Beta-blockers in the third millennium - when are they really indicated

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When are Beta-Blockers Indicated?

J Clin Basic Cardiol 2001; 4: 3

Beta-Blockers in the Third Millennium –
When are They Really Indicated?

B. N. C. Prichard, B. Graham, J. M. Cruickshank

Beta-blockers have come a long way in development since the first two used clinically, pronethalol and propranolol, were evaluated in angina pectoris, cardiac arrhythmias and phaeochromocytoma. Pharmacological development has been directed to improving both selectivity and more recently agents with additional vasodilator activity, either by alpha-receptor blockade or by other mechanisms. Therapeutic development has led to the use of beta-blockers in a wide variety of indications, principally in the cardiovascular system, but also elsewhere.

Numerous studies have confirmed the value of beta-blockers in ischaemic heart disease. They remain a most efficacious treatment for symptom relief in angina pectoris although evidence that prognosis is improved is mainly indirect. Many studies have demonstrated that beta-blockers improve prognosis post myocardial infarction; benefit being demonstrated in many categories, particular value has been shown in patients with poor left ventricular function.

The first non-predicted use of beta-blockers demonstrated was their antihypertensive effect. They are now accepted by major international guidelines as first line therapy. Beta1-selective agents are more effective than non-selective agents, and contrary to some earlier evidence based on non-selective agents, they are often effective in younger (under 65) black patients. Beta-blockers have been shown to improve prognosis in younger patients while in the elderly, diuretics appear superior in primary prevention.

Since early reports of propranolol precipitating heart failure, studies with bisoprolol, carvedilol and metoprolol have established that beta-blockers carefully titrated even when added to a treatment regimen including ACE-inhibitors give a dramatic improvement in survival. Diabetes was another area where beta-blockers were considered to have disadvantages. While beta2-blockade should be avoided in patients on insulin, hypoglycaemic episodes are not rendered more of a problem by beta1-selective blockade. A recent important study in type 2 diabetes has shown that tight control of blood pressure resulted in an improvement of various prognostic indicators, with results with atenolol treated patients throughout being at least as good as with the captopril treated subjects.

Some supposed contra-indications to beta-blockade have been previously over-emphasised. Notably, patients with chronic airways obstructive disease frequently tolerate beta-blockade well and will benefit, eg, post infarction, although beta1-selective agents should be used. Quality of life investigations show that beta1-selective drugs are well tolerated when compared to other drugs including ACE-inhibitors. J Clin Basic Cardiol 2001; 4: 3–9.

Key words: beta-blocker, morbidity, mortality, diabetes, hypertension

Beta-adrenergic blocking drugs were conceived by Sir James Black when he reasoned that a drug to inhibit the effect of sympathetic nerve stimulation and catecholamines on the heart would be valuable in angina pectoris, arrhythmias and phaeochromocytoma. Papers describing the first beta-blocker pronethalol reported initial clinical trials in this area [1]. Since the early 1960’s there has been continuing progress in the field of beta-blockade, now therefore for over 35 years, both in terms of pharmacological development and in the wider appreciation of the clinical application, with continuing interesting developments [2].

The beta-adrenergic blocking drugs differ in various aspects. Non-selective agents blocking both beta1-receptors, eg at sympathetic innervation of the heart, and beta2-receptors, eg in bronchial and vascular smooth muscle. Propranolol, the archetypal agent, also has membrane stabilising activity or local anaesthetic effects, though this property does not contribute to its therapeutic effects. Propranolol is a pure antagonist, whereas drugs like pindolol besides blocking the beta-receptor also have some stimulatory action, ie partial agonist effect.

A major thrust of development of beta-blockers has been the search for and the introduction of agents with increasing selectivity for the beta1-receptor, in contrast to their lesser effect on the beta2-receptor. The beta1-receptor mediates the effects of sympathetic nerve stimulation completely, and circulatory catecholamines mostly, on the heart and renin release, whereas the beta2-receptor mediates bronchial and vascular dilatation [1]. Drugs with other properties have also been introduced such as beta1-blocking activity, eg carvedilol, a non-selective blocker which also has an anti-oxidant [3], or nebivolol, a highly selective beta1-selective agent which has a nitric oxide dependant vasodilator property [4]. It seems that the therapeutic use of beta-blockers resides in their beta1-blocking action.

Therapeutic Use of Beta-Blockers

Black originally suggested that beta-blockers would be clinically useful in conditions where the effect of the sympathetic nerves to the heart and the action of circulating catecholamines was deleterious, notably angina pectoris, arrhythmias and phaeochromocytoma. Studies with the first clinically evaluated beta-blocker pronethalol (reported in 1963) confirmed this prediction [1]. Sympathetic stimulation was known to increase the gradient in congenital outflow tract obstruction and propranolol, the first widely evaluated beta-blocker, was found to inhibit the increase. An important further development was the first study which suggested that propranolol reduced mortality after myocardial infarction [5].

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There have also been developments in the use of beta-blockers which were surprising, a theme recently taken up by Cruickshank [2], describing some recent developments. Firstly, the initial report that beta-blockers lowered the blood pressure came in 1964 [6]; this effect had not been seen to animal experiments and as beta-blockers increased peripheral resistance, for some time there was resistance to the concept of the mode of action of beta-blockade. There is evidence that the long acting nitrate, isosorbide, added to beta-blockade increases exercise tolerance [14] or gives additional relief of angina symptoms [15], even if not so effective as nifedipine [16].

Beta-blockers combine well in the symptomatic relief of angina with dihydropropyridine calcium antagonists [17], eg nifedipine, with greater relief from propranolol and nifedipine in combination than either agent alone [18]. In one large study (total n = 551) verapamil, and amiodipine plus atenolol reduced the number of ischaemic episodes with Holter monitoring, whereas amiodipine alone force-titrated to 10 mg/day resulted in significantly more ischaemia than placebo. All three active treatments increased acute exercise tolerance compared to placebo [19]. While intravenous use in combination is best avoided because of the possible development of heart block, the combination of propranolol and verapamil was noted to give a greater increase in exercise tolerance over placebo than either drug alone [20]. Similar observations have been made with a combination with diltiazem [21].

**Indication for beta-blockers in angina**

Besides being a most efficacious group of drugs in the relief of symptoms of angina pectoris [13], they may improve prognosis. There are no long term mortality studies in angina, the rationale for supposing a possible benefit comes mainly from studies post myocardial infarction [22–24].

It has however been shown that the beta-selective bisoprolol reduces mortality in high risk patients with evidence of myocardial ischaemia on wall motion studies with dobutamine undergoing major vascular surgery. Cardiac death rate in the bisoprolol group (n = 59) was 3.4 %, 17 % in the standard care group (n = 52) (p = 0.02). The incidence of non-fatal myocardial infarction was 0 % and 17 % respectively (p < 0.001) [25].

A follow up of the total ischaemic burden bisoprolol study (TIBBS) in patients with angina pectoris found that those patients in the 8 week study randomised to bisoprolol had a total event rate (death, acute myocardial infarction, hospital admission for unstable angina pectoris) after 1 year open follow up, of 22.1 %, compared to an event rate of 33.1 % in those patients who received nifedipine for the initial eight weeks. At one year with the physician able to change treatment, beta-blockers were still being used in 47 % of the bisoprolol group, in 32 % of the nifedipine group (p = 0.008), whereas the figures for calcium antagonists were 21 % and 26 % respectively [26].

**Myocardial Infarction**

Beta-blocking drugs are well established as agents that reduce mortality post myocardial infarction [1, 27]. Non-selective and beta-selective agents appear to be of similar efficacy but agents that possess significant partial agonist effect, intrinsic sympathomimetic action, are less effective [27]. The class III anti-arrhythmic activity which is possessed by the beta-blocker sotalol is no advantage; sotalol itself only gives a modest non-significant reduction in mortality post infarction [28] while the non-beta-blocking d-isomer of sotalol, which just...
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Most beta-blocking studies post infarction were performed prior to the use of thrombolysis, aspirin and ACE-inhibitors, however there is evidence that beta-blockers should still be administered as part of current treatment [30]. Beta-blockers given acutely shortly after hospital admission to thrombolysed patients reduced re-infarction rate by 48% compared to those where beta-blockade was delayed by one week [32]. In the TEAHAT study [33] the best effect of re-PA on infarct size was seen in patients who were also given metoprolol. Beta-blockers added to ACE-inhibitors in patients with ventricular dysfunction improve prognosis [34], and in the US heart failure study with carvedilol added to ACE-inhibition the incidence of sudden death was reduced by 50% [35].

Gottlieb et al. [36] recently reported a most interesting survey of post infarction beta-blockade usage in over 200,000 patients. They reported benefit regardless of systolic blood pressure, age, ejection fraction or even in patients with co-existent chronic obstructive pulmonary disease, often regarded as a contra-indication to beta-blockade (Table 1).

Hypertension

Beta-blockers were only slowly accepted as treatment for hypertension [7] and even seven years after the first reports of the hypotensive effect of pronethalol [6] and propranolol [37, 38] some concluded that because of the reduction in cardiac output and the rise in peripheral resistance, beta-adrenergic blocking drugs should not be used routinely in the treatment of hypertension [39]. Beta-blockers are now regarded as a first line choice of treatment in hypertension along with diuretics, by the Joint National Committee [39], the British Hypertension Society [40] and a first line alternative with various antihypertensives by WHO/ISH [41].

Efficacy

While the mode of action of beta-blockers in hypertension is not clear, it does seem to be a function of beta1-blockade [1, 42]. It was noted in the early evaluation of beta-blockade that adrenaline in the presence of beta2-blockade resulted in a greater rise of blood pressure because its beta2-vasodilator effect, is inhibited [43]. It is possible therefore that beta2-blockade antagonises the modest background vasodilator effect of circulating adrenaline, which reduces the fall in blood pressure in those patients over 60 years. This may be the reason that a 2–3 mmHg greater fall in blood pressure is seen with beta1-blockade compared to non-selective blockade. It has been found that no fall in blood pressure is seen with selective beta2-blockade (IC118551) [1].

Several large clinical trials have shown that beta-blockers, atenolol [44-46] or acebutolol [47] are similar in antihypertensive effect to examples from the major classes of hypotensive drugs. In a large survey of veterans hypertension clinics it was found that blood pressure control with beta-blockers was similar to other agents, with or without a diuretic [48].

Bisoprolol was possibly the most beta1-selective agent generally available [49]. There is some suggestion that bisoprolol may control hypertension more effectively than atenolol [49–51]. Nebivolol is even more selective, but as yet there is only limited data comparing it with other beta-blockers [4].

Combination treatment in hypertension

Combination versus single drug regimens are valuable in the treatment of hypertension [52, 53]. A large factorial study involving a total of 512 patients utilised bisoprolol 2.5 mg, 10 mg or 40 mg, hydrochlorothiazide 6.25 mg or 25 mg, and placebo, given in all possible combinations [54]. Blood pressure was lowered to less than 70 mmHg diastolic in 61% of patients by the combination of bisoprolol 2.5 mg and hydrochlorothiazide 6.25 mg. In another study the value of bisoprolol 5mg and hydrochlorothiazide 6.25 mg was confirmed [55], and Prisant et al. [56] reported that the combination with low dose hydrochlorothiazide controlled blood pressure to a similar extent to amiodipine, while each treatment was more effective than enalapril.

Effect of age and race on the antihypertensive effect of beta-blockers in hypertension

There have been suggestions that the response of blood pressure to beta-blocking drugs in the elderly and blacks was poor, although much of the evidence which led to this view was based on studies with non-selective beta-blockers [1].

In the study of bisoprolol, hydrochlorothiazide and the combination of the two, Frishman et al. [55] reported no reduction in the fall of blood pressure in those patients over 60 years compared to those below that age with bisoprolol alone or the combination of bisoprolol and hydrochlorothiazide. The double blind parallel group study of six different antihypertensive regimens [44, 45] did not find any age-related response to atenolol in white patients, 65% below 60 years old were successfully controlled compared to 72% of those over 60 years.

Jamerson and DeQuattro [57] analysed thirteen clinical trials in African Americans published between 1988 and 1993. They found less reduction of blood pressure with ACE-inhibitors and beta-blockers in contrast to diuretics and calcium channel blockers. Materson et al [44, 45] observed that blacks under 60 showed a 51% response rate to atenolol, 65% below 60 years old were successfully controlled compared to 72% of those over 60 years.

Table 1. Risk of death in 2 years post-infarction (%). After Gottlieb et al. [36]

<table>
<thead>
<tr>
<th>Systolic B.P (mmHg)</th>
<th>Beta-block (n)</th>
<th>No beta-block (n)</th>
<th>Absolute reduction</th>
<th>Relative risk (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100</td>
<td>16.9 (2679)</td>
<td>28.1 (7778)</td>
<td>11.2</td>
<td>0.60 (0.57–0.63)</td>
</tr>
<tr>
<td>100–139</td>
<td>10.4 (26350)</td>
<td>17.2 (92510)</td>
<td>6.8</td>
<td>0.60 (0.57–0.63)</td>
</tr>
<tr>
<td>&gt; 140</td>
<td>9.8 (40000)</td>
<td>14.6 (71926)</td>
<td>5.0</td>
<td>0.66 (0.61–0.71)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>11.3 (29312)</td>
<td>18.7 (67184)</td>
<td>7.4</td>
<td>0.60 (0.57–0.63)</td>
</tr>
<tr>
<td>&gt; 80</td>
<td>15.3 (23467)</td>
<td>24.0 (47959)</td>
<td>8.7</td>
<td>0.64 (0.58–0.70)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>23.5 (412)</td>
<td>34.5 (2400)</td>
<td>11.0</td>
<td>0.60 (0.58–0.80)</td>
</tr>
<tr>
<td>20–49</td>
<td>15.3 (23920)</td>
<td>25.4 (47192)</td>
<td>10.1</td>
<td>0.60 (0.57–0.63)</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>11.6 (24787)</td>
<td>19.3 (35527)</td>
<td>7.7</td>
<td>0.60 (0.57–0.63)</td>
</tr>
<tr>
<td>COPD</td>
<td>16.8 (9228)</td>
<td>27.8 (35586)</td>
<td>11.0</td>
<td>0.60 (0.57–0.63)</td>
</tr>
</tbody>
</table>
**Primary prevention in hypertension**

Several prospective trials have shown that diuretics and beta-blockers reduce the development of complications of hypertension, most clearly seen with stroke and heart failure, less clear with coronary heart disease [58, 59]. When data in men under age 65 from the Medical Research Council [60] and the IPPPHS [61] studies were grouped to compare diuretic and beta-blocker treatment, non-selective propranolol and oxprenolol respectively, it was found with beta-blockade there was a 28 % lower cardiovascular mortality (p = 0.03), 21 % lower non-fatal plus fatal coronary heart disease (p = 0.04), while total mortality also showed a trend to be less on beta-blockade (18 %, p = 0.09) [62]. The HAPPY trial with the beta1-selective agents metoprolol and atenolol, versus

There are various possible mechanisms for benefit in reduction in mortality in patients treated with carvedilol [74]. The combined US carvedilol studies suggested a 65 % carvedilol reduces mortality in patients with heart failure anti-oxidant activity , several studies have shown that

In a comparison of the drugs used to achieve tight control of the blood pressure it was found that a BP 143/81 mmHg
was achieved with atenolol 50 or 100mg OD (n = 358) and with captopril 144/83 mmHg; 25 or 50 mg bd (n = 400) [80]. There was a non-significant trend in favour of atenolol with any diabetes endpoint, deaths due to diabetes, all cause mortality, myocardial infarction, stroke, peripheral vascular disease and microvascular disease, besides heart failure and sudden death. A higher glycaemic haemoglobin for the first four years was seen with atenolol but not for the last five years of the study. The incidence of hypoglycaemic problems did not differ. Compliance was similar for the first four years but then it was 80 % for captopril, 74 % for atenolol in terms of patient years follow-up (p = 0.0001). This was mainly the result of bronchospasm (6 %) and claudication or cold feet (4.9 %) on atenolol, offset to some degree by cough (4 %) on captopril.

The mechanism of benefit from β1-blockade may be that in type 2 diabetes the high insulin levels stimulate noradrenaline release [81, 82]. This consequent increased sympathetic activity with the various possible complications [83] can be inhibited by β2-blockade.

### Chronic obstructive pulmonary disease

Patients who have even relatively severe chronic obstructive pulmonary disease can tolerate beta-blockers well, and its coexistence should not be regarded as a contra-indication to beta-blockade use. A β2-selective agent should be used as if there is a beta-responsive component, then less block will occur and the patient will respond to β2-agonist bronchodilatation even if larger than normal doses are needed [1]. As discussed above in a large survey of patients post-myocardial infarction and co-existent chronic obstructive pulmonary disease benefit in terms of improved survival at least as much as patients without this complication [36].

### Peripheral vascular disease

Beta-blockers are well recognised to cause cold extremities. A β2-selective drug or an agent with partial agonist activity might then be regarded as a better choice. In the absence of peripheral vascular disease effect of beta-blockers on the peripheral circulation is not otherwise important. In patients with severe peripheral vascular disease beta-blockers should only be used with great care. In less severe obstructive disease beta-blockers did not have important effects on the peripheral circulation and may even improve flow, by a reversed steal effect, to the diseased area [1, 84].

### Lipids

Beta-blockers, at least the non-selective drugs without partial agonist activity, increase triglyceride levels, 20–50 %, and lower HDL-C levels, 10–20 %. The β1-selective agents have lesser effects, they overall decrease HDL-C by 7–10 %, increase triglycerides 10–20 %. Drugs with marked partial agonist activity such as pindolol have little effect on lipids, least effect being from a selective agent which also has agonist activity [85–87]. The mechanism of triglyceride increase in non-selective beta-blockade may be that α-stimulation unopposed by β2-adrenergic activity reduces lipoprotein lipase activity. Less effect would be expected from β1-blockade, or indeed with non-selective blockade plus α-blockade as has been recorded with labetalol. The reduction of lipoprotein lipase action reduces cata bolism of triglycerides and VLDL. Triglyceride and cholesterol ester exchange between VLDL and HDL leads to triglyceride enrichment of HDL, and increased catabolism of HDL-C [87].

Notwithstanding any effect beta-blockers may have on lipid profile, it has not prevented them from being useful in the long-term treatment of various cardiovascular disorders.

### Quality of life

Croog et al. [88] compared propranolol, methyldopa and captopril, and found that captopril resulted in a better quality of life compared to propranolol, in turn better than methyldopa. However, what was observed with the non-selective lipid soluble propranolol was not the same with all beta-blockers. It was later found that the β1-selective atenolol had a similar quality of life score to ACE-inhibitors [89], while the non-selective propranolol was found to have a poorer global score, in accord with the findings of Croog et al. [88]. Others have confirmed that atenolol was similar to captopril [90]. Fletcher et al. [91], in a large double-blind randomised parallel group study, observed that the ACE-inhibitor cilazapril and atenolol had a similar quality of life assessment, both superior to nifedipine. The highly selective β1-selective bisoprolol was found to be similar to enalapril [92]. The combination of low dose (6.25 mg) hydrochlorothiazide and bisoprolol was reported to have a similar quality of life to amlodipine with a trend to be better than enalapril [49]. The TOMHS study showed that acebutolol and chlorthalidone were significantly better than placebo in a global assessment of the various measures of quality of life, while doxazosin and enalapril did not differ from placebo and amlodipine just failed to reach accepted level of significance [93]. Those beta-blockers such as carvedilol with additional peripheral vasodilator action have also been shown to have similar quality of life scores to ACE-inhibitors [94]. Overall β1-selective agents have little if any adverse effect on quality of life [95].

### Conclusions

As we enter the third millennium, beta-blocking drugs remain established in a wide variety of indications. The important indications, in terms of the numbers treated, are: Ischaemic heart disease, as a symptomatic treatment for angina pectoris and in secondary prevention after myocardial infarction, hypertension as a first line drug according to current guidelines. More recently beta-blockers have become accepted, after careful dose escalation, in the treatment of heart failure. Beta-blockers also have a useful place in glaucoma, migraine and a wide variety of other indications. They have a useful place as a prophylactic in migraine and useful applications in a variety of other conditions, although they account for relatively few prescriptions when compared to the main indications discussed above, cardiac arrhythmias, congenital obstruction of the outflow tract, phaeochromocytoma, etc.

Diabetes had been regarded as a relative contra-indication, but recent evidence indicates this should no longer be the case. Similarly beta-blockers should not necessarily be withheld, when otherwise indicated, in patients with co-existent less severe peripheral vascular disease, chronic obstructive pulmonary disease without an important reversible component, although clearly a β1-selective agent should be used.

### References

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