor	☐	☐
	Diuretic	☐	☐
OR	Was not Randomised	☐	☐

ANTIHYPERTENSIVE MEDICATION PRESCRIBED:
List antihypertensive medication and dose prescribed at randomisation.

MEDICATION	DOSAGE / REGIMEN

Genetic Study Consent signed Yes ☐ No ☐ Blood collected Yes ☐ No ☐

Other Sub-Studies None ☐ ABP ☐ LVH ☐ QOL ☐ OTHER _____ (print clearly) ☐
(please tick one box to indicate involvement or none)

White copy: Data Management Centre Pink copy: Regional Centre Blue copy: Patient File

☐☐ ☐☐ ☐☐ DMC Date: _____ DMC Signature:

☐☐☐☐ RN ID: _____ RN Signature:

Second Australian
ANBP2
National Blood Pressure Study

Regional Centre ☐☐☐ Patient ID ☐☐☐☐☐☐

Baseline Visit 3 – Randomisation Visit
Additional information for subjects allocated treatment

To be completed by the Research Nurse. Send original to the Data Management Centre and retain a copy for the patient file. Please complete **ALL** questions.

Subject Initials ☐☐☐ **Date of visit** ☐☐ ☐☐ ☐☐ **Practice ID** ☐☐☐☐ **GP ID** ☐☐☐☐

Medicare Number ☐☐☐☐ ☐☐☐☐☐ ☐ ☐

Important Information to be collected for subjects randomised to a treatment group

Subject's

Current Address _____ Telephone No ( ) _____

_____

_____ pc

Please record up to 3 Contacts, at least one with a different address

1. Contact Person

Mr/Mrs/Ms/Miss _____ Relationship _____

Address _____ Telephone No ( ) _____

_____

_____ pc

2. Contact Person

Mr/Mrs/Ms/Miss _____ Relationship _____

Address _____ Telephone No ( ) _____

_____

_____ pc

3. Contact Person

Mr/Mrs/Ms/Miss _____ Relationship _____

Address _____ Telephone No ( ) _____

_____

_____ pc

White copy: *Data Management Centre* ***Pink copy:*** *Regional Centre* ***Blue copy:*** *Patient File*

☐☐ ☐☐ ☐☐ _____ ☐☐☐☐ _____

DMC Date: **DMC Signature:** **RN ID:** **RN Signature:**

Second Australian
ANBP2
National Blood Pressure Study

Regional Centre ☐☐☐ Patient ID ☐☐☐☐☐☐

Inclusion / Exclusion Criteria and Concurrent Medication Form

To be completed by the Research Nurse and GP Investigator. Send original to the Data Management Centre and retain a copy for the patient file. Please complete **ALL** questions.

Subject Initials ☐☐☐ **Date this Form Completed** ☐☐ ☐☐ ☐☐ **Practice ID** ☐☐☐☐ **GP ID** ☐☐☐☐

This section is to be completed by the GP Investigator
Please tick YES or NO for each question

	Yes (✓)	No
Absence of any recent history of cardiovascular morbidity or serious intercurrent illness*	☐	☐
Capable of and willing to provide informed consent	☐	☐
Ambulant and capable of attending the practice	☐	☐
Absence of non-fatal cardiovascular event (as defined as an end-point) in the past 6 months	☐	☐
Absence of accelerated or malignant hypertension*	☐	☐
Absence of dementia	☐	☐
Absence of life threatening illness considered likely to cause death within the 5 year study period*	☐	☐
Absence of any absolute contraindication to or specific indication for an ACE inhibitor or a diuretic*	☐	☐
Do you consider the patient suitable for the study?	☐	☐
Are all answers YES?	☐	☐

GP Investigator Signature: _____

*See overleaf for details

CONCURRENT CHRONIC MEDICATION
Please complete this list by recording all medications being taken,

☐ No concurrent medication or

MEDICATION	DOSAGE REGIMEN	DATE STARTED	PRIMARY REASON FOR USE

White copy: Data Management Centre Pink copy: Regional Centre Blue copy: Patient File

☐☐ ☐☐ ☐☐ DMC Date: _____ DMC Signature:

☐☐☐☐ RN ID: _____ RN Signature:

Second Australian
ANBP2
National Blood Pressure Study

Regional Centre ☐☐☐ Patient ID ☐☐☐☐☐☐

Antihypertensive Medication Withdrawal Entry Visit Form

WAD Visit No **1**

This section is to be completed by the GP Investigator. Please complete **ALL** questions.
Record visit in patient case-notes.

Subject Initials ☐☐☐ Date of visit ☐☐ ☐☐ ☐☐ Practice ID ☐☐☐☐ GP ID ☐☐☐☐

Antihypertensive Drug History

Duration of current Antihypertensive therapy ☐☐ *years and* ☐☐ *months*

Blood pressure prior to current course of therapy (Pre-treatment BP) ☐☐☐ / ☐☐☐

Blood Pressure
3 measurements required. If BP measurements 2 & 3 differ by 10 mmHg systolic or by 6 mmHg diastolic take further measurements until two consecutive measurements are within these limits.
(DBP = Korotkoff Phase V)

Systolic	Diastolic
☐☐☐	☐☐☐
☐☐☐	☐☐☐
☐☐☐	☐☐☐
☐☐☐	☐☐☐
☐☐☐	☐☐☐

Average of last 2 measures ☐☐☐ ☐☐☐

Study BP criteria:
SBP ≥160 mmHg **OR** DBP ≥90 (if SBP ≥140mmHg)

Check List
(Tick YES or NO for each question)

	Yes (✓)	No
1. Do you as the GP consider the subject suitable for drug withdrawal?	☐	☐
2. Is the subject willing to withdraw from drug therapy?	☐	☐
3. Does the subject cease medication at this visit?	☐	☐

Follow - Up Action Plan
(Research Nurse to complete)

	Yes (✓)	No
4. Is the subject continuing in the WAD program?	☐	☐

Next Visit Date: ☐☐ ☐☐ ☐☐

5. Has the subject been exited from the study?	☐	☐

CURRENT ANTIHYPERTENSIVE MEDICATION

☐ NONE or,

List all antihypertensive medications prior to this visit and the change in or cessation of drug following this visit

MEDICATION	DATE COMMENCED	CURRENT DOSAGE REGIMEN	STEP DOWN DOSAGE AT THE END OF THIS CONSULTATION

White copy: *Data Management Centre* ***Pink copy:*** *Regional Centre* ***Blue copy:*** *Patient File*

☐☐ ☐☐ ☐☐ DMC Date: _____ DMC Signature:

☐☐☐☐ RN ID: _____ RN Signature:

Second Australian
ANBP2
National Blood Pressure Study

Regional Centre ☐☐☐ Patient ID ☐☐☐☐☐☐

WAD Visit Form

WAD Visit No ☐ To be completed by the GP Investigator / Research Nurse. Please complete **ALL** questions. **Record visit in patient case notes.**

Subject Initials ☐☐☐ **Date of visit** ☐☐ ☐☐ ☐☐ **Practice ID** ☐☐☐☐ **GP ID** ☐☐☐☐

Plasma Creatinine Enter result if available: ☐☐☐ µmol/L (Limit ≤ 200 µmol/L)

Blood Pressure *Arm:* Right ☐ Left ☐

Cuff size: Standard (>33 cm) ☐ Alternate (33-45 cm) ☐ Obese (>45 cm) ☐

Blood Pressure
(3 measurements required)
If BP measurements 2 & 3 differ by 10 mmHg systolic or by 6 mmHg diastolic take further measurements until two consecutive measurements are within these limits. (DBP = Korotkoff Phase V)

Systolic	Diastolic
☐☐☐	☐☐☐
☐☐☐	☐☐☐
☐☐☐	☐☐☐
☐☐☐	☐☐☐
☐☐☐	☐☐☐
Average of last 2 measures	
☐☐☐	☐☐☐

Study BP criteria:
SBP ≥160 mmHg **OR** DBP ≥90 (if SBP ≥140mmHg)

Check List
(Tick YES or NO for each question)

	Yes (✓)	No
1. Has the subject been free of drugs for at least 1 week?	☐	☐
2. Does the average blood pressure satisfy the study criteria?	☐	☐
3. Does the subject cease medication at this visit?	☐	☐
4. Is the subject continuing in the WAD program?	☐	☐

Follow - Up Action Plan

If 1&2 are YES, Baseline Visit 2 appointment required.
If 1 is YES & 2 is NO & WAD Visit<6, WAD appointment required.
If 1 is YES & 2 is NO & WAD Visit=6, *provide GP LETTER.*

	Yes (✓)	No
5. Has a WAD Visit appointment been made?	☐	☐
6. Has a Baseline Visit 2 appointment been made?	☐	☐
7. Has the subject exited from the study?	☐	☐

If YES, complete PATIENT EXIT FORM

Next Visit Date: ☐☐ ☐☐ ☐☐

CURRENT ANTIHYPERTENSIVE MEDICATION: List all current antihypertensive medication

☐ NONE or,

MEDICATION	DATE COMMENCED	CURRENT DOSAGE REGIMEN	STEP DOWN DOSAGE AT THE END OF THIS CONSULTATION

White copy: Data Management Centre Pink copy: Regional Centre Blue copy: Patient File

DMC Date: ☐☐ ☐☐ ☐☐ DMC Signature: _____

RN ID: ☐☐☐☐ RN Signature: _____

ANBP2
National Blood Pressure Study

Regional Centre ☐☐☐ Patient ID ☐☐☐☐☐☐

Demographic and Risk Factor Information 1

To be completed by the participant and RN for all patients allocated to a treatment group at randomisation.
Please complete **ALL** questions

Subject Initials ☐☐☐ Date of visit ☐☐ ☐☐ ☐☐ Practice ID ☐☐☐☐ GP ID ☐☐☐☐

Country of Birth

☐☐☐☐☐☐☐☐☐☐☐☐☐☐

If not born here, years lived in Australia? ☐☐

Level of Education

1. Never attended school
2. Primary school
3. Some high school
4. Completed high school
5. University, CAE or other tertiary training

☐

Age when left school ☐☐

Marital Status

1. Never married
2. Currently married
3. Separated but not divorced
4. Divorced
5. Widowed
6. Defacto relationship

☐

Clinical Measurements
(Record from history if results available within past 12 months, request if unavailable)

Random Glucose	☐☐☐	(mmol/L)
Total Cholesterol	☐☐☐	(mmol/L)
HDL Cholesterol	☐☐☐	(mmol/L)
Serum Potassium	☐☐☐	(mmol/L)

Blood Cholesterol

	Yes (✓)	No
Have you ever had a raised cholesterol in the past?	☐	☐
On medication to lower your cholesterol?	☐	☐

Diabetes Mellitus

Have you been told you have diabetes?	☐	☐
If YES, what type of treatment are you on now?		
1. Diet alone	☐	☐
2. Oral agents	☐	☐
3. Insulin	☐	☐

Age when first diagnosed ☐☐

Cigarette Smoking

Current Status:
1. Never smoked 2. Still smoking 3. Ex-smoker ☐

If 2 or 3, average number of cigs / day ☐☐☐

If 2 or 3, age when started smoking ☐☐

If 3, (Ex-smoker), year stopped 19☐☐

Alcohol Intake

Current Status: 1. Never 2. Current drinker 3. Ex-drinker ☐

If 2 or 3, how often do/did you usually drink alcohol? ☐
1. Don't drink alcohol
2. Less than once per week
3. 1 or 2 days/week
4. 3 or 4 days/week
5. 5 or 6 days/week
6. Every day

On a day that you do/did drink alcohol, how many drinks would you usually have? ☐
1. 1 to 2 drinks
2. 3 to 4 drinks
3. 5 to 8 drinks
4. 9 to 12 drinks
5. 13 to 20 drinks
6. More than 20 drinks

Which beverage do/did you most commonly drink? ☐
1. beer 2. red wine 3. white wine 4. spirits

	Yes (✓)	No
At any time, did you drink more at the weekend?	☐	☐
If YES, how many drinks between Fri-Sun?	☐☐☐	
If Ex-drinker, when did you stop?	19☐☐	

Physical Activity

	Yes (✓)	No
In the past 2 weeks, did you walk for recreation or exercise?	☐	☐
If YES, how many times spent walking?	☐☐	
In the past 2 weeks, did you do any other vigorous activity for recreation or exercise?	☐	☐
If YES, how many times?	☐☐	

Family History of Heart Attack or Stroke

	Yes (✓)	No	Uncertain
Did either of your parents suffer a heart attack or stroke?	☐	☐	☐

White copy: Data Management Centre Pink copy: Regional Centre Blue copy: Patient File

DMC Date ☐☐ ☐☐ ☐☐ DMC Signature _____

RN ID ☐☐☐☐ RN Signature _____

Second Australian

ANBP2

National Blood Pressure Study

Regional Centre ☐☐☐ Patient ID ☐☐☐☐☐☐

Demographic and Risk Factor Information 2

To be completed by the GP Investigator and/or the Research Nurse for all patients allocated to a treatment group at randomisation. Please complete **ALL** questions.

Subject Initials ☐☐☐ **Date of visit** ☐☐ ☐☐ ☐☐ **Practice ID** ☐☐☐☐ **GP ID** ☐☐☐☐

HISTORY

	Yes (✓)	No
History of hypertension?	☐	☐
If YES, was it treated?	☐	☐
History of Angina Pectoris?	☐	☐
If YES, duration in years	☐☐ years	
History of other Atherosclerotic Diseases?		
Claudication	☐	☐
Stroke	☐	☐
Transient Ischaemic Attack	☐	☐
Renal Artery Stenosis	☐	☐
History of Myocardial Infarction?	☐	☐
(Refers to most recent infarect if more than one)		
If YES, was diagnosis Definite	☐	☐
Indeterminate	☐	☐
If YES, was it a Re-Infarction	☐	☐
History of Cardiac Failure?	☐	☐
History of Gout?	☐	☐

THERAPEUTIC PROCEDURES

Has this patient had:

	Yes (✓)	No
Coronary Artery Bypass Graft?	☐	☐
If YES, date of CABG	☐☐ ☐☐ ☐☐	
Coronary Angioplasty?	☐	☐
If YES, date of CA	☐☐ ☐☐ ☐☐	

OTHER IMPORTANT DISEASES? (Cardiovascular and other)

1 _____

2 _____

3 _____

4 _____

5 _____

To be completed by the Research Nurse

MAIN OCCUPATION of Bread Winner?
between *your* age 30-60 years.
(Give full title e.g. accounts clerk, floor tiler, civil engineer, master chef, etc)

_____

_____

_____

Main Tasks performed in that occupation?

_____

_____

_____

_____

_____

	Yes (✓)	No
Was this your OWN business?	☐	☐

White copy: Data Management Centre Pink copy: Regional Centre Blue copy: Patient File

DMC Date: ☐☐ ☐☐ ☐☐ DMC Signature: _____

RN ID: ☐☐☐☐ RN Signature: _____

Second Australian
ANBP2
National Blood Pressure Study

Regional Centre ☐☐☐ Patient ID ☐☐☐☐☐☐

Patient Exit Form

To be completed by the Research Nurse and GP Investigator at the visit the subject exits from the **pre-randomisation phase** of the study. Send original to the Data Management Centre and retain a copy for the patient file. Please complete ALL questions.

Initials (FML) ☐☐☐ **Date of Exit** ☐☐ ☐☐ ☐☐ **Practice ID** ☐☐☐☐ **GP ID** ☐☐☐☐

	Yes (✓)	No
1. Has the subject had any adverse event related to withdrawal of antihypertensive drugs?	☐	☐

If YES please describe

2. What was the reason the subject was withdrawn from the study?

	Yes (✓)	No
Subject withdrew consent to continue	☐	☐
GP withdrew consent to continue	☐	☐
Adverse reaction to drug withdrawal	☐	☐
Accelerated hypertension	☐	☐
Cardiac arrythmias	☐	☐
Cardiac failure	☐	☐
Angina	☐	☐
Other cardiovascular syndromes	☐	☐
Other reason	☐	☐

If Other reason, please describe

White copy: Data Management Centre Pink copy: Regional Centre Blue copy: Patient File

☐☐ ☐☐ ☐☐ DMC Date: _____ DMC Signature:

☐☐☐☐ RN ID: _____ RN Signature:

ANTIHYPERTENSIVE AGENTS

Brand Name	Generic Name	Code
Accupril	Quinapril	1
Accnorm	Captopril	1
Adalat	Nifedipine	3
Adalat Oros	Nifedipine	3
Agon SR	Felodipine	3
Aldactone	Spironolactone	4
Aldomet	Methyldopa	6
Aldomet M	Methyldopa	6
Aldopren	Methyl dopa	6
Alphapress	Hydralazine	7
Altace	Ramipril	1
Amizide	Hydrochlorothiazide plus Amiloride	4
Amprace	Enalapril	1
Amidal	Amiloride	4
Anpec	Verapamil	3
Ansec SR	Verapamil	3
Anselol	Atenolol	2
Apresoline	Hydralazine	7
Aprinox	Bendrofluazide	4
Aptin	Alprenolol	2
Asig	Quinapril	1
Atacand	Candesartan cilexitil	8
Avapro	Irbesartan	8
Avapro HCT	Irbesartan + hydrochlorthiazide	8+4
Barbloc	Pindolol	2
Betaloc	Metopropol	2
Blocadren	Timolol	2
Brevibloc	Esmolol	2
Burinex	Bumetamide	4
Capace	Captopril	1
Capoten	Captopril	1
Captohexal	Captopril	1
Cardizem CD	Diltiazem	3
Cardizem SR	Diltiazem	3
Cardol	Sotalol	2
Carduran	Doxazosin	5
Catapres 100	Clonidine	6
Catapres 150	Clonidine	6
Chlotride	Chlorothiazid	4
Coras	Diltiazem	3
Corbeton	Oxprenolol	2
Cordilox Oral	Verapamil	3
Cordilox SR	Verapamil	3
Coversyl	Perindopril	1
Cozaar	Losartan	8
Dapa-tabs	Indapamide	4
Daramide	Dichlorphenamide	4
DBL captopril	Captopril	1
Deralin	Propranolol	2
Diamox	Acetazolamide	4
Dichlotride	Hydrochlorothiazide	4
Dilatrend	Carvedilol	2
Diltahexal	Diltiazem	3
Diltiamax	Diltiazem	3
Dilzem	Diltiazem	3
Diulo	Metolazone	4
Dyazide	Hydrochlorothiazide plus Triamterene	4
Edecril	Ethacrynic Acid	4
Enduron	Methyclothiazide	4
Enduron M	Methyclothiazide	4
Enzace	Captopril	1
Esidrix	Indapamide	4
Felodur ER	Felodopine	3
Frusehexal	Frusemide	4
Gopten	Trandolapril	1
Hydopa	Methyldopa	6
Hydrene25/50	Hydrochlorothiazide plus triamterene	4

Brand Name	Generic Name	Code
Hydrodiuril	Hydrochlorothiazide	4
Hydrozide	Amiloride	4
Hygroton	Chlorthalidone	4
Hytrin	Terazosin	5
Inderal	Propranolol	2
Inhibace	Cilazapril	1
Insig	Indapamide	4
Isoptin	Verapamil	3
Isoptin Oral	Verapamil	3
Isoptin SR	Verapamil	3
Kaluril	Amiloride	4
Karvea	Irbesartan	8
Kredex	Carvedilol	2
Lasix	Frusemide	4
Lasix High Dose	Frusemide	4
Loniten	Minoxidil	7
Lopresor	Metopropol	2
Lozide	Indapamide	4
Metohexal	Metoprolol	2
Micardis	Telmisartan	8
Midamor	Amiloride	4
Midoride	Amiloride	4
Minax	Metopropol	2
Minipress	Prazosin	5
Mipraz	Prazosin	5
Modizide	Hydrochlorothiazide plus Amiloride	4
Moduretic	Hydrochlorothiazide plus Amiloride	4
Monopril	Fosinopril	1
Monoplus	Fosinopril + hydrochlorthiazide	1+4
Napamide	Indapamide	4
Naride	Indapamide	4
Natrilix	Indapamide	4
Natrilix SR	Indapamide	4
Nifecard	Nifedipine	3
Norvasc	Amlodipine	3
Noten	Atenolol	2
Nudopa	Methyldopa	6
Nyefax	Nifedipine	3
Odrik	Trandolapril	1
Plendil ER	Felodipine	3
Pritor	Telmisartan	8
Prasig	Prazosin	5
Presolol	Labetalol	2
Pressin	Prazosin	5
Prinivil	Lisinopril	1
Ramace	Ramipril	1
Renitec	Enalapril	1
SBPA Atenolol	Atenolol	2
SBPA Captopril	Captopril	1
SBPA Diltiazen	Diltiazem	3
SBPA Nifedipine	Nifedipine	3
Sotocor	Sotalol	2
Sotohexal	Sotalol	2
Spiractin	Spironolactone	4
Tenlol	Atenolol	2
Tenormin	Atenolol	2
Tensig	Atenolol	2
Trandate	Labetalol	2
Trasicor	Oxprenolol	2
Tritace	Ramipril	1
Uremide	Frusemide	4
Urex	Frusemide	4
Urex Forte	Frusemide	4
Urex M	Frusemide	4
Veracaps SR	Verapamil	2
Verahexal	Verapamil	2
Visken	Pindolol	2
WL-Captopril	Captopril	1
WL-Diltiazen	Diltiazem	3
Zestril	Lisinopril	1

CODE; 1 = ACEI 2 = β blocker 3 = Ca antagonist 4 = diuretic
5 = α blocker 6 = central acting 7 = other 8 = A II antagonist 28/05/02

Dept of Epidemiology &
Preventive Medicine

«id»

MANAGEMENT OF HYPERTENSION IN GENERAL PRACTICE

1. Personal details

Please shade circles (don't tick)

- **Age** 20-35○ 36-50○ 51-65○ >65○
- **Sex** male○ female○
- **Vocational registration** Yes○ No ○
- **Practice** full-time○ part-time ○

2. Clinical case

Mr Keith Wilson is an otherwise well 50-year-old male who has recently been seeing you with a blood pressure of 180/100 mmHg on three occasions.

Assuming advice on lifestyle changes have been given and his other risk factors are normal, which of the following drugs would you most likely use to start therapy?

Rank in order first preference (1) to last (6).

Please put a number in each of the squares.

ACE inhibitor (e.g. Tritace, Renitec) ☐

All blocker (e.g Karvea, Avapro) ☐

Beta blocker (e.g. Betaloc, Tenormin) ☐

Dihydropyrodine calcium channel blocker CCB (e.g. Adalat Norvasc) ☐

Diuretic (e.g. Chlotride, Natrilix, Moduretic) ☐

Non dihydropyrodine calcium channel Blocker CCB (e.g. Isoptin, Cardizem) ☐

3. Your opinion

We would like to know your impression of the profiles of ALL of following antihypertensive drug groups.

Please shade a circle beside each option.

	Poor		Neutral		Excellent
BP Lowering	1	2	3	4	5
ACE inhibitors	○	○	○	○	○
Beta blockers	○	○	○	○	○
Dihydropyrodine CCB	○	○	○	○	○
Non dihydropyrodine CCB	○	○	○	○	○
Diuretics	○	○	○	○	○
All blockers	○	○	○	○	○
Short- term side-effects					
ACE inhibitors	○	○	○	○	○
Beta blockers	○	○	○	○	○
Dihydropyrodine CCB	○	○	○	○	○
Non dihydropyrodine CCB	○	○	○	○	○
Diuretics	○	○	○	○	○
All blockers	○	○	○	○	○
Long-term side-effects					
ACE inhibitors	○	○	○	○	○
Beta blockers	○	○	○	○	○
Dihydropyrodine CCB	○	○	○	○	○
Non dihydropyrodine CCB	○	○	○	○	○
Diuretics	○	○	○	○	○
All blockers	○	○	○	○	○

Cost to government	Low		Med		High
ACE inhibitors	○	○	○	○	○
Beta blockers	○	○	○	○	○
Dihydropyrodine CCB	○	○	○	○	○
Non dihydropyrodine CCB	○	○	○	○	○
Diuretics	○	○	○	○	○
All blockers	○	○	○	○	○

Which of the following is/are the recommended first line treatment for uncomplicated primary hypertension?

Please shade the appropriate circle(s)

ACE inhibitors..... ○
All blockers..... ○
Beta blockers ..... ○
Dihydropyrodine calcium channel blockers..... ○
Non dihydropyrodine calcium channel blockers..... ○
Diuretics..... ○

Don't know ○

Thank you for participating in this study. Please return your form in the reply paid envelope provided.

Publications and conference presentations

Publications and conference presentations generated from this thesis are listed in the following.

Original Peer Reviewed Publications

Articles

Nelson MR, Krum H, Reid CM, McNeil JJ. A systematic review of subject baseline characteristics as predictors of maintenance of normotension after withdrawal of antihypertensive drugs. Am J Hypert. 2001;14: 98-105.

Nelson, MR, Reid, CM, Peeters, A, McNeil, JJ, Krum, H. PBS/RPBS cost implications of trends and guideline recommendations in the pharmacological management of hypertension in Australia 1994-1998. Med J Aust. 2001;174:565-568.

Reid CM, Ryan P, Nelson M *et al* on behalf of the ANBP2 Management Committee. General practitioner participation in the Second Australian National blood Pressure Study (ANBP2). Clin and Exper Pharm and Physiol. 2001;28:663-667.

Letters

Nelson M. Stopping antihypertensive drugs in general practice. [Letter]. British Journal of General Practice. 50(454):407, 2000 May.

Nelson MR, Reid CM, Peeters A, McNeil JJ, Krum H. PBS/RPBS cost implications of trends and guideline recommendations in the pharmacological management of hypertension. Med J Aust. 2002;176:190.

Proceedings, programs and abstracts.

Nelson M, Krum H, McNeil JJ, Ryan P, Wing LMH, Reid CM. A nested case control study of the withdrawal of antihypertensive drugs in general practice - rationale and design. High Blood Pressure Research Council of Australia 19th Annual Scientific Meeting program and abstracts, Fremantle, 1997.

Nelson M, Reid CM, Krum H, McNeil JJ. A survey of Victorian GPs' knowledge, attitude and stated practice of the initiation of antihypertensive drugs in primary hypertension. High Blood Pressure Research Council of Australia 21st Annual Scientific Meeting program and abstracts, Melbourne, 1999.

Nelson MR, McNeil JJ, Peeters A, Reid CM, Krum H. Cost implications of current trends and guideline recommendations in the pharmacological management of hypertension in Australia. High Blood Pressure Research Council of Australia 22nd Annual Scientific Meeting program and abstracts, Sydney, 2000.

Nelson MR, Reid CM, McNeil JJ, Ryan P, Wing LWH, Krum H. Short term predictors of maintenance of normotension post withdrawal of antihypertensive drugs in the Second

Australian National Blood Pressure Study (ANBP2). High Blood Pressure Research Council of Australia Inc, Melbourne, 2001.

Nelson MR, Reid CM, McNeil JJ, Ryan P, Wing LWH, Krum H. Short Term Predictors of Maintenance of Normotension Post Withdrawal of Antihypertensive Drugs in the Second Australian National Blood Pressure Study (ANBP2). J Am Coll Card 39(9)343B.

Original Peer Reviewed Publications: In Preparation or Submitted

Nelson MR, Reid CM, Krum H, Muir T, Ryan P, McNeil JJ. Predictors of successful maintenance of normotension on withdrawal of antihypertensive drugs in an elderly general practice population. A prospective study in the ANBP2 cohort. Submitted to Br Med Jour.

Nelson MR, McNeil JJ, Reid CM, Krum H. Factors influencing General Practitioner adherence to hypertension guidelines: questionnaire survey. Submitted to Journal of Pharmaco-economics.

Nelson MR, Reid, CM Krum, H, Ryan P, Wing LWH, McNeil JJ. Short term predictors of maintenance of normotension post withdrawal of antihypertensive drugs in the Second Australian National Blood Pressure Study (ANBP2). Submitted to Am J Hypertens.

Conference Presentations

Oral (Peer reviewed)

Nelson MR. The withdrawal of antihypertensive medication in the elderly in general practice, appropriate management of selected patients? 40th Annual Scientific Convention RACGP, Hobart, 1997.

Nelson MR. Withdrawal of antihypertensive drugs in general practice – rationale and design. 15th WONCA World Conference, Dublin, Ireland, 1998.

Nelson MR. Withdrawal of antihypertensive drugs in the Second Australian National Blood Pressure Study. Interim results. 41st Annual Scientific Convention RACGP, Melbourne, 1998.

Nelson MR, Reid CR, McNeil JJ, Krum H, Muir TH. Predictors of the short-term maintenance of normotension post withdrawal of antihypertensive drugs in ANBP2. WONCA Asia Pacific Regional Conference, Taipei, 1999.

Nelson MR, Reid CR, Krum H, Muir TH, Ryan P, McNeil JJ. A study of the withdrawal of antihypertensive drugs in the elderly in Australian general practice. International Clinical Trials Symposium, Sydney, 1999.

Nelson MR, Peeters A, Reid CR, Krum H, Ryan P, McNeil JJ. Cost implications of current trends in antihypertensive drug prescribing in general practice. Are we getting

best value for our patient's dollar? 42nd Annual Scientific Convention RACGP, Adelaide, 1999.

Nelson MR, Reid CR, Krum H, Ryan P, McNeil JJ. Can the elderly have their antihypertensive drugs ceased? The experience of attempting drug withdrawal in 25,000 Australian general practice patients. 42nd Annual Scientific Convention RACGP, Adelaide, 1999.

Nelson MR, Reid CR, Krum H, Ryan P, McNeil JJ. Why don't GP's follow clinical guidelines on the management of hypertension? 43rd Annual Scientific Convention RACGP, Townsville, 2000.

Nelson MR. Does our preference for first line antihypertensive drugs have adverse effects on the taxpayer? 44th Annual Scientific Convention RACGP, Sydney, 2001.

Invited speaker

Nelson MR. Hypertension. Can the elderly have their antihypertensive medication ceased? 7th Commonwealth Pharmaceutical Association Conference and Australian Pharmaceutical Congress, Melbourne, 1999.

Nelson MR. Controversies in the Management of Hypertension in General Practice. The 3rd Conference of the Pan-Arab Hypertension Society, Abu Dhabi, UAE, 2000.

Nelson MR. Detection and Management of Hypertension in General Practice. Barriers and difficulties. The 3rd Conference of the Pan-Arab Hypertension Society, Abu Dhabi, UAE, 2000.

Poster

Nelson M, Krum H, McNeil JJ, Ryan P, Reid CM. Withdrawal of Antihypertensive Drugs (WAD) in the Second Australian National Blood Pressure Study (ANBP2). A Nested Case Control Study Conducted In General Practice. The Alfred Research Symposium, Melbourne, 1997.

Nelson M, Krum H, McNeil JJ, Ryan P, Reid CM. Which Factors Predict Successful Maintenance Of Normotension On The Withdrawal Of Antihypertensive Medication? An Evidence-Based Review Of The Literature. The Alfred Research Symposium, Melbourne, 1997.

Nelson M, Krum H, McNeil JJ, Ryan P, Wing LMH, Reid CM. A nested case control study of the withdrawal of antihypertensive drugs in general practice - rationale and design. 19th Annual Scientific Meeting High Blood Pressure Research Council of Australia, Fremantle, 1997.

Nelson M, Reid CM, Krum H, McNeil JJ. A survey of Victorian GPs' knowledge, attitude and stated practice of the initiation of antihypertensive drugs in primary

hypertension. 21st Annual Scientific Meeting High Blood Pressure Research Council of Australia, Melbourne, 1999.

Nelson M, Reid CM, Krum H, McNeil JJ. Why don't GP's follow clinical guidelines on the management of hypertension? General Practice Evaluation Program Conference, Hobart, 2000.

Nelson M, McNeil JJ, Peeters A, Reid CM, Krum H. Cost implications of current trends and guideline recommendations in the pharmacological management of hypertension in Australia. High Blood Pressure Research Council of Australia 22nd Annual Scientific Meeting, Sydney, 2000.

AJH 2001; 14:98–105

A Systematic Review of Predictors of Maintenance of Normotension After Withdrawal of Antihypertensive Drugs

Mark Nelson, Christopher Reid, Henry Krum, and John McNeil

Background: The identification and treatment of hypertension in the general community has contributed to the reduction in strokes and coronary heart disease observed during the past 30 years. However, concerns have arisen that some patients may be receiving unnecessary antihypertensive drug therapy leading to wasted resources and the potential for adverse drug effects. Once therapy has been started, treating physicians have difficulty in selecting patients for withdrawal and have concerns regarding patient safety and their own legal liability.

Procedures: This study reviews and consolidates information from published studies to identify known predictors of the successful maintenance of normotension after antihypertensive drug withdrawal. The predictors were identified by determining the proportion of subjects with various baseline characteristics who remained normotensive while off medication for at least 12 months. From these data we have developed a clinical algorithm to help identify patients in whom antihypertensive drug withdrawal might be considered. This may assist primary care physicians in achieving successful withdrawal of antihypertensive therapy among selected hypertensive patients.

Results: The most consistent predictors identified were blood pressure (BP) (lower pretreatment, on treatment, and after withdrawal), nature of pharmacotherapy (fewer agents and lower dose), and preparedness to accept dietary intervention (weight and sodium reduction).

Conclusions: On the basis of this information, a trial of withdrawal of antihypertensive medication might be recommended for patients who have mildly elevated, uncomplicated BP that is well controlled on a single agent, and who are motivated and likely to accept lifestyle changes. Am J Hypertens 2001;14:98–105 © 2001 American Journal of Hypertension, Ltd.

Key Words: Withdrawal, antihypertensive drugs, predictors.

Approximately 10% of adults in Western countries are receiving long-term treatment with antihypertensive drugs.[1] A proportion of these may be receiving treatment inappropriately, either because pharmacologic therapy was commenced without appropriate justification or because their hypertension has resolved with lifestyle change. Once treatment is started physicians are often reluctant to withdraw therapy because of the difficulty in distinguishing between those patients who need and those who do not need continued treatment.

Unnecessary drug treatment is costly to society and to individuals, and places subjects at risk of the adverse effects of drug treatment. However, drug withdrawal may also be a concern because of issues such as drug withdrawal effects and possible legal liability if cardiovascular events occur during or shortly after ceasing therapy.

In the present study we have systematically reviewed published studies on withdrawal of antihypertensive drugs to identify consistent predictors of successful cessation of therapy through an analysis of subject baseline characteristics and study criteria. The information was presented as an algorithm that might be of value to primary care physicians.

Methods

Articles examining withdrawal of antihypertensive drug therapy were identified from MEDLINE using various topic-related key words. Additional articles were identified from the bibliographies of these publications. Using this approach we believe that we have identified all English-

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Table 1. Pivotal study design, sample population characteristics and size, and inclusion criteria for withdrawal of antihypertensive drugs (WAD) where predictors of success were investigated

Study	Study Type and Sample Population N (N WAD)	DBP (mm Hg)		Duration of Treatment (years)
		Pretreatment	At Withdrawal	
Alderman et al[3]	Observational. Unselected union members (mean age 55.7 year). 157 (88)	≥95 on 2 visits	<85 (<65 y) <90 (≥65 y)	≥0.5
DISH[6-8]	Multicenter RCT in 30–69 yr with dietary intervention (Na/K or wt reduction) 496 (415)	1st visit ≥95 2nd visit ≥90	<95 SBP <180	≥5
Grimm et al[19]	RCT, placebo-controlled with double blinding. Males aged 45–68 given KCl or placebo post WAD plus low sodium diet. (287–145 placebo)	NP	<90	≥3.5
Levinson et al[22]	Observational placebo controlled: mild controlled on diuretics alone. No age given. (24)	90–109	≤90	≥1
Medical Research Council[24]	Randomized controlled study on 35–64 year olds at entry. 2765 (783)	90–109	<90	6
Mitchell et al[25]	Longitudinal descriptive study of 30–70 yr in a family practice and a work site. 125 (107)	NP	NP	10.5 (average)
Morgan et al[26]	Placebo controlled randomized double blind trial on 60–79 years with dietary advice intervention. (102)	>100	<90	≥2
Myers et al[27]	Observational study of 21–80 year olds of subjects from family practice with ABPM*, family physician and nurse measurements. 246 (98)	NP	<160/95*	NP
Stamler et al[36]	RCT with nutritional intervention. Age group NP. 189 (141)	>90	<90	5
Takata et al[38]	Randomized comparison study 36–81 yr. 113 (72)	≥90	<90	NP
Thurm and Smith[39]	Observational: mild–moderate 20–65 yr hypertensives. (69)	≥90	<90	NP
TONE[42,44]	RCT of 60–80 yr in 4 academic health centers. (975)	NP	<85 on 1 drug (SBP <145)	NP

NP = not provided; RCT = randomized controlled trial; *ABPM = ambulatory blood pressure measurement; DBP = diastolic blood pressure; SBP = systolic blood pressure.

language publications examining the withdrawal of antihypertensive therapy published since the 1950s.

Each article was analyzed and key data concerning study design, definitions of hypertension and normotension, and baseline predictors were extracted. The criteria used for normotension varied among the individual studies. Therefore, successful withdrawal was defined as the maintenance of blood pressure (BP) levels below those where recommencement of drug treatment was advised 12 months after cessation of therapy. Studies with follow-up periods less than 12 months and those where the BP levels requiring recommencement of therapy were not specified were therefore excluded. Studies with very long follow-up periods were also excluded if it was not possible to estimate a 12-month success rate from the data provided by the investigators.

The monthly hazard (risk) of returning to hypertension was produced by computing the risk within each reported time interval and averaging over the interval time span. Summary relative risks describing the effects of gender, body weight reduction after withdrawal of antihypertensive drugs, and sodium reduction after withdrawal of an-

Table 2. Pivotal study recommence therapy criteria and success rates for maintenance of normotension post withdrawal of antihypertensive drugs where predictors of success were investigated

Study	Recommence Therapy BP Level (mm Hg)		% (*n*) Normotensive at 12 Months
	DBP	SBP	
Alderman et al[3]	1 visit ≥110	≥200	28% (44)
	2 visits ≥95 (<65)	≥160 (<65)	
	≥95	≥165 (≥65)	
DISH[6-8]	1 visit ≥105		Placebo 35%
	2 visits ≥100		Wt loss 60%
	3 visits ≥95		Salt restrict 52%
Grimm et al[19]	1 visit ≥115		56% (160)
	2 visits ≥95		57% (81) KCl
	3 visits ≥90		54% (79) Placebo
Levinson et al[22]	1 visit >114		21% (5)
	2 visits >99		
	3 visits >94		
	6 month av >90		
Medical Research Council[24]	>90		Diuretic M 44%, F 54%
			β-blocker M 47%, F 28%
Mitchell et al[25]	>90		37% (38)
Morgan et al[26]	2 visits >90		10%
Myers et al[27]	≥160/95*		51% (50)
Stamler et al[36]	1 visit >105		Group 1 44%
	2 visits >99		Group 2 15%
Takata et al[38]	1 visit ≥105		Diuretic 41% (12)
	2 visits >95		ACEI 37% (11)
Thurm and Smith[39]	≥90		23% (16)
TONE[42,44]	1 visit ≥110	≥190	34% (NA↓)
	2 visits ≥100	≥170	37% (wt loss)
	3 visits ≥90	≥150	44% (both)
			16% (control)

BP = blood pressure; M = male; F = female; ACEI = angiotensin converting enzyme inhibitor; other abbreviations as in Table 1.
* Represents ambulatory blood pressure measurement.

tihypertensive drugs, on the likelihood of requiring recommencement of therapy were determined using the DerSimonian and Laird random effects model, together with tests for heterogenity of effects across the studies.[2] Because there was little heterogeneity, the summary relative risks reduce to those obtained from a fixed effect model.

Results

Forty-one studies were identified, with majority of which described observational studies or patients withdrawn from drug therapy during the run in phase of a clinical trial.[3–45] Seven studies were excluded because of a follow-up period of less than 12 months,[14,17,20,32–34,37] nine because of the absence of any estimate of success at 12 months,[4,9,10,13,15,28,35,40,43] five because of the absence of criteria related to the recommencement of therapy,[5,11,18,20,30] and eight because baseline characteristics provided could not be linked to an estimate of success at 12 months.[12,14,16,21,23,31,41,45] The remaining twelve studies were considered to represent the pivotal studies and are summarized in Tables 1 and 2.[3,6–8,19,22,24–27,36,38,39,42,44]

Table 3 show that the most consistent predictors identified among these studies were BP (lower pretreatment, on treatment, and after withdrawal), pharmacotherapy (fewer agents and lower dose), and dietary intervention (weight and sodium reduction).

In most of the individual studies information about potential predictors of return to hypertension was not provided in a form that allowed a summary measure of effect to be determined. Most commonly the characteristics of those with normotension were compared to those with recurrent hypertension at 12 months without individual data provided. The exceptions were for gender and those studies where an intervention was introduced.

A simple meta-analyses for these characteristics are shown in Table 4. Weight reduction and salt restriction after withdrawal of antihypertensive drugs (WAD) were both statistically significant predictors of maintenance of normotension. Gender was not a predictor.

Fig. 1 shows the risk of patients returning to hypertension at varying times after drug withdrawal among groups not receiving lifestyle intervention. It shows that the risk of return to hypertension is greatest in the first 6 months. However, the risk continues after this time.

Table 3. Pivotal studies that tested predictors of success

Study	[38]	[39]	[6–8]	[36]	[3]	[24]	[22]	[26]	[25]	[19]	[42]
Blood pressure											
Pretreatment level	–	↓	↓	+			–				
On treatment	–		–			+[1]			↓[2]		↓[3]
1 month post WAD	↓				↓						
Therapy											
Duration	–	–					–		↑		↓
Type	-					+			–		–
Monotherapy			+	+							
Dose level				+					–		
Subject											
Age at WAD	–		–			–			–		–
Sex	–		–						–		
Race		–									–
Family history							–				
Body weight											
AT WAD			–				–		–		–
After WAD			↓	↓			–				↓
Smoking			–								–
Alcohol				+							–
Vascular disease											+
Family history	–						–				
Exercise											–[4]
Organs											
Heart											
LV mass	–							–			
Heart rate							–		–		
ECG				–							
Heart rate									–		
Kidneys											
Electrolytes							–				
Renin profile	–		↑				–				
Na/K excretion							–				
Proteinuria	–										
Interventions											
Diet			↓	+[5]				–[6]			↓[7]
K supplements										–	
Stress tests									–		

ECG = electrocardiogram; LV = left ventricular; other abbreviation as in Table 1.

Statistically significant association: + = direction not specified or not relevant, ↓/↑ = direction of effect that predicted maintenance of normotension post WAD. No statistically significant association = –.

[1] men only; [2] standing diastolic blood pressure plus longer duration of normotension on drugs but not lying BP; [3] SBP only; [4] baseline, [5] alcohol, weight, and sodium reduction; [6] for increased potassium and decreased sodium; [7] Na reduction.

Discussion

In the pivotal studies reviewed the most consistent predictors of successful antihypertensive drug withdrawal were relatively low levels of BP, both before treatment was started and during therapy with a single drug. Adoption of lifestyle changes, such as reduced body weight and reduced sodium intake, after withdrawal were also useful predictors.

In a meta-analysis, reduced body weight and sodium restriction were also confirmed to be statistically significant predictors. These findings imply that a trial of drug withdrawal is most likely to be successful in patients with one or more of these characteristics, especially if the lifestyle changes are adopted.

These conclusions are based on a review of information from 12 studies shown in Tables 1 and 2. Most of these studies involved withdrawal of previous drug therapy as a prelude to participation in a clinical trial. The cohorts were then observed and the characteristics of those in whom hypertension recurred were compared with those in whom it remained low.

There are several limitations of the data from which the predictors are observed. The participants involved were not necessarily representative of hypertensive patients in general and the predictors examined varied from study to study and were not defined in a consistent fashion.

All studies, however, had at least 12 months of follow-up. In the absence of lifestyle interventions, success rates averaged approximately 42% over all studies with follow-up periods of this duration. With a single exception,[13] the studies with follow-up periods between 2 and 5 years show similar rates of maintenance of normotension to

Table 4. A meta-analyses of baseline characteristics as predictors of subjects who had antihypertensive drugs withdrawn and maintained normotension off medication at 12 months

Predictor	Study	Proportion*	RR	CI	*P*	Heterogeneity *P* Value
Sex						
Male	[4] [24] [25] [26]	280/595	0.96	0.85–1.08	.51	.54
Female	[38] [39]	266/513				
Body weight post WAD						
Weight loss	[7] [36] [42]	274/475	1.13	1.16–1.48	<.001	.97
No weight loss		291/666				
Sodium restriction post WAD						
Yes	[7] [26] [42]	353/699	1.30	1.17–1.45	<.001	.71
No		329/857				

* Proportion with predictor who remained normotensive at 12 months after withdrawal of antihypertensive drugs.
CI = confidence interval; other abbreviation as in Tables 1 and 3.

those where the follow-up period was limited to 12 months.[3,12,13,16,24,36,42,44] The available information suggests that the rate of recurrence slows after 6 months (Fig. 1).

Many studies have noted that several weeks or months commonly elapse between the cessation of drug treatment and the return of BP to higher levels. This is believed to result from a reduction in hypertrophy in smaller arteries during treatment that reverses the elevated peripheral resistance.[20] A considerable period may elapse before such hypertrophy redevelops. This illustrates the need to institute long-term monitoring of the BP of patients withdrawn from antihypertensive therapy with the aim of detecting a return of hypertension. As seen in Fig. 1 such monitoring needs to be most diligent in the first 6 months after withdrawal.

It may be that the majority of patients for whom drug withdrawal is appropriate are those in whom therapy was commenced inappropriately. To avoid unnecessary drug therapy various national authorities have emphasized the importance of confirming the diagnosis repeatedly before starting treatment. For example, the US Joint National

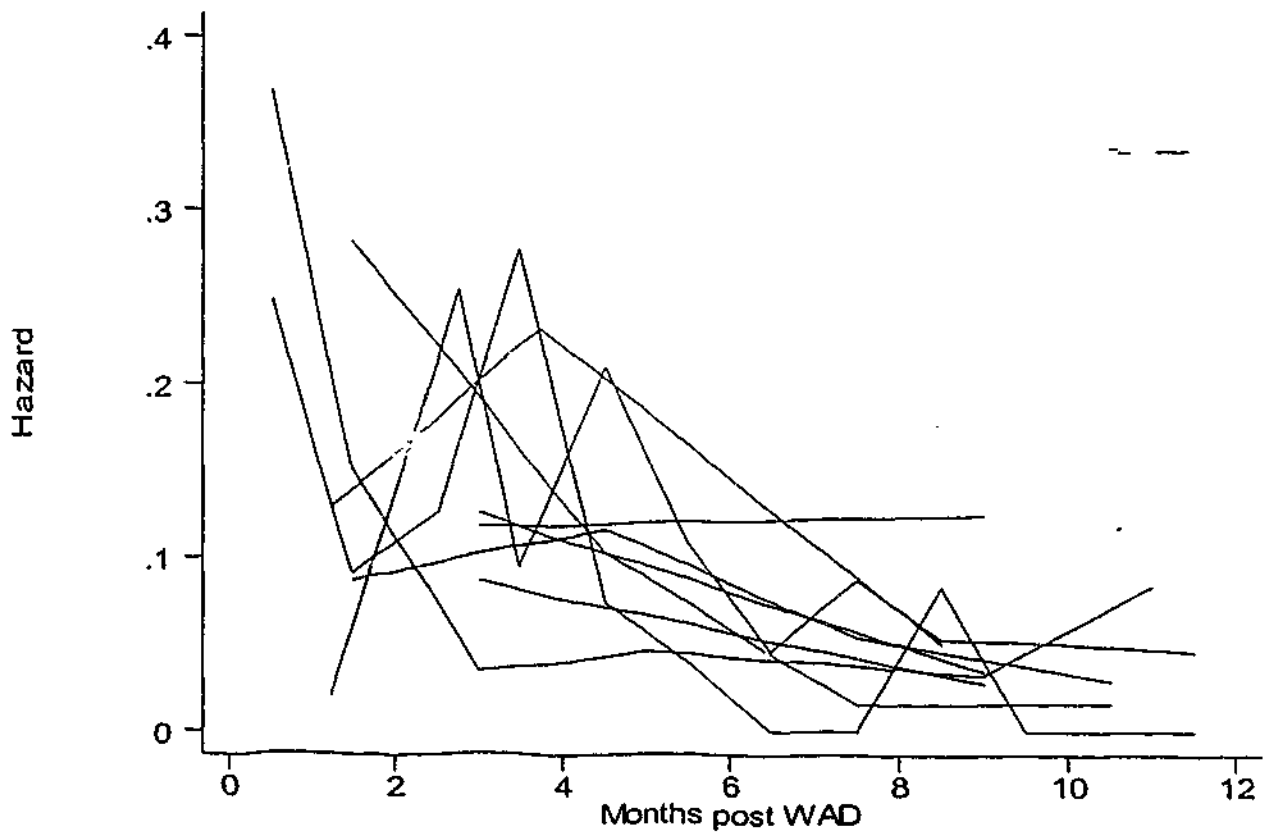

FIG. 1. A multiple linear plot for studies with data of the "natural history" (ie, without a lifestyle intervention or placebo) of withdrawal of antihypertensive drugs and subsequent risk of return to hypertension over 12 months ($n = 9$).[7,12,16,21,22,25,36,38,42] The monthly hazard of returning to hypertension was produced by computing the risk within each reported time interval and averaging over the interval time span. WAD = withdrawal of antihypertensive drugs.

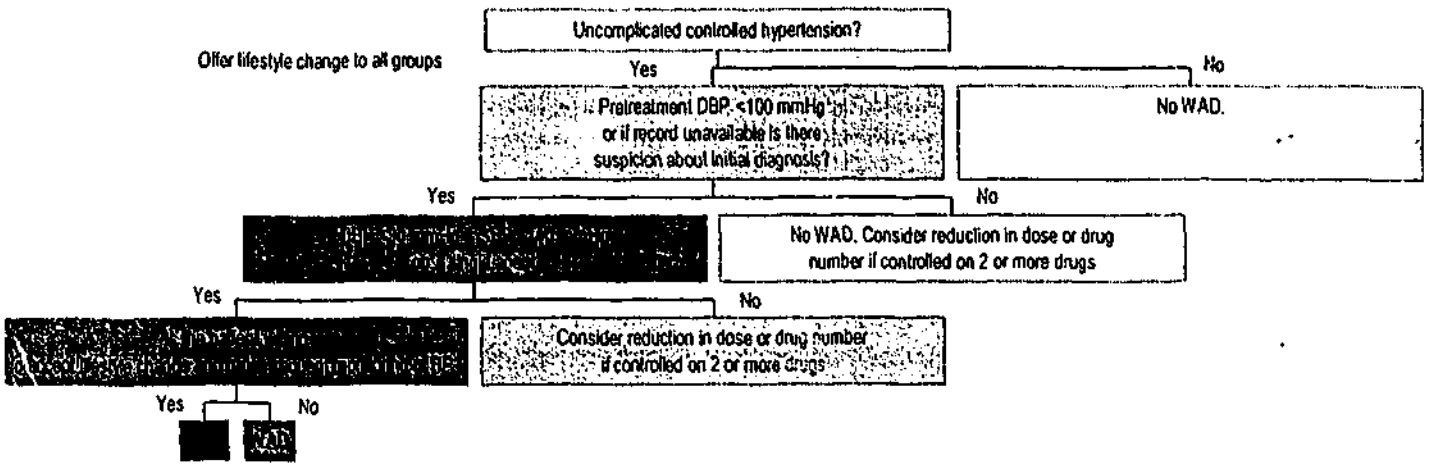

FIG. 2. Algorithm demonstrating a proposed sequence of decisions to determine which patients should be considered for withdrawal of antihypertensive drugs. Depth of box shading represents increasing likelihood of successful maintenance of long-term normotension. As lifestyle changes have been shown to double the rate of maintenance of normotension after withdrawal of antihypertensive drugs they should be offered to all patients in whom drug withdrawal or reduction is being contemplated. DBP = diastolic blood pressure; SBP = systolic blood pressure; BP = blood pressure; other abbreviation as in Fig. 1.

Committee on the Detection, Evaluation and Treatment of High Blood Pressure has recommended that the decision to treat mild-to-moderate BP elevation should be based on the results of at least two BP readings on at least three separate occasions.[46]

The importance of these recommendations was emphasized by the results of the Australian Therapeutic Trial in Mild Hypertension.[47] Despite entry criteria that required a mean diastolic BP (from four recordings over two visits) in the range of 95 to 110 mm Hg, 48% of those randomized to placebo still decreased below this level during the 3 years of follow-up.

The subsequent availability of 24-h BP monitoring has also revealed the presence of white coat hypertension where BP, which becomes elevated during the stress of a medical encounter, returns to normal levels at other times.

The percentage of patients who are correctly started on therapy but who subsequently become normotensive is likely to be much smaller than the percentage where therapy was inappropriately commenced. However, it was notable in this review that adoption of appropriate lifestyle changes was identified as a consistent predictor of successful drug withdrawal. This is in keeping with the results of several major trials that have shown that a reduction in body weight, reduced salt and alcohol intake, and an increase in physical activity may be sufficient to reduce marginal BP elevations to normotensive levels.[6,7,36,42] Because long-term compliance with such interventions is low, continued monitoring of BP is appropriate in these patients.

Few studies commented on the adverse effects of drug withdrawal, particularly rebound hypertension, which may accompany the sudden cessation of clonidine or the rebound hypersensitivity to adrenergic stimuli that accompanies sudden cessation of β-blockers.[48,49] The latter is well characterized and may be incorrectly attributed to a recurrence of elevated BP. The symptoms, principally tachycardia in response to mild exertion, may lead to rebound angina and myocardial infarction and should be avoided by a slow and graded withdrawal of treatment. Programs that encourage drug withdrawal in selected patients should emphasize the importance of drug withdrawal symptoms and the strategy to avoid them.

Fig. 2 presents an algorithm designed to assist primary care physicians. This algorithm is derived from this systematic review and is intended as only a guide. It has not been tested on a clinical population and therefore, no formal estimates of success rates are provided. Patients who do not meet all of the criteria may still be suitable for drug withdrawal, although success is likely to be lower. The need to continue to attend regular BP checks should be emphasized to all patients, especially in the first 6 months. It is also recommended that behavioral modification be encouraged as clinical trials have shown that such interventions roughly double the rate of successful maintenance of normotension after withdrawal of antihypertensive drugs.[6–8,26,42]

The current recommendations by expert committees support periodic reassessment of drug therapy for hypertension for reduction in dosage and number of drug groups[50] and withdrawal of antihypertensive drugs in certain circumstances with adequate follow-up.[46,51,52]

In conclusion, if antihypertensive medication is withdrawn from selected patients with mild-to-moderate hypertension, then approximately 42% of these patients are likely to remain normotensive for periods in excess of 12 months. The studies that have established this have had varying designs, patient populations, and even definitions of hypertension. Predictors of success have been identified in a number of these studies and would suggest the long-term well-controlled mild hypertensive patients on single agent therapy are appropriate candidates for a trial of withdrawal of antihypertensive medication, especially if they are willing to undertake lifestyle changes.

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PBS/RPBS cost implications of trends and guideline recommendations in the pharmacological management of hypertension in Australia, 1994–1998

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ABSTRACT

Objectives: To determine the extent to which "current guidelines" for the management of hypertension are reflected in the prescribing of antihypertensive drugs in Australia over the period 1994–1998, and to examine the cost implications of actual and recommended prescribing patterns.

Design: Federal Government and consumer cost estimates modelled on prescribing patterns and guideline recommendations over the period 1994–1998.

Setting: Prescribing on Federal Government pharmaceutical schemes over the 1994–1998 period.

Main outcome measures: Estimates of Pharmaceutical Benefits Scheme/Repatriation Pharmaceutical Benefits Scheme cost changes in Australian dollar values.

Results: The implementation of current guidelines for patients with uncomplicated hypertension taking monotherapy alone could have reduced drug costs by $45–$108 million in 1998.

Conclusions: Current prescribing patterns indicate that clinical practice has pre-empted the results from clinical trials of newer, more expensive agents and that clinicians' prescribing patterns do not closely reflect current recommendations.

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THE TREATMENT OF PATIENTS with mild to moderate hypertension is usually initiated with an agent from one of four major drug classes. These are thiazide diuretics, β-blockers, calcium-channel blockers (CCBs), or agents acting on the renin–angiotensin system (RAS). The efficacy of the members of these groups in lowering blood pressure is similar and, although differences may be observed between agents in single symptoms, no major differences occur in their overall burden of adverse effects.[1-4] However, the CCBs and RAS agents are three to nine times more costly than β-blockers and thiazide diuretics.[5]

Until recently, only thiazide diuretics and β-blockers had been shown to reduce the long term sequelae of hypertension (myocardial infarction and stroke). Largely because of this, expert committees in several countries including Australia recommended that drug therapy in uncomplicated mild to moderate hypertension should be commenced with one of these agents.[6-9] Over the past two years, large-scale morbidity/mortality trials have been completed comparing these drugs with CCBs and RAS agents — these trials have not shown the more costly therapies to be superior.[2-4,10]

Despite the consistency of the advice from various national committees, the recommendations have not been widely accepted by prescribers, who have generally chosen to initiate therapy with CCBs and RAS agents.

In this study, we examined trends in the use of the major antihypertensive drug groups and determined the cost implications of these trends. Particular attention was directed to the additional costs resulting from the use of CCBs and RAS agents in the uncomplicated clinical setting, where the less expensive drugs have been shown to have equivalent long term efficacy.

For editorial comment, see page 556

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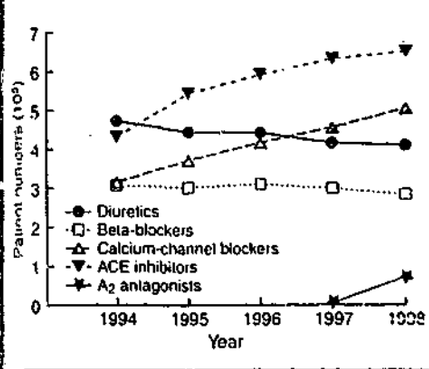
METHODS

PBS/RPBS expenditure

Expenditure on specific classes of cardiovascular therapy through the Pharmaceutical Benefits Scheme (PBS) and the Repatriation Pharmaceutical Benefits Scheme (RPBS) from 1994 to 1998 was provided by the Analysis Section, Pharmaceutical Benefits Branch, Commonwealth Department of Health and Aged Care. This expenditure includes components for the professional services of the dispensing pharmacist as well as the cost of the drug and patient contribution.

The patient copayment for PBS/RPBS drugs in 1998 was $3.20 for concession card holders and $20.00 for others, unless a brand price premium or a therapeutic group premium was levied on a particular drug, in which case there was additional cost to the patient (average, $1.60; range, $0.22–$6.08). If a "safety net" of $166.40 (concessional category) or $612.60 (general category) was exceeded in a calendar year for an indi-

1: Patients receiving cardiovascular drugs for hypertension in Australia, 1994–1998



vidual or family, then further out-of-pocket payments were zero or $3.20, respectively.

With some drugs, the patient copayment covers the total cost; in these instances the Commonwealth makes no contribution to the cost and these prescriptions are not recorded in the PBS/RPBS data. The PBS/RPBS data also omit expenditure on medications provided directly from public hospital pharmacies.

Patients receiving therapy

Total numbers of Australian patients receiving therapy with specific drug groups were determined using data from the Australian Pharmaceutical Index (API) and the Australian Medical Index (AMI). The API reports sales of specific drugs from wholesaler to community pharmacies, but does not include drugs supplied to public hospitals. The AMI collects detailed prescribing information (including age, sex, and primary diagnoses) from a stratified sample of general practitioners. By dividing the total quantity of drugs sold (from the API) by the average daily dose (provided by the AMI) and assuming continuous therapy, the total number of individuals receiving a specific drug can be estimated.

Proportion of hypertensive patients with specific comorbidities

An estimate of the distribution of comorbidity among mild to moderate hypertensive patients was made from data from the Second Australian National Blood Pressure Study (ANBP2).[11,12] During the screening phase of this study, 25 867 hypertensive patients were identified from general practices in all Australian mainland States/Territories, with 3783 of these meeting the criteria for randomisation. For a pre-randomisation visit, information was collected from these individuals about their comorbidity and prescribed medications. Using these data as a baseline, costs were estimated on 30%, 40%, and 50% contraindications for older agents.

Costs

Estimates were made of the differences in costs of antihypertensive drug therapy with current prescribing patterns and with prescribing in accordance with guidelines.[6] The estimate was confined to individuals free of significant comorbidity that might make a CCB or an RAS agent a preferred therapy.

RESULTS

Trends in the number of hypertensive patients prescribed the major classes of antihypertensive drugs from 1994 to 1998 are shown in Box 1. The estimated number of individuals receiving antihypertensive medication under the scheme increased by 27% (from 965 000 to 1 223 000). Almost 60% of these individuals were prescribed a single drug for their hypertension.

Over the five-year period, about 80% of RAS agents were prescribed primarily for the treatment of hypertension, and the number of prescriptions for this indication increased at a rate of 10% annually. A similar pattern was observed with CCBs, 75%–80% of which were prescribed primarily for hypertension, with an average increase of 7% per year. By contrast, prescribing of β-blockers for hypertension increased by 1%, while that of thiazide diuretics decreased by 1% annually (hypertension was principal indicator in about 70% of prescriptions for β-blockers and about 50% of prescriptions for thiazide diuretics).

The proportion of patients with mild to moderate hypertension with comorbidity likely to influence prescribing was estimated from information supplied by entrants to ANBP2. Because entrants to this study were aged 65–84 years, these data provide an imprecise indicator of comorbidity in the general population of people with hypertension. Among these entrants, 10% have established coronary heart disease (angina or myocardial infarction), and 8% have diabetes. Sixteen per cent of those receiving monotherapy had an identified comorbidity. Given the limitations of this dataset, the proportion was modelled on

2: Daily cost in 1998 of each class of commonly prescribed antihypertensive drug

	Cost of agent PBS/RPBS* ($m per annum)	Use for hypertension†	Cost for hypertension ($m per year)	Hypertension patient numbers‡	Cost per patient (cents per day)
RAS agents		81.5%		723 000	
Government	256.3		208.9		79.2
Consumer	79.7		64.9		24.6
Total	336.0		273.8		103.8
Calcium-channel blockers		78.2%		504 300	
Government	155.5		121.6		66.0
Consumer	44.4		34.7		18.9
Total	199.9		156.3		84.9
Diuretics		52.4%		410 400	
Government	24.8		13.0		8.7
Consumer	7.4		3.9		2.6
Total	32.2		16.9		11.3
β-Blockers		65.5%		282 200	
Government	33.3		21.8		21.2
Consumer	11.3		7.4		7.2
Total	44.6		29.2		28.4

* Data from Pharmaceutical Benefits Branch. † Data from Australian Medical Index. ‡ Data from Australian Pharmaceutical Index. RAS = renin–angiotensin system.

3: Estimated cost of single-agent therapy for uncomplicated hypertension, 1998

	Estimated actual	Estimates after redistribution (change)* 30%	40%	50%
Thousands of patients receiving monotherapy in each drug class				
Agents acting on the renin–angiotensin system	434	172 (−262)	230 (−204)	288 (−146)
Calcium-channel blockers	303	172 (−131)	230 (−73)	288 (−15)
Thiazide diuretics	246	404 (+158)	346 (+100)	288 (+42)
β-Blockers	169	404 (+235)	346 (+177)	288 (+119)
Total cost per year ($m)				
Government	219.2	135.4	159.7	184.1
Consumer	66.5	41.7	49.0	56.0
Total	285.7	177.1	208.7	240.1
Change		(−108.6)	(−77.0)	(−45.6)

*Estimated patients receiving each drug class, and estimated costs, if all patient regimens were based on a diuretic (50%) or β-blocker (50%), but 30%, 40% or 50% of patients had indications for other agents or contraindications to these agents.

30%, 40%, or 50% clinical indication/contraindication for newer agents.

The cost of each class of medication was determined assuming 1998 prices quoted in the PBS/RPBS and converted to a daily cost (Box 2). From Box 3, an estimated reduction in PBS/RPBS expenditure of $45–$108 million would have been made in 1998 if patients without comorbidities receiving monotherapy were prescribed therapy according to the Australian guidelines.

DISCUSSION

In 1992, an Australian consensus conference recommended that, unless clinical reasons existed for choosing an alternative agent, the first drug to be used in mild to moderate hypertension should be a thiazide diuretic or a β-blocker.[6] When comorbidity exists, specific advice is given (Box 4). Since then, several other bodies, including the US National Institutes of Health, the British Hypertension Society and the National Heart Foundation of Australia, have released guidelines with similar recommendations.[7-9] The major exception is the WHO/ISH 1999 guidelines, which do not specify a preferred drug class.[13]

The rationale for recommending a thiazide diuretic or a β-blocker stemmed principally from the lack of large-scale morbidity–mortality trials confirming a favourable risk–benefit ratio with RAS agents or CCBs. More recently, such data have become available. Of the four published studies, none has demonstrated that RAS agents or CCBs are more effective than thiazide diuretics or β-blockers in preventing coronary events or prolonging survival (Box 5).[2-4,10] Other, similar studies (including ANBP2) will report their results in coming years.

Our analysis indicates that the Australian government spends a minimum of $45 million annually as a result of Australian doctors' overlooking established guidelines for the management of mild to moderate hypertension. This is the difference between current expenditure on first-line therapy for mild to moderate hypertension without comorbidity and the expenditure that would be incurred if thiazide diuretics or β-blockers were prescribed routinely as the initial therapy. The figure is likely to be a substantial underestimate, as it is based on a number of conservative assumptions and does not include Commonwealth expenditure through public hospitals. However, this is offset by the PBS/RPBS capturing much more of the cost of the newer, more expensive agents than thiazide diuretics or β-blockers.

In the absence of proven additional benefit on medium- to longer-term cardiovascular outcomes, the choice of RAS agents or CCBs could be justified if they were better tolerated by most patients or had a lower incidence of serious adverse effects. However, the few published studies have found no major differences existing in the proportions of patients that must cease treatment because of adverse effects. In the INSIGHT study, for example, 1259 of the CCB group ($n=3157$), compared with 1043 of the diuretic group ($n=3164$), withdrew because of adverse events.[2] Although there are a variety of specific adverse effects associated with the specific drug groups, no studies have demonstrated a difference in the overall burden of adverse effects.

Nevertheless, thiazide diuretics and β-blockers are not appropriate initial therapies for all patients. Some patients will be unsuited to either of these agents because of comorbidity (eg, a combination of type 2 diabetes and asthma that forms a contraindication to both drugs). Comorbidity may also provide an indi-

4: Current recommendations for initiation of drug therapy for mild hypertension

Comorbidity	Australian guideline (1994)[6]	NHF (1999)[9]	BHS (1999)[8]	JNC-VI (1997)[7]	WHO/ISH (1999)[13]
Uncomplicated	Diuretic *or* β-Blocker	Diuretic *or* β-Blocker	Diuretic *or* β-Blocker	Diuretic *or* β-Blocker	Not specified
Angina	β-Blocker	β-Blocker *or* CCB	β-Blocker *or* CCB	β-Blocker *or* CCB	β-Blocker *or* CCB
Diabetes (type 2)	ACE inhibitor	Not specified	Not specified	1. ACE inhibitor† 2. CCB *or* Diuretic	1. ACE inhibitor† 2. Diuretic *or* β-Blocker
Lipid disorders*	1. α-Blocker† 2. ACE inhibitor *or* CCB	Not specified	α-Blocker	α-Blocker	α-Blocker

*The greater risk of combined cardiovascular events (particularly congestive heart failure) demonstrated recently with doxazosin versus chlorthalidone has raised questions as to the safety of α-blockers, which should no longer be seen as appropriate first-line agents.[14]
† Drug 1 is first preference.
ACE = angiotensin-converting enzyme. CCB = calcium-channel blocker.

5: Large-scale comparative outcome trials for older and newer antihypertensive agents

Study (design)	Subject numbers	Subject characteristics: Age (years)	Sex M (F)	Blood pressure (mmHg)	Drugs	Cardiovascular disease endpoints: Event rate (per 1000 patient-years)	RR (95% CI)
STOP-2[3] (PROBE)	6614	70–84	2196 (4418)	SBP ≥180 DBP ≥105	ACE inhibitor/calcium channel blocker	43.6	0.96 (0.86–1.08)
					β-blocker/diuretic	44.9	
CAPPP[10] (PROBE)	10985	25–66	5864 (5111)	DBP ≥110	Captopril	11.1	1.05 (0.90–1.22)
					β-blocker/diuretic	10.2	
INSIGHT[2] (RDBCT)	6321	55–80	3929 (3392)	≥150/95 SBP ≥160	Nifedipine	18.2	1.10 (0.91–1.34)
					Co-amilozide	16.5	
NORDIL[4] (PROBE)	10881	50–74	5290 (5591)	DBP ≥100	Diltiazem	16.6	1.00 (0.87–1.15)
					β-blocker/diuretic	16.2	

SBP = systolic blood pressure. DBP = diastolic blood pressure. PROBE = prospective, randomised, open, blinded endpoint study. RDBCT = randomised, double-blind, comparative trial.

cation for other agents. Other patients will have tried one or other of these agents and been found intolerant. In this study, we assumed that up to 50% of individuals would be more appropriately treated with an ACE inhibitor or CCB.

Without evidence of clinical superiority in most patients, the relative cost of drug therapy becomes a major factor in determining the appropriate choice of therapy. Cost comparisons are complicated by the complex system by which Australian medication costs are shared between government and patients.

Our analysis did not take into account any difference in cost that might come about because of a difference in monitoring requirements or in the costs of managing adverse effects. There are no specific recommendations for electrolyte monitoring in the product information sheets, commercial drug compendia, or the *Australian medicines handbook*, and no apparent reason why any specific drug would require more intensive clinical monitoring.[15] On the other hand, it is conceivable that the costs associated with the clinical management of adverse effects might be greater with one or other agent; however, there is presently insufficient information to quantify these differences.

Prescriber preference for the more expensive antihypertensive drugs is likely to involve a combination of factors. There is a perception that these agents are more "modern", more potent, and better tolerated. These perceptions have been enhanced by widespread reference in advertising material to surrogate measures (eg, effect on lipid levels), with an expectation of improved cardiovascular outcomes. The pharmaceutical industry, which is largely responsible for creating these perceptions through extensive advertising of these drugs, would argue that unless newer agents are continually introduced to supplant older agents the process of pharmaceutical innovation will be threatened.

Clinical practice appears to have preempted the newer clinical trials and, contrary to evidence to date, has assumed the superiority of newer agents. Thus, clinicians are often not prescribing according to current recommendations. Possible reasons why this is occurring are that clinicians are unaware of the guidelines or find them impractical, or they are influenced by personal or patient preference, or because drug marketing selectively promotes newer agents.

ACKNOWLEDGEMENTS

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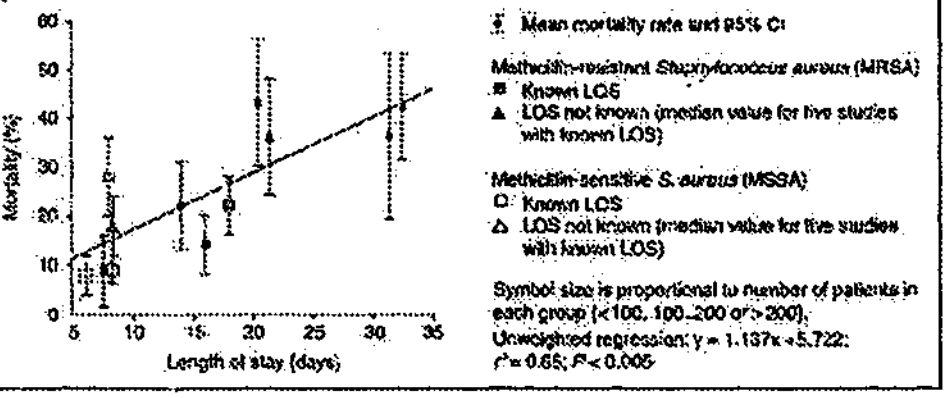
Mortality rate versus hospital length of stay before bacteraemia (LOS) in patients with MRSA or MSSA bacteraemia



group status (MRSA or MSSA) failed to achieve significance in any iteration of the regression, while LOS remained a significant predictor of mortality risk.

This suggests that, with *S. aureus* bacteraemia, mortality rate increases with length of time in hospital before the bacteraemia. The likely explanation is that patients residing in hospital for longer periods are sicker. Moreover, they are more likely to have been exposed to antibiotics, leading to increased risk of acquiring an *S. aureus* strain that is methicillin-resistant. The mortality risk is no different for MRSA versus MSSA bacteraemia if LOS, a surrogate marker for severity of patient illness, is taken into account. The difference that Whitby et al observed between the groups of patients with MRSA and MSSA bacteraemia could be accounted for by the difference in LOS between these groups.

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In Reply: We thank Hurley for his comments on our meta-analysis.[1] However, we strongly dispute that our analytical technique is flawed, and argue that we have been extremely cautious in drawing our conclusions. Hurley's contention is that hospital length of stay before bacteraemia (LOS) is a surrogate for severity of underlying disease and risk for colonisation with methicillin-resistant *Staphylococcus aureus* (MRSA), and that these factors explain the higher mortality in patients with MRSA.

We agree that LOH may be a confounder. It may be an effect modifier, whereby patients in hospital for longer may be more ill, and therefore more susceptible to infection with and death from MRSA. Both are intuitive and biologically plausible conclusions. In fact, we referred to these possibilities in our Discussion, writing that "patients who ultimately become infected with MRSA are more seriously ill than those who become infected with MSSA [methicillin-sensitive *S. aureus*]" and "separating the effect of the bacteraemia *per se* from the effects of patients' underlying disease and treatment is a major problem when comparing outcomes". We also cautioned readers that available published data on mortality made it impossible for us to adjust for numerous potential confounders, including LOH, as the information given did not link these potential confounders with the outcome in individual patients.

Hurley has not, as he suggests, undertaken an analysis that would allow him to control correctly for the potential confounder, LOH. He, like us, used "group-as-a-unit" data, but, although the groups are homogeneous for MRSA or MSSA, they are heterogeneous for LOH. Adequate examination of and control for potential confounders requires either individual patient data or data from homogeneous groups. Hurley has attempted to use analysis normally reserved for individual data.[4] His analysis was analogous to treating the data as though from an ecological study, a design in which control of confounding is difficult,[5] and thus does not permit him to draw his conclusions.

Our analysis (not presented in our original article) of only those studies where the authors attributed mortality to bacteraemia[6-8] found that the magnitude of effect remained (fixed-effect relative risk, 2.27; 95% CI, 1.75–2.96; $P < 0.001$; test for heterogeneity, $\chi^2 = 6.14$, $df = 4$, $P = 0.19$).

As MRSA bacteraemia is a rare event and published studies are small, the statistical ability to control for confounding and effect modification is limited. Until sufficient suitable data for individual patients are available for analysis, we have remained restrained in our assessment. Mindful that MRSA bacteraemia is associated with increased mortality, regardless of the cause, we hold with our original conclusion that "our findings justify ongoing surveillance and proactive management of MRSA in healthcare facilities".

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PBS/RPBS cost implications of trends and guideline recommendations in the pharmacological management of hypertension

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To the Editor: The article by Nelson et al[1] estimates Pharmaceutical Benefits Scheme and Repatriation Pharmaceutical Benefits Scheme (PBS/RPBS) savings if hypertensive patients on monotherapy were prescribed the agents recommended in guidelines; however, the analysis contains algebraic errors and insufficient sensitivity analyses. The question of excessive costs through the use of expensive agents for which there is no evidence of increased benefit for most patients is an important one, but the estimates of extent of overuse should be methodologically sound. The

three main concerns we have with the paper's estimates are as follows:

* The total number of patients on monotherapy in Box 3 of the article adds to 1.1 million, whereas elsewhere the authors state that 60% of all 1.2 million Australian patients treated for hypertension are on monotherapy, giving an estimate of 0.72 million. (These estimates of 60% and 1.2 million are not referenced in the article.) One reason for this discrepancy is that the authors have treated the sum of column 4 in Box 2 as patients, not patient-years of treatment (some patients are on dual or triple therapy), leading to a 40% overestimate of numbers of patients on monotherapy reported in Box 3.

* Utilisation of prescription drugs is recorded by PBS/RPBS only if the cost to patient is subsidised. Therefore, PBS/RPBS expenditure divided by total patient numbers (Box 2) underestimates consumer cost for diuretics and β-blockers, both of which cost less than the non-concessional copayment. Of total PBS/RPBS scripts, 16% are for non-cardholders,[2] and the cost per script to these patients is about three to four times the prevailing 1998 cardholder copayment. As a rough estimate, total consumer cost for these agents may need to be doubled, and their omission is therefore material. Although non-concessional patients still have a saving, it is less than that estimated in the article.

* Sensitivity analysis should have been performed on the following critical assumptions: (1) proportion of use for hypertension for each class of drugs, (2) the number of unsubsidised users of diuretics and β-blockers, and (3) the proportion of patients on each agent who are on monotherapy.

It is vital that the current scrutiny by all stakeholders of PBS/RPBS expenditure be informed by reasonable estimates of inappropriate utilisation. The contribution made by the authors in developing a technique to estimate appropriate use for this group of drugs is valuable. However, use of unreferenced estimates of key variables, insufficient application of sensitivity analyses, algebraic errors and inappropriately combining PBS with non-PBS data may cloud rather than shed light on this issue.

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IN REPLY: We thank Pekarsky and Ewald for their comments.

It is difficult to estimate the percentage of patients on monotherapy from any source. We used data from IMS Health (http://www.ims-global.com/) to determine the number of person-years of exposure to drugs prescribed with a principal indication of hypertension. Some of these drugs were prescribed as a sole agent if the script was for this single drug alone. Exposure for such agents was expressed as a percentage of the total exposure of this drug. For example, angiotensin-converting enzyme (ACE) inhibitors were sole agents in 63.9%. In the other 36.1%, the co-prescribed drugs may have been another antihypertensive drug or another type of drug altogether. Corresponding figures for calcium-channel blockers were 61.3%, for diuretics 53.6%, and for β-blockers 60.0%. As an approximation, we used the estimation that 60% of patients were likely to have been on monotherapy for hypertension. Adding the number on monotherapy for each drug gives an estimate of 1.2 million for the total population on monotherapy for hypertension. Therefore, the total number on drugs is likely to be greater than the 1.2 million as estimated in our article. However, the essential figure is that of 1.2 million for monotherapy, which we stand by.

It is true that a minority of prescriptions (16%) are written for people without a concession card and that these are more likely to pay the full cost of a cheaper drug. Our economic perspective was that of the PBS/RPBS. Hence, consumer costs were only included where the government made a copayment. It is acknowledged in the Methods section that "with some drugs, the patient copayment covers the total cost; in these instances the Commonwealth makes no contribution to the cost and these prescriptions are not recorded in the PBS/RPBS data" (*page 566*). It is also stated in the Discussion that the PBS/RPBS captures "much more of the cost of the newer, more expensive agents than thiazide diuretics or β-blockers" (*page 567*).

We chose to limit our sensitivity analysis to the key issue of redistribution of agents after initiation of monotherapy. The data we presented allow interested parties to conduct their own further sensitivity analyses, such as those suggested by Pekarsky and Ewald. □

Correction

Re: "Impairment bible" [book review of *Guides to the evaluation of permanent impairment*], by Ganora A, in the 21 January issue of the Journal (*Med J Aust* 2002; 176: 82). By editorial error, the reviewer's name was misspelled Gandora.

We apologise to Dr Ganora for the error.

MEDicine or MADness

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TO THE EDITOR: In his recent Commentary on hastening death in terminally ill patients,[1] Hunt may not have fully appreciated a very cogent point made in the research by Douglas and colleagues.[2] The surgeons surveyed clearly reported the intent of their prescribing. This is contrary to Hunt's assertion that "Intention is inherently subjective...complex [and] ambiguous". Some surgeons gave a dose appropriate to the symptoms, others deliberately increased the dose beyond direct symptomatic control, and a few deliberately ended life, at times with no explicit request. As Douglas points out, the dose of a medication given will be an important clue in this. Good clinical practice is about minimum effective dose (MED), not maximum administrable dose (MAD). This is the case for all patients, whether they are near the end of life or not.

Hunt also states that "The duty of doctors is to strive to satisfy the wishes and interests of their patients and their patients' loved ones".[1] This is a disturbing comment if left unqualified. There is a broader accountability for doctors to the community through the registration process, quality assurance and continuing education, and the criminal code. If the article by Douglas et al highlights nothing else, it should be clear that there are certain members of the medical profession who believe that they are above the law and have control over the life and death of their patients, with no external review.[2] It is frightening that such paternalism still exists. Unfortunately, the Dutch experience of tolerating euthanasia does not appear to