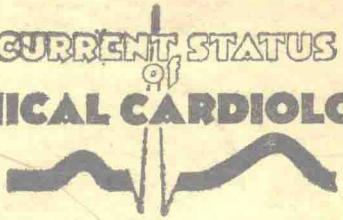
CURRENT STATUS OF CLINICAL CARDIOLOGY



Series Editor J.P. Shillingford

DRUGS IN THE MANAGEMENT OF HEART DISEASE

Edited by A. Breckenridge

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OF
CLINICAL CARDIOLOGY

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DRUGS IN THE MANAGEMENT OF HEART DISEASE

Edited by A. Breckenridge

Professor of Clinical Pharmacology
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Preface

In any textbook, basic scientific knowledge, and the art of clinical practice should be brought together in a rational manner and this volume on cardiovascular therapy attempts to achieve this aim. It deals with five selected areas – hypertension, angina and coronary artery disease, heart failure and anticoagulant therapy. Clearly not all branches of cardiovascular therapeutics could be included; a separate section on anti-arrhythmic drugs is noticeably absent but it is proposed that this omission will be rectified in other volumes in the series. In general, textbooks on therapeutics tend to be ephemeral; as new discoveries are made and evaluated, medical practice changes. This volume then summarizes current opinion up to mid 1984 and gives, we believe, a reasoned account of present views. The contributors are all clinical pharmacologists with a wealth of clinical experience. The therapeutic advice given is well founded and the underlying scientific basis is clearly explained. The book is aimed at postgraduates, but should the undergraduate care to dip into it, we hope he will be informed and thereby educated.

A. Breckenridge

Series Editor's Note

The last few decades have seen an explosion in our knowledge of cardiovascular disease as a result of research in many disciplines. The tempo of research is ever increasing, so that it is becoming more and more difficult for one person to encompass the whole spectrum of the advances taking place on many fronts.

Even more difficult is to include the advances as they affect clinical practice in one textbook of cardiovascular disease. Fifty years ago all that was known about cardiology could be included in one textbook of moderate size and at that time there was little research so that a textbook remained up to date for several years. Today all this has changed, and books have to be updated at frequent intervals to keep up with the results of research and changing fashions.

The present series has been designed to cover the field of cardiovascular medicine in a series of, initially eight volumes which can be updated at regular intervals and at the same time give a sound basis of practice for doctors looking after patients.

The future volumes will include the following subjects: heart muscle disease; congenital heart disease, invasive and non-invasive diagnosis; ischaemic heart disease; immunology and heart disease; irregularities of the heart beat; and each is edited by a distinguished British author with an international reputation, together with an international panel of contributors.

The series will be mainly designed for the consultant cardiologist as reference books to assist him in his day-to-day practice and keep him up to date in the various fields of cardiovascular medicine at the same time as being of manageable size.

J.P. Shillingford
British Heart Foundation

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1
Drug treatment of hypertension

J.H. SILAS

INTRODUCTION

Hypertension is a very common condition with a prevalence rate which depends on its definition and the age group screened. In patients aged 45 to 64 years, a diastolic blood pressure of 90, 95 and 100 mmHg or more may be found in 40%, 26% and 16% of subjects respectively[1]. Community screening programmes were encouraged by the observation that only half the subjects with high blood pressure had already been identified. However, as 75% of patients considered for treatment have diastolic pressures below 105 mmHg, it is possible that many patients with apparent hypertension may receive life-long drug treatment unnecessarily.

MAKING THE DIAGNOSIS

After initial screening it is essential to confirm that hypertension is sustained. Blood pressure often falls dramatically on repeated examination and at least three further visits are necessary before drug treatment is started. The major trials in mild hypertension have shown that almost a third of patients obtain goal blood pressure (diastolic $\leqslant$90 mmHg) by periodic observation alone[2,3]. This is independent of the use of placebo tablets or the time between visits.

Avoiding errors

Errors in the measurement of blood pressure often result in inappropriate treatment of spurious hypertension with resultant adverse effects. Guidelines for the measurement of blood pressure have been published[4]. A mercury sphygmomanometer should be used as aneroid sphygmomanometers need frequent calibration. Tight sleeves must be avoided; the arm should be supported so that the cubital fossa is level with the base of the heart. Higher blood pressures are recorded when the arm is dependent or unsupported. The cuff should be deflated at

a rate of 2–3 mm per second. The appropriate cuff size must be used, with smaller cuffs in children and larger ones in the obese. The American Heart Association's recommended cuff width/arm circumference ratio is 0.40. The regular cuff which measures 12 × 23 cm is appropriate only for adults with arm circumference of less than 33 cm. For moderately obese subjects (arm circumference 33–41 cm) a large cuff should be used (15 × 33 cm). Use of a standard cuff in obese subjects results in errors proportional to the arm circumference[5]; there is no way of guessing what the blood pressure might have been had the appropriate cuff been used. Rarely a thigh cuff may be required (18 × 36 cm) for arm circumference > 41 cm, but particularly in women this is virtually impossible to use. It has been suggested that a third of normotensive, obese subjects may be wrongly classified as hypertensive.

All major epidemiological and therapeutic surveys in hypertension have based their findings on *sitting* phase 5 diastolic values. Regrettably in most hospital practice supine values are recorded. However, supine blood pressure may be 19/8 mmHg higher than sitting values, suggesting that many patients are receiving inappropriate treatment (Table 1.1)[6].

Table 1.1 Mean blood pressure according to posture[6]

	Normotensive	*Untreated hypertensive*
Supine	125/64	159/98
Standing (arm horizontal)	102/60	138/90
Sitting (arm horizontal)	108/64	140/90

The number of readings taken at each clinic visit seems less important and suggestions vary from a single reading to the lowest of three and the mean of three. The last averages errors and reduces the number of patients required for clinical trials.

AVOIDING DRUG TREATMENT

Drugs may be avoided if blood pressure can be lowered to acceptable levels by other measures.

Withdrawal of drugs causing hypertension

Some drugs cause a rise in blood pressure and should be withdrawn whenever possible. The main offenders nowadays are non-steroidal anti-inflammatory agents, e.g. indomethacin and steroid drugs. The combined oral contraceptive pill will increase blood pressure slightly in most women[7] even if a 30 μg oestrogen preparation is used. The progesterone component is probably unimportant and in normotensive women the progesterone-only pill does not elevate blood pressure[8].

Weight reduction

Hypertension is the most common risk factor in obesity. It is not an artifact, as the association persists when the appropriate cuff is used. The association may be stronger for women and for diastolic blood pressure. Dietary restriction has been shown to lower blood pressure even without a reduction in salt intake, on average by 2.5–3.0/1.5–2.3 mmHg for each kilogram lost[9]. Most obese patients may not need drugs, but non-compliance rates are high even in committed units. Referral to a dietitian may improve results.

Reducing alcohol intake

Moderate alcohol consumption is associated with a rise in blood pressure[10]. Reducing alcohol consumption may lower blood pressure through weight reduction, but more rapid falls in blood pressure (−11/7) have been observed during abstinence in moderate drinkers (4 pints (2.3 litres) of beer per day)[11]. This work needs to be extended to larger populations. At present it seems reasonable to restrict alcohol consumption to 40 g per day (2 pints of beer or two double whiskies a day) since subjects consuming this quantity do not appear to have higher blood pressures than abstainers.

Reducing salt intake

Although populations consuming very small quantities of salt have a low incidence of hypertension, there is no definite agreement as to the benefits or feasibility of modest salt restriction in the community or of benefits in individual patients except in those with severe renal impairment.

Smoking

Cessation of smoking is justified in its own right, although studies have failed to show a relationship with high blood pressure. In hypertensive patients the risk of cardiovascular death is 3.6 times higher in smokers than in non-smokers, while accelerated hypertension and renovascular hypertension occur only rarely in non-smokers. However, on stopping smoking patients may gain weight and blood pressure may rise slightly; dietary advice is therefore necessary.

THE PRESSURE TO TREAT

There is no doubt of the benefits of treating moderate to severe hypertension (diastolic blood pressure $\geq$ 115 mmHg) or those in malignant phase. A large proportion of these patients will have cardiovascular complications or symptoms. The place of drug treatment in patients

with diastolic pressures above 105 mmHg is also established, although the group studied by the US Veterans Administration was atypical of the general population – comprising only men, 60% of whom had pre-existing cardiovascular disease[12]. The debate about whether to treat mild hypertension is gradually being resolved. The best evidence to date comes from the Australian trial of *uncomplicated* mild hypertension (95–109 mmHg) in men and women aged 18–69 years. The cardiovascular morbidity and mortality was reduced by drug treatment, particularly those with diastolic blood pressure of 100 or more[13,14]. Whether the benefit extends to blood pressures of 95–99 is less certain. What is clear is that we must treat a very large number of people to help a few. Twelve lives were saved and a further 30 complications were prevented as a result of 7000 patient years of treatment. In uncomplicated cases, therefore, treatment is initiated when the diastolic blood pressure is consistently 100 mmHg or more. Contrary to popular practice young patients (< 40 years) do not require treatment at lower pressures for they are *less* likely to suffer complications in the succeeding few years.

In contrast, when target organ damage is present (cardiomegaly, ischaemic heart disease, renal impairment, stroke) the risks are much higher, even with diastolic pressures in the 90–99 mmHg range[15] and treatment is therefore advisable. Some of these patients will require treatment for other reasons e.g. β-blockers for ischaemic heart disease, diuretics for heart failure. Diabetes is often ignored as an indication for aggressive treatment. However, epidemiological studies have shown blood pressure to be an important prognostic factor in the development of large and small vessel complications in insulin-dependent and non-insulin-dependent diabetics, even through blood pressures in the 'normal' range[16,17]. Furthermore, there is now evidence to suggest that early treatment of borderline hypertension delays the progression of diabetic nephropathy[18] and I advise treating diabetics with diastolic blood pressures at or above 90 mmHg.

Systolic hypertension

It is unfortunate that trials in hypertension have used diastolic blood pressure as the major criterion for treatment. Systolic blood pressure is probably a better predictor of cardiovascular risk with a 30% increased risk for every 10 mm rise in systolic blood pressure. In hypertension trials diastolic blood pressures of 100 mmHg are usually associated with systolic blood pressures of about 155–160 mmHg. Therefore, pressures of 160 or more may be considered worthy of treatment. When the systolic blood pressure is disproportionately high, i.e. diastolic blood pressure < 95 mmHg as occurs in isolated systolic hypertension, the calculation of mean arterial pressure (diastolic + $\frac{1}{3}$ pulse pressure) is a useful guide. For example a blood pressure of 170/90 is equivalent to 152/100 (mean pressure 117 mmHg). I therefore

recommend treatment for calculated mean arterial pressures of above 115 mmHg.

Hypertension in the elderly

There is no hard evidence upon which to base the treatment of hypertension in the elderly. The Australian Mild Hypertension Trial included patients up to the age of 69, and I therefore take elderly to mean 70 or over. At this age treatment is only considered if the patient is free from serious non-cardiovascular disorders which may in their own right affect the quality of life or longevity. Physiological age is more important than chronological age. Symptomatic cardiovascular disease warrants treatment in its own right – for example for heart failure, angina and transient cerebral ischaemic attacks. In asymptomatic 70–75-year-olds who are fit, I use drug treatment if mean arterial pressure is 125 mmHg or more. This will include many with isolated systolic hypertension ($\geqslant$200 mmHg). Their risks are greatly increased and sudden stroke may cause years of disability. The European Working Party on mild hypertension in the elderly has demonstrated that carefully titrated drug treatment is well tolerated, the principles of drug treatment being similar to those in younger subjects.

PRINCIPLES OF DRUG TREATMENT

Drug treatment is a burden for the patient who should understand the reasons for lifelong treatment and the need to continue with non-pharmacological measures. Because a third of patients may be non-compliant, it is important to simplify drug treatment, recommending as few different preparations as possible, preferably on a once-daily basis. It is rarely necessary to exceed the known ceiling dose of a drug and the price of doing so is usually an increase in side-effects. One should be aware that for any given patient the maximum tolerated dose may be lower than the suggested ceiling dose and it is therefore wise to start off with a small dose and increase it gradually, no more often than every 2 weeks. The majority of patients, even with mild hypertension, require more than one drug to control their blood pressure, and in this situation combined preparations are particularly useful but only if they are available in the recommended doses. They should *not* be used as first line treatment. Treatment should be geared towards lowering the blood pressure below 150/90 mmHg (or mean arterial pressure $\leqslant$110). In the elderly a figure of 160/100 (or mean arterial pressure $\leqslant$120) may be acceptable. Patients should be free from side-effects and the quality of life should be unchanged or improved. Assessment of blood pressure response should be made in the outpatient clinic and patients rarely need be admitted for treatment, except in the management of emergencies such as accelerated hypertension or heart

failure. The stepped care approach to treatment entails starting with a β-blocker or diuretic, then the combination if necessary. A third drug may be added if control is inadequate.

β-ADRENORECEPTOR ANTAGONISTS

From a chance observation these drugs have become first line agents in the treatment of hypertension. Ten different β-blockers are available in the United Kingdom. All attenuate exercise-induced increases in heart rate and lower blood pressure to a similar extent at the appropriate dose. They differ mainly in their ancillary pharmacological properties and in their physiochemistry which influences their fate and some clinical effects. Only the most commonly used agents are considered (Table 1.2).

Table 1.2 Characteristics of commonly used β-blockers

Drug	*β_1-Selective*	*Partial agonist activity*	*Lipid solubility*	*Ceiling dose** mg/day
Propranolol	No	No	Yes+	160
Oxprenolol	No	Yes	Yes	160–240
Pindolol	No	Yes++	Yes	20–30
Metoprolol	Yes	No	Yes	200
Nadolol	No	No	No	80
Atenolol	Yes	No	No	100

*In hypertension

Pharmacokinetics

Differences in lipid solubility correlate well with the kinetic properties of these drugs. The more lipid soluble agents are better absorbed but because they are extensively metabolized they have lower oral bioavailability and short half-lives of elimination (2–5 hours). The metabolism of some β-blockers exhibit polymorphism and wide interpatient variability in plasma drug concentration may be seen. In contrast, water soluble agents are eliminated by the kidney and they have half-lives of 7–20 h. In non-uraemic subjects less interpatient variability in plasma concentration is seen. Lipid soluble agents are more likely to penetrate the central nervous system and this may influence side-effects.

Mechanism of action

This is poorly understood but the principal prerequisite is β_1-blocking activity. The following observations are important:

(1) *Reduction in cardiac output.* There is a fall in cardiac output during acute and chronic dosing but this correlates poorly with

reduction in resting blood pressure both between individuals receiving the same compound and between different compounds. For example, the reduction in cardiac output is less marked with drugs which possess partial agonist activity, yet blood pressure control is similar.

(2) *Effect on total peripheral resistance.* Those who respond to β-blockade may show no change or only a slight reduction in total peripheral resistance long term. In this respect β-blockers differ from other antihypertensive agents.

(3) *Inhibition of the renin angiotensin system.* All β-blockers reduce exercise-stimulated plasma renin activity – an effect which must therefore be mediated via β_1-adrenoreceptors[19]. The majority of studies in selected patients have shown a correlation between blood pressure response and either pretreatment plasma renin activity or a change in plasma renin activity. It is suspected that inhibition of the renin angiotensin system results in a decrease in direct and indirect pressor effects of angiotensin II. Stimulation of angiotensin II presynaptic receptors on the postganglionic neuron enhance the release of noradrenaline. In addition longer term effects through aldosterone may explain why β-blockers do not cause fluid retention and false tolerance unlike most antihypertensive agents, except diuretics and converting enzyme inhibitors.

(4) *Decreased sympathetic outflow.* In contrast to some animal studies there is no evidence in man to support the view that β-blockers reduce sympathetic outflow by a centrally mediated effect. However, stimulation of presynaptic β-adrenoreceptors on the postganglionic neuron augment release of noradrenaline and β-blockers may reduce exercise mediated catecholamine release at this site. Basal plasma catecholamine concentrations, however, are not altered.

(5) *Alteration in baroreflex arc.* A resetting of baroreceptors has been suggested. However, β-blockers do not influence the sensitivity of the baroreceptor reflex arc. Subsequent changes in the reflex may be secondary to long term reduction in blood pressure *per se*.

Dose interval and daily dose

The duration of β-blocking effect is much greater than the half-life as pharmacological activity declines in a linear fashion while the fall in plasma concentration is an exponential one. The antihypertensive effect persists beyond the β-blocking effect and some authorities suggest that even β-blockers with short half-lives (2–4 h) may be prescribed once daily in hypertension. However, this practice may be associated with greater variability in blood pressure control with frank

loss of control at some times in the day[20]. These compounds should be prescribed twice daily in hypertension while agents with longer half-lives (>7 h) are best administered once daily.

The ceiling dose of these drugs is much lower than formerly suggested. Increasing the dose beyond that indicated (Table 1.2) should be considered only if non-compliance is excluded and if inadequate β-blockade is demonstrated. In general it is best to start with half the ceiling dose and if necessary to double the dose. The maximum effect may be seen within a fortnight.

Slow release formulations

Several slow release formulations of shorter acting β-blockers are available. Only long acting propranolol 160 mg once daily[21] can be recommended on the strength of its sustained β-blocking and antihypertensive effects. The slow release film-coated formulations of both oxprenolol (160 mg) and metoprolol (200 mg) are ineffective in both respects. The antihypertensive response to oxprenolol is not improved by doubling the dose of this preparation[22]. Metoprolol durules 200 mg once daily result in 10–11% β-blockade at 24 hours. The effectiveness of this preparation over 24 h in hypertension is disputed.

Efficacy

When used correctly β-blockers lower blood pressure in the majority of patients. The fall in blood pressure when used as a single agent varies between 14/10 and 27/19 mmHg, being greater in patients with higher pretreatment blood pressure. In the Veterans Administration (VA) study of mild to moderate hypertension[23] (diastolic blood pressure 95–114 mmHg) propranolol alone reduced diastolic blood pressure to less than 90 in 62% of white patients and 54% of black patients. Significant additive effects are seen with diuretics, a combination which achieves goal blood pressure in 70–80% of patients with mild hypertension[24]. In this respect, however, the combination is marginally less effective than reserpine 0.1 mg daily plus thiazide, emphasizing that the major advantage of β-blockers is their wide margin of safety.

Adverse effects

Some adverse effects of β-blockers are related specifically to unwanted effects on β-adrenoreceptors. As such they may be prevented by prior patient selection and reduction in dose. In general, therefore, patients with a history of asthma should not receive β-blockers as this is the only life-threatening complication of these agents. Previous heart failure is also a contraindication, except when it has been caused by severe hypertension. A large number of other side-effects occur for reasons

Table 1.3 Adverse effects leading to withdrawal in hypertensive patients receiving atenolol ($n=543$) or propranolol ($n=390$)[25]

Adverse effect	*Propranolol*	*Atenolol*
Bronchospasm	13	2
Worsening claudication	9	1
Heart failure	1	2
Cold extremities	3	1
Indigestion	3	3
Vivid dreams/insomnia	2	0
Bradycardia	*	1
Depression	2	0
Impotence	1	0
Fatigue	1	0
Paraesthesia	2	0
Diarrhoea	1	1
Dizziness	0	1
Total (%)	38 (9.7%)	12 (2.2%)

*Not assessed in same way

that are not specifically related to the effects on β-adrenoreceptors. The majority are central nervous system effects and fatigue which may be more frequent with lipid soluble agents. For some reason pindolol is particularly liable to cause sleep disturbances. There is some evidence to support the view that side-effects decrease with increasing hydrophilicity and cardioselectivity. This is illustrated in comparisons of side-effects with atenolol and propranolol in the same blood pressure clinic, although high doses of both agents were used[25] (Table 1.3). In the UK Medical Research Council (MRC) trial of mild hypertension cumulative withdrawals over a 5 year period were only 10% higher in those taking propranolol than in the placebo group[26] (Figure 1.1). Most of these withdrawals were due (in decreasing order of importance) to central nervous system disorders (lethargy, nausea, dizziness), breathlessness, cold extremities and impotence. Whether the use of a selective hydrophilic agent would have been associated with fewer withdrawals is uncertain. In one large survey only cold extremities and fatigue were more common after atenolol than placebo[27].

Bradycardia and heart failure

Most people tolerate bradycardia without symptoms, unless there is associated left ventricular dysfunction. Bradycardia is not an indication for drug withdrawal unless the heart rate falls below 40 or heart block supervenes, but occasionally symptomatic ventricular escape beats or dizziness may necessitate a change in treatment. In such patients a switch to an agent with partial agonist activity will result in a return to a near-normal heart rate. Patients who develop heart failure on β-blockers may do so with small doses[28] and regardless of the presence of partial agonist activity.

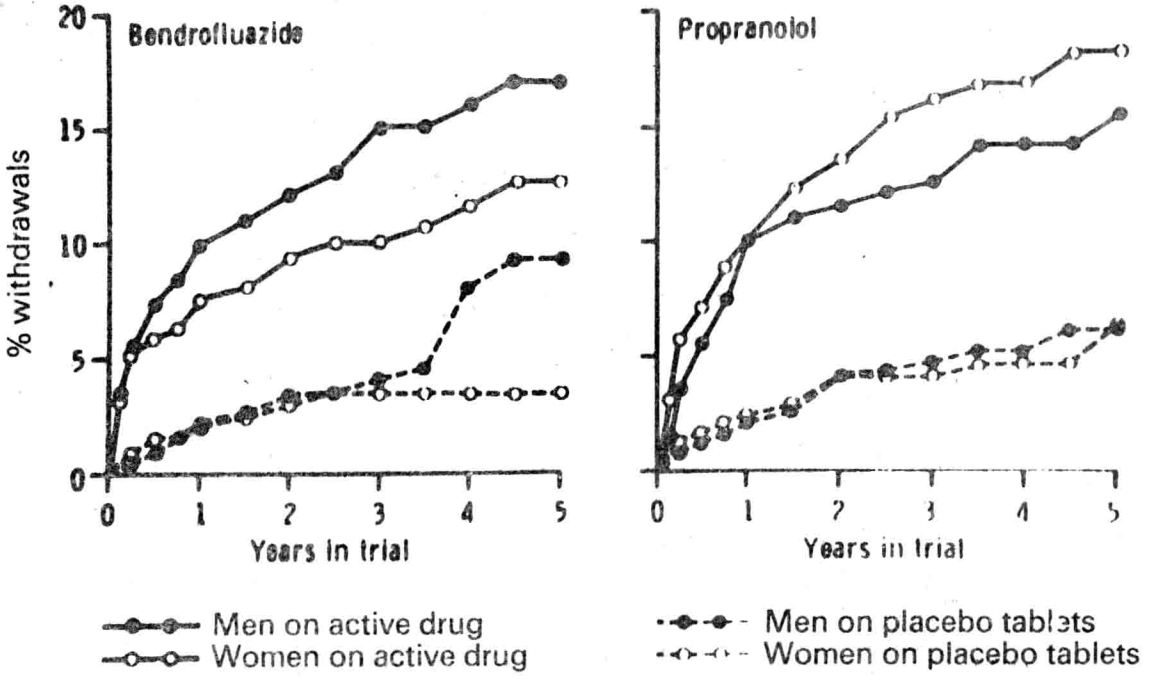

Figure 1.1 Cumulative percentage withdrawals from randomized treatment owing to suspected adverse reactions to primary drug – MRC trial in mild hypertension[26]. (Reproduced with permission from the *Lancet*)