# DEBATES IN MEDICINE

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BETA BLOCKADE IN HYPERTENSION;
DOES THE MOLECULE MATTER?

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# BETA BLOCKADE IN HYPERTENSION; DOES THE MOLECULE MATTER?

"Low-dose thiazides and [or] beta blockers should be accepted universally as suitable first-line therapy for the vast majority of hypertensive patients."
*(Editorial, Lancet 1991;338;1300).*

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# INTRODUCTION

The relationship of elevated resting blood pressure to an increased risk of cerebrovascular and cardiovascular events is well accepted [1,2]. The value of intervention aimed at reducing abnormally high blood pressure – whether by drugs, diet, change in lifestyle, or by a combination of these – to reduce the risk of coronary heart disease (CHD) and stroke has also been established [3,4]. Indeed, a fairly modest (5–6mmHg) reduction in diastolic blood pressure (DBP) (which is actually the mean effect of treatment in the randomised trials [5]) produces a significant reduction in risk of stroke and CHD [5] (Fig 1).

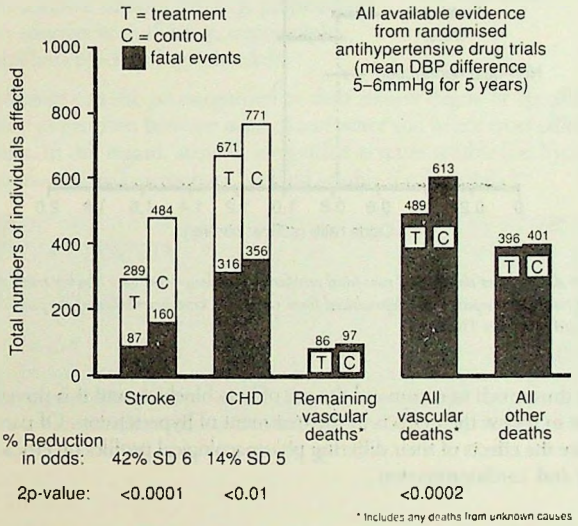


*Fig 1. Crudely summated results of the unconfounded randomised trials of antihypertensive drug therapy. (Reproduced from ref. 5 by kind permission of the publishers of the Lancet.)*

There are many effective antihypertensive agents – beta blockers, diuretics, angiotensin converting enzyme (ACE) inhibitors, calcium antagonists, and alpha blockers – but not all have been shown to reduce morbidity and mortality. In fact, data on 'hard' cardiac and cerebrovascular end-points are available only for beta blockers and diuretics. Beta blockers reduce the incidence both of stroke [6–11] in all ages of patient, and of myocardial infarction (MI) in the middle-aged

hypertensive [12,13]. This is evident from an analysis of two primary prevention studies [10,14], where there were significantly fewer ($p<0.05$) coronary events in men in the beta blocker group, compared to the diuretic group. In the peri-infarction period, beta blockers reduce vascular death, reduce infarct size, and prevent a threatening infarct from proceeding to myocardial necrosis [15,16]. In infarct survivors, beta blockers are accredited as reducing morbidity and mortality, particularly sudden death (Fig 2) [17].

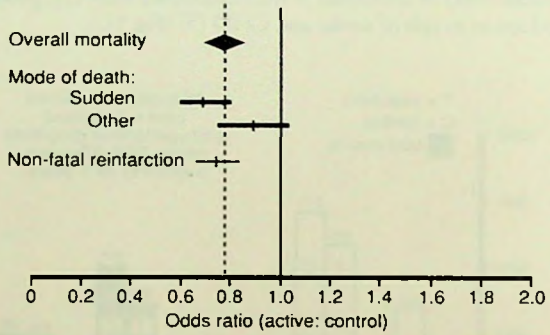


***Fig 2.*** *Sudden death, other death, and non-fatal reinfarction in long-term beta blocker trials that reported these end-points separately. (Reproduced from ref. 17 by kind permission of the publishers of Progress in Cardiovascular Diseases.)*

There is thus much to commend the use of beta blockers, and it is therefore appropriate to review their effects in the treatment of hypertension. Of particular relevance are the effects of their differing pharmacological profiles on efficacy, tolerability and 'cardioprotection'.

## PROPERTIES OF BETA BLOCKERS

Originally, beta blockers were classified by their relative specificity for $beta_1$ adrenergic receptors ($beta_1$ selective or cardioselective) and/or by their ability to mimic sympathetic stimulation (intrinsic sympathomimetic activity – ISA). Recently, sub-groups have been identified having either $beta_1$ selectivity with $beta_2$ ISA, or possessing both alpha and beta blocking properties.

Thus, beta blockers can be regarded as belonging to one of six sub-groups:

- $Beta_1$ selective (cardioselective) without ISA (e.g. atenolol, metoprolol)
- $Beta_1$ selective (cardioselective) with ISA (e.g. acebutolol)
- $Beta_1$ selective (cardioselective) with $beta_2$ ISA (e.g. celiprolol)
- Non-selective without ISA (e.g. propranolol)
- Non-selective with ISA (e.g. oxprenolol)
- Alpha/beta blockers (e.g. labetalol).

Beta blockers can also be categorised by their relative degree of lipophilicity, i.e. their ability to partition between octanol and water and hence cross cellular membranes. In this regard, atenolol is regarded as water soluble (i.e. hydrophilic) while propranolol and metoprolol are lipid soluble (i.e. lipophilic).

### *SUMMARY POINTS*

- Beta blockers vary:
  (i) In beta-adrenoreceptor selectivity
  (ii) In ISA
  (iii) In lipid solubility.
- Some agents possess alpha and beta blocking properties.

## PHARMACOLOGICAL EFFECTS

### *Cardioselectivity*

The advantage of cardioselective beta blockers over non-selective agents can be demonstrated in at least six areas:

(a) Relative blood pressure lowering effects
(b) In airways disease
(c) In insulin-dependent diabetic hypertension
(d) In smokers
(e) During exercise
(f) On serum lipids.

#### *(a) Blood pressure lowering*

An analysis of published clinical trials [18] suggests that, at the recommended doses, cardioselective beta blockers, such as atenolol, are more effective hypotensive agents. They reduce resting DBP by about 4mmHg more than their non-selective counterparts, such as propranolol. The explanation may be that cardioselective agents exert little effect on the peripheral $beta_2$ receptors, whereas non-selective agents can give rise to unopposed alpha vasoconstriction due to blockade of the peripheral $beta_2$ receptor.

#### *(b) Airways*

Figure 3 shows the comparative effects on $FEV_1$ of a variety of beta blockers, before and after isoprenaline [19]. All doses produced adequate beta blockade as shown by their effect on heart rate. Placebo caused a small fall in $FEV_1$, as did atenolol, but all other beta blockers induced a fall of over 25%, with the non-selective agents having most effect. After isoprenaline, atenolol was the only beta blocker to increase $FEV_1$ above baseline. Thus atenolol was the most cardioselective agent of those studied and, like other cardioselective agents, may be used with caution in patients with underlying airways disease, since any increase in airways resistance which may occur can be reversed by bronchodilator therapy. Non-selective agents, however, are contra-indicated.

#### *(c) Diabetes*

Following the i.m. administration of insulin to subjects receiving placebo, a non-selective beta blocker, or a cardioselective beta blocker [20] (Fig 4), the blood sugar concentration falls to the same degree. However, recovery from hypoglycaemia was similar in the placebo and atenolol groups, but was significantly delayed in the propranolol group. Other work [21,22] supports the preferential use

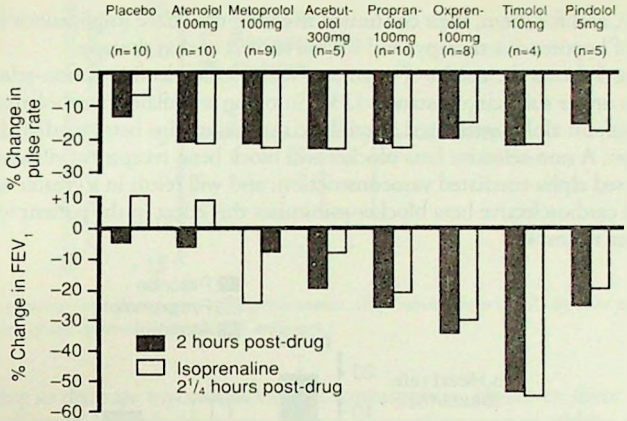


*Fig 3. Effect of beta blockers on pulse rate and $FEV_1$ before and after isoprenaline. (Reproduced from ref. 19 by kind permission of the publishers of the British Heart Journal.)*

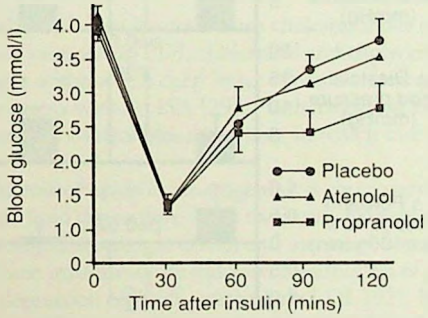


*Fig 4. Insulin-induced hypoglycaemia and beta blockers. (Data from ref. 20 by kind permission of the publishers of the British Medical Journal.)*

of a cardioselective agent when a beta blocker is used in insulin-dependent diabetic hypertensives. It may, however, modify the tachycardia of hypoglycaemia, and both the patient and physician must be aware of the risk of masking this feature.

### *(d) Smoking*

Smoking is a major risk factor for CHD and stroke. Stopping smoking is important first advice given to hypertensive patients. Not all patients can comply,

however, and for them, their continued smoking may have implications for the choice of hypotensive therapy, and for the success of that therapy.

Figure 5 shows the results of treatment with cardioselective or non-selective beta blockers under such circumstances [23]. Smoking stimulates catecholamine release, with resultant alpha$_1$-mediated arteriolar constriction plus beta$_2$-mediated dilatation. A non-selective beta blocker will block beta$_2$ receptors, will allow unopposed alpha-mediated vasoconstriction, and will result in a greater rise in DBP. A cardioselective beta blocker minimises this effect in the patient who continues to smoke.

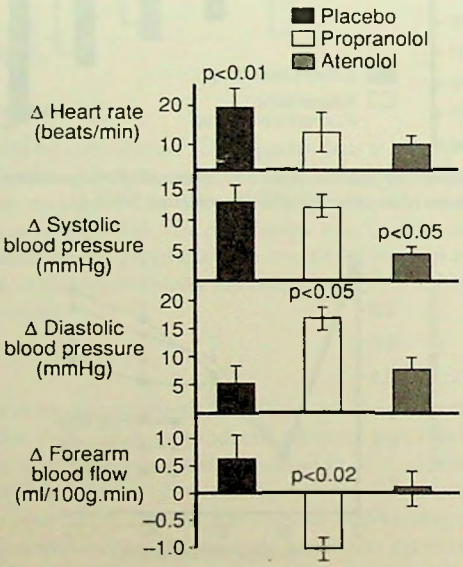


*Fig 5. Haemodynamic effects of smoking. (Reproduced from ref. 23 by kind permission of the publishers of the European Journal of Clinical Investigation.)*

### *(e) Exercise*

Control of exercise blood pressure [24] is an important measure of the effectiveness of any antihypertensive agent. Figure 6 shows that exercise performance is unchanged with a cardioselective agent, while a non-selective agent clearly impairs performance by a presumed beta$_2$ receptor mechanism in the peripheral musculature [25]. An additional advantage is the fact that beta blockers are known to inhibit the catecholamine-stimulated rise in free fatty acids during stress [26],

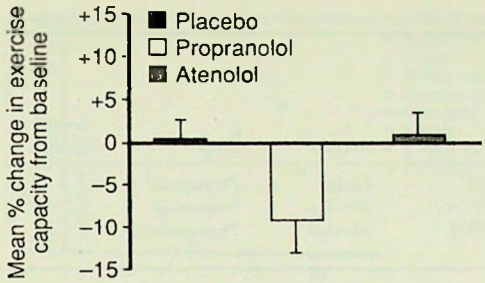


*Fig 6. Effect of exercise conditioning on work performance. (Reproduced from ref. 25 by kind permission of the publishers of the American Journal of Cardiology.)*

and by doing so decrease myocardial oxygen consumption. However, these metabolic effects of beta blockade may hamper the performance of athletes and heavy manual labourers.

### *(f) Lipids*

Beta blockers cause little change in total serum cholesterol but may lower serum HDL cholesterol and raise serum LDL cholesterol and triglycerides [27–31]. Cardioselective agents without ISA exert lesser effects on these parameters than non-cardioselective agents without ISA [29]. Furthermore, at low doses, cardioselective agents can control blood pressure, in which case these changes are minimal [28].

The timing of the role of lipids in atherogenesis is controversial. Endothelial damage may precede lipid deposition. Thus the intimal effects of hypertension, smoking, stress (increased adrenergic drive), and increased blood flow velocity may be early features. These insults may be followed by adhesion of platelets to the damaged wall and deposition of lipids, particularly LDL [32]. Beta blockers lower blood pressure, reduce adrenergic drive, and reduce peak blood velocity [33]. In addition, in animal studies, cardioselective agents protect against endothelial damage induced by chloralose anaesthesia [34]. Recent work suggests that cardioselective agents reduce the binding affinity between proteoglycans in the vessel wall and serum LDL [32]. Thus, despite effects on lipid levels, beta blockers, particularly cardioselective agents, may mitigate against the development of atherosclerosis. This is supported by an animal model (Table 1) in which, despite serum lipid changes, a non-selective beta blocker was highly effective in preventing coronary atheroma [35–37]. These observations may explain the apparent paradox whereby beta blockers raise serum lipid levels but reduce morbidity and mortality from ischaemic heart disease.

*Table 1. Effect of beta blockers on coronary atherosclerosis in cholesterol-fed animals.*

| *Study* | *Animal* | *Drug* | *Serum lipids* | *Amount of coronary atherosclerosis irrespective of lipid levels* |
|---|---|---|---|---|
| *Reinis et al., 1976 [35]* | *Cocks* | *Propranolol* | ↑ | ↓ *(60%)* |
| *Pick and Glick, 1977 [36]* | *Monkeys* | *Propranolol* | ↑ | ↓ *(60%)* |
| *Kaplan et al., 1987 [37]* | *Monkeys (stressed)* | *Propranolol* | ↑ | ↓ *(60%)* |

*Nine more studies show that various beta blockers retard aortic atherosclerosis.*

## *SUMMARY POINTS*

- Cardioselective beta blockers reduce resting DBP to a greater degree than non-selective agents.
- Cardioselective beta blockers have advantages for patients with insulin-dependent diabetes, with airways disease, and for those who cannot stop smoking. Additionally, they do not interfere with exercise performance.
- Beta blockers do not affect total cholesterol but lower serum HDL cholesterol and raise LDL cholesterol and triglycerides. With cardioselective agents these changes are minimised.
- Cardioselectivity opposes some of the fundamental pathological processes involved in atherosclerosis.
- The potentially adverse effects of beta blockers on serum lipids are offset by their benefits in patients with ischaemic heart disease.

### *Intrinsic sympathomimetic activity (ISA)*

Beta blockers vary widely in the degree to which they possess ISA. It has been claimed that agents with pronounced ISA provide 'cardiac support' and have a better lipid profile than other class members.

An analysis of all the published trials [18], however, has shown that beta blockers without ISA, such as atenolol, reduce DBP by about 4mmHg more than agents with ISA, such as oxprenolol and pindolol. This is likely to arise because the cardioselective agent without ISA reduces cardiac output to a greater degree than a similar agent with ISA.

Furthermore, agents with ISA, such as pindolol, are less well tolerated; they cause a significantly greater incidence of muscle cramp than do their cardioselective counterparts [38].

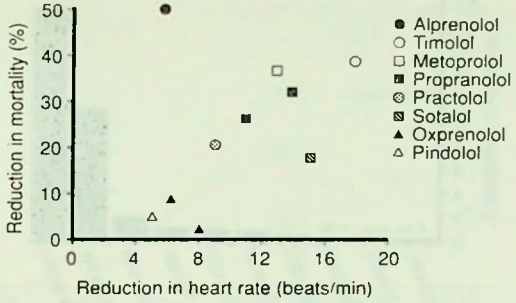


*Fig 7. Correlation between mortality reduction and heart rate reduction in post-infarct beta blocker trials. (Reproduced from ref. 39 by kind permission of the publishers of the American Journal of Cardiology.)*

Beta blockers with non-selective ISA have proved relatively ineffective in reducing morbidity and mortality for infarct survivors [17], although those with beta$_1$-selective ISA, such as aceburolol, have shown significant benefit [39]. Kjekshus [40] has suggested that this is because those agents have little or no effect on resting heart rate due to the presence of their non-selective ISA (Fig 7).

### *SUMMARY POINTS*

- Cardioselective beta blockers reduce resting DBP to a greater degree than non-selective agents with ISA.
- Non-selective agents with high ISA have had little success when used as secondary preventative agents post-MI, despite their 'beneficial' effects on serum lipids.

## *Hydrophilicity*

There is a wide range in the lipid or water solubility of beta blockers [41] (Fig 8). What are the implications of this aspect for their antihypertensive efficacy and tolerability?

### *(a) Half-life*

Hydrophilic drugs usually are not metabolised and are excreted unchanged by the kidney. As a consequence, they tend to have long plasma and pharmacodynamic half-lives. This would be expected to give predictable pharmacodynamic actions, and might be an explanation for the results in a 24-hour ambulatory monitoring

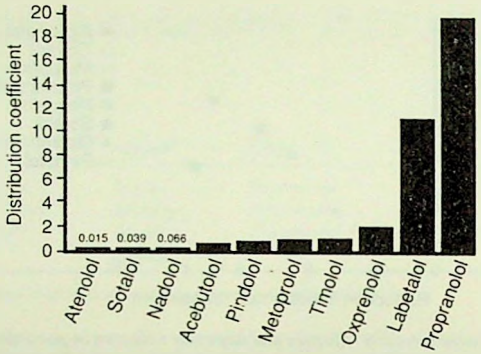


*Fig 8. Distribution coefficients in octanol/aqueous buffer for several beta blockers. (Adapted from ref. 41.)*

trial, in which hydrophilic atenolol was more effective over 24 hours in lowering mean arterial pressure than the more lipophilic agents, metoprolol and pindolol [42] (Fig 9).

### *(b) Dosing frequency*

A long half-life allows once-daily dosing, thus encouraging a higher level of patient convenience and compliance [43]. Multiple daily dosing is required with many lipophilic beta blockers unless they are specially formulated.

### *(c) Interactions*

Hydrophilic agents are relatively insensitive to alterations in hepatic enzyme activity. Pharmacokinetic interactions based on this action are therefore unlikely. Combination therapy with other agents is simplified and safer [41].

### *(d) CNS effects*

Lipophilic beta blockers, because they are more likely to cross the blood-brain barrier than hydrophilic agents, may cause CNS disturbances. A comprehensive review [44] has shown that a hydrophilic agent has a lower incidence of CNS-related side effects than lipophilic agents (Table 2; [45]).

### *(e) Quality of life*

Hypertension is an asymptomatic condition and, as such, drug therapy designed to reduce blood pressure and, hopefully, increase survival, should cause minimal

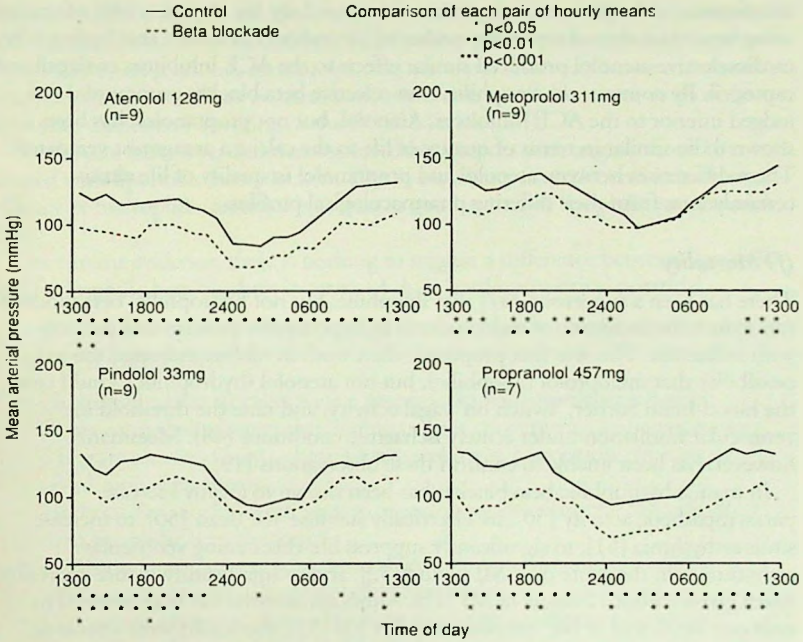


*Fig 9. Antihypertensive control during 24 hours. Between-patient comparison for four beta blockers. (Reproduced from ref. 41 by kind permission of the publishers of the British Medical Journal.)*

*Table 2. Beta blockers and CNS side effects during antihypertensive therapy. (Data from ref. 45.)*

| *Beta blocker* | *Incidence of vivid dreams* | *Incidence of sleep disturbance* |
|---|---|---|
| *Atenolol* | *4/48 (8%)* | *9/48 (19%)* |
| *Pindolol* | *9/39 (23%)* * | *15/39 (38.5%)* ** |
| *Propranolol* | *10/25 (40%)* * | *10/25 (40%)* ** |

* *p<0.01*
** *p<0.1*

interference in the patients' enjoyment of normal daily life. A review [46] of studies using beta blockers and reporting quality of life indices has shown that hydrophilic, cardioselective atenolol produced similar effects to the ACE inhibitors enalapril and captopril. By contrast, the lipophilic, non-selective beta blocker propranolol was judged inferior to the ACE inhibitors. Atenolol, but not propranolol, has been shown to be similar in terms of quality of life to the calcium antagonist verapamil. These differences between atenolol and propranolol in quality of life almost certainly arise from their differing pharmacological profiles.

### *(f) Mortality*

There has been a suggestion [47] that lipophilic, but not hydrophilic, beta blockers can reduce the incidence of sudden death in hypertensive patients and patients with ischaemia. This was first proposed when work in rabbits indicated the possibility that metoprolol (lipophilic), but not atenolol (hydrophilic), could cross the blood-brain barrier, 'switch on' vagal activity, and raise the threshold for ventricular fibrillation under acutely ischaemic conditions [48]. Meesmann, however, has been unable to confirm these observations [49].

In man, a hydrophilic beta blocker has been shown to greatly increase parasympathetic activity [50], to 'electrically stabilise' the heart [50], to increase sinus arrhythmia [51], to significantly suppress life-threatening ventricular arrhythmias in the acute post-MI period [52], and to significantly reduce mortality when given within 12 hours of MI [15]. Although atenolol has been assessed in only one small trial of late intervention after MI [53], the results were similar to those of propranolol (and hydrophilic acebutolol [39]) in that mortality was reduced by over 50% in those who continued receiving treatment. In a very recent publication of a statistical analysis of the post-infarction beta blocker data, Lewis [54] has shown no difference in cardioprotection between hydrophilic and lipophilic agents.

With regard to primary prevention of MI in hypertensive patients, there is evidence [10,12] that lipophilic propranolol has a modest benefit in middle-aged subjects (particularly non-smoking men). However, the Heart Attack Primary Prevention in Hypertension (HAPPHY) Study Steering Committee [55] concluded that any apparent differences in benefit between hydrophilic atenolol and lipophilic metoprolol could be due to chance. Death rates in the HAPPHY study were lower in patients receiving the hydrophilic agent than in patients receiving the lipophilic agent (6.93 vs. 7.89 deaths per 1000 patient-years).

In elderly patients with mild to moderate hypertension, it is now established that diuretics should be first-line therapy [56]. If, however, the patient has had a recent MI or has angina, a beta blocker may be more appropriate. Hydrophilic atenolol-based therapy prevents strokes, but seems not to prevent MI in elderly hypertensive patients. Both are probably class effects of beta blockers, since in the

Swedish STOP-HT trial of elderly patients with hypertension [8], the incidence of MI was unaffected by three different beta blockers with widely differing degrees of lipophilicity, i.e. pindolol, metoprolol, and atenolol. This trial, however, was of short duration, and effects on cardiovascular events may take longer to show (as seen with cholesterol lowering in the POSCH trial; [57]).

Some have recommended that hypertensive patients with angina should be treated with lipophilic beta blockers. This is surprising since the anti-ischaemic efficacy of hydrophilic atenolol is at least as good as that of lipophilic propranolol [58].

On current evidence, there is nothing to suggest a difference between lipophilic and hydrophilic beta blockers in terms of their 'cardioprotective' potential.

### *SUMMARY POINTS*

- Hydrophilic beta blockers have a pharmacokinetic profile which often allows once-daily dosing, thus aiding patient convenience and compliance. They are also less likely to have pharmacokinetic interactions with other co-administered agents.
- Hydrophilic beta blockers, such as atenolol, produce fewer CNS side effects than lipophilic beta blockers.
- Hydrophilic atenolol produces a quality of life profile similar to ACE inhibitors but superior to lipophilic propranolol.
- On current evidence, there is nothing to suggest a difference between lipophilic and hydrophilic beta blockers in terms of their cardioprotective potential.

### *Co-existing Alpha Blockade*

Published clinical trials [18] show that cardioselective beta blockers, such as atenolol, reduce resting DBP by about 2mmHg more than those with both alpha and beta blocking properties.

Although beta blockers with co-existing alpha blockade have potential value in the treatment of hypertension because of their relatively beneficial effects on serum lipids, there are no long-term studies to assess their value in cardioprotection.

## BACK TO BASICS

The management of hypertension is a major and difficult clinical challenge. The need for and the benefits of therapy are undisputed, but when the condition affects a major proportion of the population and causes no symptoms, therapy must be acceptable in the long term, free of adverse effects, and convenient as well as effective.

There are many hypotensive agents, but there have been few large-scale comparative studies in the style of the ISIS investigations of MI therapy. Choosing the best therapy for a given patient must rely in part on scientific evidence and in part on hopefully logical and apposite inferences. If the fundamental abnormality in hypertension could be identified (if such exists!), then that might logically be the optimal focus for therapy. Yet increasingly, it is the secondary effects of hypertension that seem to dictate management.

There is no consensus on optimal first-line drug therapy for hypertension; beta blockers, ACE inhibitors, diuretics and calcium antagonists each have their protagonists. The purpose of this review is not to prove superiority of one agent *vis à vis* another, but rather to draw attention to the proven benefits of cardioselective beta blockade, as well as the implications of a hydrophilic or lipophilic pharmacological profile. We should bear in mind that ACE inhibitors and calcium channel blockers have attractive features but *no* mortality data to match diuretics and beta blockers.

Cardioselective beta blockers have an appeal through their precision of action, their simplicity of metabolism and distribution, and through their impressive performance in the management of ischaemic heart disease. We have identified benefits of such selectivity in the management of hypertension and have examined the controversy of how beta blockers may influence the process of atherogenesis. Our supportive conclusions for the use of cardioselective beta blockers must, as a minimum, merit consideration when choosing therapy.

A further consideration is the lipid or water solubility of the beta blockers. Hydrophilic agents are associated with fewer pharmacological interactions with co-administered agents and fewer CNS side effects than lipophilic agents, and therefore have fewer adverse effects than lipophilic agents upon quality of life. In addition, their long half-lives permit less frequent dosing.

Hopefully the difficult problems of the management of hypertension may yield to research – the optimal initial and the subsequent sequential approach may be revealed by new studies. However, we should not underestimate the very great difficulty in mounting a trial which will reliably tease out the drug with the best risk/benefit ratio amongst today's effective hypotensive agents. In practice, few patients have isolated hypertension. Many have other problems – angina, arrhythmia, diabetes, obesity, heart failure. In that case, we do have some

reasonable clinical grounds for choosing one drug over another. In the case of symptomless mild hypertension, we would make a strong plea for the use of cardioselective beta blockade and/or thiazide diuretics.

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