Beta-blockers continue to surprise us

J. M. Cruickshank

Introduction

Beta-blockers are well established in the treatment of coronary heart disease and hypertension but until fairly recent times many doctors would have considered the prescription of beta-blockers to patients with heart failure as contraindicated and to patients with type II diabetes as relatively contraindicated. However, we now know that (a) beta-blockers can significantly reduce mortality in patients with stable heart failure[1] and that this benefit for both ischaemic and non-ischaemic failure is due to beta1 selective blockade[2,2a]; (b) the recent publications of the classic U.K. Prospective Diabetes Study Group (UKPDS) have changed the way we think about beta-blockers and the treatment of type II diabetics with hypertension[3,4]. Other recent surprising results (Table 1) are (i) the SOLVD heart failure study[4a], which indicated that, in contrast to enalapril, beta-blockers were renoprotective (in both the placebo and ACE-inhibitor groups) (Table 2); (ii) perhaps less surprising, but of considerable importance, is the study showing that bisoprolol significantly reduced peri-operative mortality and non-fatal attacks in non-cardiac vascular surgical patients[4b], and (iii) in elderly hypertensives atenolol-based treatment, in contrast to diuretic-based treatment, did not prevent heart attacks[16].

There has been a long held bias for the use of ACE inhibitors and against the use of beta-blockers in diabetes. This is possibly understandable when one considers a typical hypertensive type II diabetic who might be obese and insulin resistant with a high fasting blood triglyceride concentration, high fasting blood sugar and glycated haemoglobin (HbA1c) levels, a low HDL cholesterol concentration and might be on insulin therapy. Prior to the UKPDS publications the choice of antihypertensive agent, between an ACE inhibitor and a beta-blocker, to treat such a patient would not have been difficult. A negative beta-blocker image in diabetes had been fostered by results on mainly surrogate end-points for cardiovascular events:

1. A typical beta-blocker tends to increase triglycerides and lower high density lipoprotein (HDL) levels[5].
2. A typical beta-blocker tends to increase fasting blood sugar[5], HbA1c[6] and insulin resistance[5,6].
3. A non-selective beta-blocker can prolong insulin-induced hypoglycaemia and mask hypoglycaemic signs[5].
4. In the MRC mild hypertension study[7] there was a trend to increased withdrawals on propranolol, (vs placebo), due to impaired glucose tolerance.
5. Beta-blockers cause patients to increase weight by 1–2 kg[8].
6. In the post-myocardial infarction BHAT Study[9] significantly more oral hypoglycaemic agents were required in the propranolol, vs placebo, group.
7. The mere presence of diabetes was too often viewed as a ‘contra-indication’ to beta-blocker use[10].

By stark contrast, a strong positive ACE inhibitor image for diabetes was widely accepted because:

1. ACE inhibitors are blood lipid ‘neutral’, with no significant effect on triglycerides, high density lipoprotein and low density lipoprotein (LDL) levels[11].
2. ACE inhibitors tend to reduce insulin resistance[12,13], possibly independent of blood pressure effects[13].
3. ACE inhibitors lead to a postponement of the development of clinical, overt diabetic nephropathy[12], possibly independent of blood pressure effects[13].

Key Words: Beta-blockers, beta, selective beta-blockers, type II diabetes, hypertension, ACE inhibitors, captopril, atenolol, bisoprolol, UK Prospective Diabetes Study (UKPDS).

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Table 1 Some recent ‘surprising’ information relating to beta-blockers

| 1. Beta-blockers significantly reduce mortality in stable ischaemic and non-ischaemic heart failure |
| 2. Beta1 selective blockade was at least as effective as ACE inhibition in reducing morbidity and mortality in type II diabetics with hypertension |
| 3. In contrast to enalapril, beta-blockade was renoprotective in patients with mild heart failure |
| 4. Beta1 selective blockade reduced peri-operative mortality and non-fatal heart attacks in patients undergoing non-cardiac vascular surgery |
| 5. Beta1 selective blockade, in contrast to diuretics, did not reduce the frequency of myocardial infarction in elderly hypertensives |
What has the UKPDS taught us about the treatment of the hypertensive type II diabetic?

There were 1148 mainly Caucasian type II diabetics with hypertension, mean age 56 years, just over a half were males, randomized to either tight control of blood pressure (BP<150/85 mmHg) or less tight control (BP<180/105 mmHg) and followed up for a median of 8.4 years[3]. The two main randomized treatments were the ACE inhibitor captopril or the beta-blocker atenolol[4]. The achieved mean blood pressure in the tight control group was 144/82 mmHg and in the less tight control group 154/87 mmHg; captopril and atenolol were equally effective antihypertensive agents.

The main results are shown in Fig. 1 and show that tight blood pressure control results in a significant 24% reduction in diabetes-related end-points; a significant 32% reduction in deaths related to diabetes; a significant 44% reduction in stroke; a significant 37% reduction in microvascular (mainly relating to kidney and eye) end-points. Non-significant trends were an 18% reduction in all-cause mortality, a 21% reduction in myocardial infarction and a 49% reduction in peripheral vascular disease. This is in accord with the results of the recently published HOT study[14] where diabetics particularly benefited from good blood pressure control.

Some interesting observations on the effects of tight blood pressure control on individual end-points were:
1. A significant 56% reduction in heart failure; a non-significant 49% reduction in amputations; a non-significant 42% reduction in renal failure.
2. Figure 2 shows trends favouring the beta-blocker for all seven primary clinical end-points (relating to any diabetes-related end-point, deaths related to diabetes, all-cause mortality, myocardial infarction, stroke, peripheral vascular disease and microvascular disease). This seven to nil trend is a statistically unlikely event ($P<0.01$).
3. There were no significant drug effects on individual end-points but of interest was
(a) the absence of a heart failure problem with the beta-blocker (indeed compared to the beta-blocker there was a non-significant 21% excess in the captopril group) (b) that the well known anti-ventricular arrhythmic properties of beta-blockers may have been associated with the non-significant 142% excess (compared to the beta-blocker) in sudden deaths in the captopril group and (c) the fear of a beta-blocker causing, or worsening, peripheral vascular disease was not borne out, indeed there was a non-significant 48% excess of amputations in the captopril group; peripheral vascular disease, as assessed by absent foot pulses or Doppler blood pressure recording, was the same on both drug groups.

4. Surrogate points of interest were (a) the change in albuminurea and serum creatinine over the 9 year observation period was the same in both drug groups. (b) Glycated haemoglobin (HbA1c) was significantly higher in the beta-blocker group in the first 4 years, but not in the last 5 years of observation. (c) Hypoglycaemic problems were the same in both drug groups.

5. Compliance with treatment was slightly better with captopril—80% of cases on captopril remained on treatment compared to 74% on atenolol. The main reasons for non-compliance with atenolol were bronchospasm and cold feet.

Can we explain the beta-blocker ‘surprises’

A rational explanation for unexpected results on hard clinical end-points (such as death and myocardial infarction) with beta-blockers has to account for unexpected negative, as well as positive, results. The major surprise negative results involved elderly hypertensive patients in whom beta-blocker based therapy failed to reduce the frequency of myocardial infarction[15,16] in contrast to diuretic based therapy which did[16,17]. However, some caution is necessary in interpreting the results of elderly hypertensive trials, where compliance to treatment is often poor. For example in the MRC elderly study[16] 63% of patients randomized to beta-blockade were either withdrawn or were lost to follow-up.

Beta-blockers possess properties other than an ability to lower blood pressure. On the one hand they possess anti-ischaemic, anti-arrhythmic and anti-renin/angiotension properties; prolong coronary diastolic filling time; upregulate cardiac beta 1 receptors and inhibit stimulatory anti beta 1-receptor autoantibodies[18], augment atrial and brain naturetic peptide[19], lower plasma endothelin-1 levels (carvedilol)[20], stimulate the endothelial L-arginine/nitric oxide pathway (vasodilatory beta-blockers such as nebivolol)[21] and inhibit catecholamine induced cardiac necrosis (apoptosis)[22], all of which potentially benefit patients. On the other hand, negative inotropism and an ability to increase left ventricular volume (thus increasing wall stress and oxygen requirements) are potentially harmful. Fortunately the good effects usually prevail so that (a) heart failure patients (with down-regulated cardiac beta 1 receptors, often raised beta 1 receptor antibodies in dilated cardio-myopathy, increased renin/angiotesion and sympathetic nervous activity, an increased risk of ventricular arrhythmias and a short coronary diastolic filling time due to tachycardia benefit with a reduced mortality,
particularly sudden death[23] and morbidity[1,2], (b) arteriopathies undergoing vascular surgery[40] and patients with overt ischaemia such as post-infarction cases[23] and chronic stable angina[24] benefit with a reduced mortality, fewer heart attacks and hospitalizations; (c) post-infarction patients with ventricular arrhythmias respond favourably with reduced mortality in contrast to the increased mortality associated with type I antiarrhythmic agents[23]; (d) younger–middle-aged male hypertensives[25,27], who tend to be ‘high renin’ patients[23] benefit (compared to diuretics) in terms of reduced cardiovascular mortality and coronary heart disease[29] (Table 2), Q-wave infarction and sudden death[30] (Table 3); (e) younger–middle-aged hypertensive type II diabetics, who are at high risk of coronary heart disease, benefit to a degree, at least as great as if they had been taking ACE inhibitors[4].

Elderly hypertensive patients behave differently. Certainly elderly post-infarction patients benefit from beta-blockade in terms of reduced mortality[31]. By contrast elderly hypertensive patients responded best to diuretic-based rather than beta-blocker based therapy in terms of fewer heart attacks[16]. Elderly hypertensives, in contrast to younger hypertensives, are essentially a low renin/low sympathetic activity group[26] with poor cardiac reserve[32]. Cardiac size increases with increasing age[33]. Under such conditions a further beta-blocker induced increase in heart size could increase oxygen requirements sufficiently, and possibly reduce coronary flow reserve[34], to cancel out the oxygen sparing benefits of lowering heart rate and blood pressure.

The apparent renoprotective action of beta-blockade (Table 4), in contrast to enalapril, in the SOLVD heart failure study[35], was unexpected because in hypertensives beta-blockade (certainly non-selective) tends to decrease renal blood flow and glomerular filtration rate[36]. However, in heart failure the control of renal function is complex and is influenced by the renin–angiotensin and sympathetic nervous systems. Glomerular filtration rate is maintained, in spite of a low cardiac output, by an angiotensin II-induced increase in efferent arterial tone, and ACE inhibition can thus reduce this tone and decrease glomerular filtration rate. It has been suggested[37] that beta-blockade in heart failure could have a ‘permissive’ effect on angiotensin II-dependent glomerular efferent arteriolar tone, i.e. beta-blockade would lower ACE inhibitor-induced raised plasma renin activity, decrease dependence on angiotensin II for maintaining glomerular filtration rate and allow for the safe introduction of ACE inhibitors.

The beneficial effect of beta₁ blockade upon perioperative cardiac death and non-fatal myocardial infarction in patients undergoing non-cardiac vascular surgery[48] is perhaps not so unexpected as such arteriopathies would be at increased risk of fatal ventricular arrhythmias or a ruptured atheromatous plaque in the presence of high sympathetic drive which occurs during and shortly after major vascular surgery. Beta₁ blockade has already been shown to benefit non-cardiac surgical cases over a 2 year postoperative period[49].

Table 4 Multivariate model of predictors of decrease in renal function in the SOLVD heart failure study

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>RR in enalapril group with 95% CI</th>
<th>RR in placebo group with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>1.42 (1.32–1.52) 1.18 (1.12–1.25)</td>
<td></td>
</tr>
<tr>
<td>Baseline ejection fraction</td>
<td>0.93 (0.91–0.96) 0.93 (0.91–0.96)</td>
<td></td>
</tr>
<tr>
<td>Diuretic therapy</td>
<td>1.89 (1.70–2.08) 1.35 (1.09–1.66)</td>
<td></td>
</tr>
<tr>
<td>Diabetics</td>
<td>1.33 (1.13–1.53) 1.96 (1.57–2.44)</td>
<td></td>
</tr>
<tr>
<td>Beta-blocker therapy</td>
<td>0.70 (0.57–0.85) 0.70 (0.57–0.85)</td>
<td></td>
</tr>
</tbody>
</table>

Does it matter which beta-blocker?

The answer is almost certainly Yes.

Post myocardial infarction

For survivors of myocardial infarction (with or without diabetes) there is good evidence that non-selective and beta₁ selective beta-blockers reduce mortality equally[23]. Thus beta₁ blockade appears to be the life saving ingredient and this applies also to post myocardial infarction patients with diabetes[30]. Beta-blockers that possess a significant amount of intrinsic sympathomimetic activity are less effective in reducing mortality than beta-blockers that possess no intrinsic sympathomimetic activity[23]. The possession of Class I antiarrhythmic activity (membrane stabilizing activity in beta-blockers) can even be harmful when expressed at high activity levels. Class I antiarrhythmics in the CAST (Cardiac Arrhythmia Suppression Trial) study were associated with a significant increase in mortality, unless co-prescribed with a beta-blocker[25]. However, all the available evidence indicates that the membrane stabilizing activity does not contribute to the vast majority of useful therapeutic effects or adverse reactions of beta-blockers[35]. Class III antiarrhythmic activity can be harmful. Sotalol possesses Class III activity which can give rise to proarrhythmic activity — torsade de pointes[36]. Sotalol effected only a modest, non-significant reduction in post myocardial infarction mortality[37] while d-sotalol (that possesses no beta-blocking activity but only Class III activity) actually increased post myocardial infarction mortality by 65%[38]. Even amiodarone, in the EMIAT (European Myocardial Infarct Amiodarone Trial) and CAMIAT (Canadian Amiodarone Myocardial Infarction Arrhythmia Trial) post myocardial infarction studies, appeared to be effective only when co-prescribed with a beta-blocker[35].

Thus beta₁ blockade appears to be the only property required for mortality reduction post myocardial infarction.

Treatment of heart failure

There is no longer any doubt that beta-blockers are effective in the treatment of patients with stable heart
failure receiving diuretics and ACE inhibitors[1]. Non-
selective beta-blockers are effective[1], particularly non-
selective agents with additional alpha blocking activity
such as carvedilol[39]. Beta 1 blockade appears to be the
active ingredient as evidenced by the significant reduction
in mortality, particularly sudden death, in patients with
moderate to severe heart failure with bisoprolol[2] and
metoprolol[2a]. Whether or not additional alpha blockade
is important can be determined only by a suitable prospec-
tive, randomized study comparing carvedilol with, say,
bisoprolol. Regarding the unexpected renoprotective ac-
tion of beta-blockade in patients with heart failure, beta1
selective beta-blockers would seem to be preferable to
non-selective agents as, on balance, the former are less
likely than the latter to decrease renal blood flow and
glomerular filtration rate[34a].

Catecholamine-induced myocardial necrosis (apop-
tosis) appears to arise from stimulation of the beta 1
receptor, via a cAMP-dependent process, whereas
stimulation of the beta 2 receptor, surprisingly, inhibits
apoptosis via a Gi-coupled pathway[39a]. These fascinating
data, if confirmed in man, may have important
implications, i.e. beta 1 blockade will prevent myocardial
cell death in contrast to beta 2 blockade, which could
have the opposite effect.

**Hypertensive, type II diabetic**

The two most important questions to ask are

1. Are non-selective and beta 1 selective beta-blockers
equally effective in lowering blood pressure

2. Are all beta-blockers equally safe and well-tolerated.

In order to address these questions it is helpful to have
some knowledge of the distribution of adrenoceptors
around the body and the resulting physiological effect
when the adrenoceptor is stimulated (Table 5).

**Table 5 Distribution of adrenoceptor subtypes and second messengers involved after ligand binding to receptor**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Predominant receptor</th>
<th>Physiological effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardium</td>
<td>Beta 1&gt; Beta 2</td>
<td>Stimulation of contractility and HR</td>
</tr>
<tr>
<td>Smooth muscle of bronchi</td>
<td>Beta 2</td>
<td>Bronchodilation</td>
</tr>
<tr>
<td>Blood vessel smooth muscle</td>
<td>Alpha 1</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>Alpha 2</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>Beta 2</td>
<td>Vasodilation</td>
</tr>
<tr>
<td></td>
<td>Beta 1</td>
<td>Vasodilation (coronary)</td>
</tr>
<tr>
<td>Genitourinary tract smooth muscle</td>
<td>Alpha 1</td>
<td>Muscle contraction</td>
</tr>
<tr>
<td></td>
<td>Beta 2</td>
<td>Muscle relaxation</td>
</tr>
<tr>
<td>Fat tissue</td>
<td>Alpha 2</td>
<td>Inhibition of lipolysis</td>
</tr>
<tr>
<td></td>
<td>Beta 2&gt;Beta 1 (2-1)</td>
<td>Stimulation of lipolysis</td>
</tr>
<tr>
<td>Platelets</td>
<td>Alpha 2</td>
<td>Aggregation</td>
</tr>
<tr>
<td>Liver</td>
<td>Alpha 1</td>
<td>Glycogenolysis</td>
</tr>
<tr>
<td></td>
<td>Beta 2</td>
<td>Glycogenolysis, Gluconeogenesis</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Alpha 2</td>
<td>Inhibition of insulin release</td>
</tr>
<tr>
<td></td>
<td>Beta 2</td>
<td>Stimulation of insulin release</td>
</tr>
<tr>
<td>Sympathetic terminals</td>
<td>Alpha 1</td>
<td>Inhibition of noradrenaline release</td>
</tr>
<tr>
<td></td>
<td>Beta 2</td>
<td>Stimulation of noradrenaline release</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>Beta 2</td>
<td>Glycogenolysis</td>
</tr>
<tr>
<td>Kidney</td>
<td>Beta 1</td>
<td>Renin release</td>
</tr>
<tr>
<td>CNS</td>
<td>Beta 2 Beta 1</td>
<td>?Raise BP</td>
</tr>
<tr>
<td></td>
<td>Alpha 2</td>
<td>?Lower BP</td>
</tr>
<tr>
<td>Eye</td>
<td>Beta 2</td>
<td>Increase intra-ocular pressure</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Beta 2</td>
<td>?Modulate immune function</td>
</tr>
</tbody>
</table>

In order to address these questions it is helpful to have
some knowledge of the distribution of adrenoceptors
around the body and the resulting physiological effect
when the adrenoceptor is stimulated (Table 5).

1. Are non-selective and beta 1 selective beta-blockers
equally effective in lowering blood pressure?

No, and one would not expect them to be. Beta-blockers
without intrinsic sympathomimetic activity lower blood
pressure by decreasing cardiac output, (mainly by
decreasing heart rate). Figure 3 shows that chronically
dosed atenolol, propranolol and timolol lower heart rate
and cardiac output similarly but that the non-selective
agents increase vascular resistance more than atenolol
(a combination of reflex vasoconstriction due to a low
heart rate and cardiac output) resulting in a lower mean arterial pressure with
atenolol[40]. An overview of clinical trial comparisons of
propranolol and atenolol showed that diastolic blood
pressure was some 4 mmHg lower on atenolol[41].

However, beta 1 selectivity is not an absolute property
and some agents are more beta 1 selective than others. A
beta 1 selectivity index comparison has shown that
relative to propranolol (which blocks beta 1 and beta 2
receptors to an equal degree) the hierarchy of beta 1
selectivity, in ascending order, is metoprolol, betaxolol
and atenolol (about equal) and bisoprolol[42]. This high
beta 1 selectivity of bisoprolol appears to be reflected in
superior antihypertensive properties, as evidenced in
a large (n=659), randomized comparison of atenolol
50–100 mg once daily and bisoprolol 10–20 mg once
Daily[43]. In that study, 203 patients underwent 24 h ambulatory monitoring, which revealed significantly lower systolic blood pressure and diastolic blood pressure throughout the whole 24 h with bisoprolol. Thus optimal blood pressure control is more likely to be obtained with a highly beta1 selective beta-blocker reducing the need for additional antihypertensive agents.

2. Are all beta-blockers equally safe?
No, and (as for blood pressure control) one would not expect them to be.

(i) Bronchoconstriction: In the UKPDS study[45] bronchospasm was the most common reason for non-compliance with atenolol. The greatest risk of bronchospasm occurs with non-selective beta-blockers without intrinsic sympathomimetic activity[44] where not only is induced bronchospasm more likely but also the salutary bronchodilator action of beta2 stimulants is inhibited.

The risk of bronchoconstriction and the inhibition of beta2 stimulant bronchodilation in vulnerable subjects is minimized by the use of highly beta1 selective agents. In a randomized, placebo-controlled, crossover study comparing atenolol 100 mg and bisoprolol 20 mg in 12 ischaemic patients with obstructive lung disease it was evident that both agents effected similar beta1 blockade (similar fall in heart rate over 24 h) but only atenolol caused an increase in airways resistance[45] Fig. 4. However no beta-blocker, even highly beta1 selective agents, are totally safe in patients with reversible airways disease.

(ii) Hyper/hypoglycaemia
(a) Hyperglycaemia: The effect of beta-blockade on glucose homeogenesis is complex. Beta2 stimulation (Table 3) results in an increase in liver glycogenolysis and gluconeogenesis, an increase in muscle glycogenolysis and stimulation of insulin release. Experience has indicated that non-selective beta-blockers tend to cause a small increase in blood sugar, as evidenced by the withdrawals in the propranolol group due to glucose intolerance in the MRC mild hypertensive study[7] and the increase in the prescription of hypoglycaemic agents in the propranolol group in the BHAT post infarction study[9]. However, beta1 selective agents can increase insulin resistance and HbA1c[46], though interestingly this can be prevented provided potassium and weight changes are avoided[47].

(b) Hypoglycaemia: Non-selective beta-blockers, in contrast to beta1 selective can delay the return of insulin-induced low blood sugar levels to normal and hypoglycaemic signs may be modified[49]. More importantly non-selective beta-blockers can precipitate a hypertensive response[49] which may be severe[50] and accompanied by a profound reflex bradycardia[51]. The hypertensive reaction can occasionally be of a severity to produce seizures[50–52]. These potentially dangerous haemodynamic responses to non-selective blockade are associated with the high adrenaline levels observed with hypoglycaemia. Blockade of the beta1 and beta2 stimulatory effects of adrenaline leaves an unbridled alpha constricting action resulting in a rise in blood pressure[53].

Thus beta2 blockade is inappropriate for the treatment of hypertensive type II diabetics, who may be on insulin therapy, and a highly beta1 selective beta-blocker would be the agent of choice.

(iii) Cigarette smoking: Similar, but less dramatic, blood pressure changes (than with insulin-induced hypoglycaemia) occur with non-selective, but not beta1 selective beta-blockade and cigarette smoking-induced adrenergic[54].

Such effects could account for the absence of benefit of propranolol in male hypertensive smokers, in contrast to non-smokers who experienced a fall in the frequency of heart attacks and stroke in the MRC Mild Hypertension Study[27]. In contrast, hypotensives who smoke experience fewer deaths with beta1 selective blockade[55]. Anti-ischaemic effects of propranolol in patients with coronary heart disease are also abolished by cigarette
smoking\textsuperscript{56}. Thus for smokers who require beta-blockade a highly beta\textsubscript{1} selective agent is the appropriate choice.

(iv) Blood lipids: beta-blockers have little effect on LDL cholesterol but do increase plasma VLDL and triglyceride levels and lower HDL concentration\textsuperscript{57}. The changes are more apparent with non-selective beta-blockers and may be due to effects on lipoprotein lipase responsible for the removal of endogenous triglycerides\textsuperscript{57}. Non-selective blockade exposes uninhibited alpha stimulation which inhibits the lipase responsible for degrading triglycerides; beta\textsubscript{1} selective agents permit beta\textsubscript{2} stimulation to counteract these effects. Blood lipid changes with highly beta\textsubscript{1} selective agents, such as bisoprolol, are minimal or absent\textsuperscript{68}. The clinical significance of beta\textsubscript{2} blockade-induced lipid changes is unclear, particularly as non-selective agents like propranolol and timolol have been shown to be highly effective in reducing post-infarction mortality and re-infarction\textsuperscript{54}. However beta\textsubscript{2} blockade appears to be the active ingredient in cardiovascular protection and it therefore seems logical to choose a highly beta\textsubscript{1} selective agent.

(v) Muscle metabolism and physical performance: The effect of beta-blockers on muscle metabolism and physical performance is complex and has been reviewed by Cruickshank and Prichard\textsuperscript{59}. In brief, non-selective beta-blockade affects muscle metabolism and physical performance more than beta\textsubscript{1} selective blockade. Muscle glycolysis and lactic acid release are impaired by non-selective beta-blockers, as is the Na\textsuperscript{+}/K\textsuperscript{+} pump in muscle cell membranes\textsuperscript{60}. Post exercise falls in blood glucose and increases in serum potassium are more apparent with non-selective blockade. Certainly exercise duration and training effects are more impaired by non-selective blockade and these effects are mostly apparent in aerobically, compared to anaerobically, fit subjects\textsuperscript{61}. Muscles that are aerobically fit, containing a high proportion of slow twitch fibres, are particularly affected by non-selective blockade in terms of exercise duration\textsuperscript{62}.

Thus for active, aerobically fit subjects requiring beta-blockade, a highly beta\textsubscript{1} selective agent is a sensible choice.

(vi) Beta-blockers and quality of life: A condition like hypertension, even when associated with type II diabetes, is essentially asymptomatic. It is therefore important that, to ensure compliance, antihypertensive agents do not induce side effects that impair quality of life. The term quality of life had become synonymous with ACE inhibition since the study of Croog et al.\textsuperscript{63} where propranolol and methyldopa, but not captopril, decreased quality of life. However, similar studies comparing beta\textsubscript{1} selective agents like atenolol\textsuperscript{64,65} and bisoprolol\textsuperscript{66} with ACE inhibitors could find no difference between the two types of agent and their effect on quality of life.

Some final thoughts

Few would now disagree that beta-blockers are the agents of choice in the treatment of overt coronary heart disease; have stood the test of time as highly effective drugs in the treatment of ventricular arrhythmias; and now have a useful role to play in the treatment of heart failure, on a background of diuretics and ACE inhibitors. In contrast, final views regarding the treatment of hypertension are still unfolding.
Two large, single-drug, randomized studies have shed light on the antihypertensive efficacy of various drug groups. The HANE study\(^\text{[67]}\) in 868 young to middle-aged (21–70 years) men and women found that beta\(_1\) selective atenolol was the most effective antihypertensive agent at both 8 weeks and 1 year compared to hydrochlorothiazide, nitrrendipine and enalapril. The Veterans Affairs Cooperative Study\(^\text{[69]}\) in 1105 hypertensive men addressed the interaction of age, colour, renin status and antihypertensive efficacy of hydrochlorothiazide, atenolol, clonidine, captopril, prazosin and diltiazem. The conclusion was that atenolol was best for younger (less than 60 years old) white men and that hydrochlorothiazide and diltiazem were best for older white men; prazosin was best for younger black men and diltiazem best for older black men.

The results of the above two studies appear compatible with the hypertension/mortality studies published to date. Certainly beta-blockers should not be first-line therapy for elderly hypertensives\(^\text{[69]}\); this role should be reserved for low-dose diuretics, adding a beta-blocker or other agents as required\(^\text{[70]}\). These conclusions apply also to diabetic, as well as non-diabetic, elderly hypertensives\(^\text{[71]}\). Calcium antagonists or ACE inhibitors are now an alternative first-line therapy for elderly hypertensives. The Syst-Eur trial\(^\text{[72]}\) showed that antihypertensive therapy initiated with the dehydropyridine nitrrendipine reduced the risk of stroke and cardiovascular events, and this applied also to diabetic elderly hypertensives\(^\text{[73]}\). In the STOP-2 study on elderly hypertensives\(^\text{[74]}\), ACE inhibitors were at least as effective as calcium antagonists in decreasing mortality and morbidity rates. For younger hypertensives the best results are seen with beta-blockers, at least for men\(^\text{[26,27,74]}\) (Table 1).

The recently published CAPP study\(^\text{[75]}\) showed no difference between captopril and conventional treatment (mixture of beta-blockers and thiazide diuretics) on cardiovascular end-points in younger (age 25–66 years) hypertensives. A more useful conclusion might have been possible had the diuretics and beta-blockers been randomized separately. Interestingly, in the UKPDS study on younger male and female diabetic hypertensives\(^\text{[3,4]}\), where beta\(_1\) selective blockade was at least as effective as ACE inhibition in preventing hard clinical end-points, the difference of 10/5 mmHg between less intensively and intensively treated groups was associated with a 44% reduction in the frequency of stroke and a 21% reduction in myocardial infarction frequency, figures not far removed from the results predicted for such a persistent blood pressure difference in the large epidemiological study by McMahon et al.\(^\text{[76]}\) i.e. 40% stroke reduction and 25% myocardial infarction reduction.

All of these musings seem far removed from the recent conclusions drawn by Beevers\(^\text{[77]}\) in his paper entitled ‘Beta blockade for hypertension; time to call a halt’. In his meta-analysis he combined the results of hard end-point studies involving both beta-blockers and diuretics in young and elderly hypertensives (no attempt was made to separate the two age groups) and concluded ‘Beta-blockers can also be dangerous in many hypertensive patients . . . . The time has come therefore to reconsider the endorsement of beta-blockers by the British Hypertension Society . . . . The time has come to move across to newer, safer, more tolerable and more effective antihypertensive agents . . . . I am sure that few would now concur with such extreme views.

**Conclusions**

Until recent times beta-blockers were contra-indicated in patients with heart failure and relatively contra-indicated in type II diabetics due to adverse effects on various surrogate end-points for cardiovascular events. Now, beta-blockers have a definite role in the treatment of stable ischaemic and non-ischaemic heart failure (and, unlike ACE inhibitors, appear to lessen the risk of renal dysfunction) and rival ACE inhibitors for the treatment of the hypertensive type II diabetic. The UKPDS study has shown that in hypertensive type II diabetics tight control of blood pressure was beneficial in terms of significantly fewer cardiovascular end-points. The surprise was that beta\(_1\) selective blockade was at least as effective as ACE inhibition and there were even trends favouring the beta-blocker in all seven primary clinical end-points, namely fewer total diabetes-related end-points, fewer diabetic-related deaths, a lower all-cause mortality, fewer myocardial infarctions and stroke, less peripheral vascular disease and a reduced frequency of microvascular disease (relating to eye and kidney). Compliance was slightly better with the ACE inhibitor captopril than the beta-blocker atenolol due mainly to an excess of bronchoconstriction with the latter.

Possible reasons why beta-blockade benefits patients with heart failure (including lessening the risk of renal dysfunction), ischaemics with or without ventricular arrhythmics, patients undergoing non-cardiac, vascular surgery, and younger–middle aged hypertensives with or without diabetes, in contrast to elderly hypertensives (in terms of reduced frequency of heart attacks), have been discussed.

Thus beta-blockers are the drugs of first choice for treating patients with overt coronary heart disease; now have an established place in the treatment of stable heart failure (and unlike ACE inhibitors appear to lessen the risk of renal dysfunction); reduce peri-operative cardiac mortality and non-fatal myocardial infarction in high risk patients undergoing non-cardiac surgery; reduce cardiovascular events in younger–middle aged hypertensives (certainly in males); and may even be considered the antihypertensive treatment of first choice for younger (less than 70 years) hypertensive type II diabetics. Beta\(_1\) selective blockade appears to be the active ingredient for these benefits and the use of a highly beta\(_1\) selective agent will also reduce the risk of adverse reactions, such as bronchoconstriction, associated with beta\(_2\) blockade.
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