Review

Synthèse

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Choosing a first-line drug in the management of elevated blood pressure: What is the evidence? 2: β-Blockers

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Abstract

ELEVATED BLOOD PRESSURE IS ASSOCIATED WITH an increased risk of cardiovascular illness and death. Efforts to reduce that risk have led to recommendations for a wide array of nondrug and drug therapies. Choosing the optimal first-line drug for hypertensive patients should address a hierarchy of treatment goals: decrease in morbidity and mortality associated with hypertension, decrease in blood pressure, good tolerance, dosing convenience and low cost. This article examines the evidence for β-blockers as a class of first-line antihypertensive drugs in light of these treatment goals. The evidence indicates that β-blockers are probably not as effective in reducing morbidity and mortality as low-dose thiazide diuretics and that there may be significant differences in effectiveness among various β-blockers.

Published evidence for the use of thiazides in managing hypertension indicates that thiazides, given at a low dose, are the drugs of first choice.[1] However, for a variety of reasons, we cannot rely on a single drug class to treat hypertensive patients. In this article I compare the evidence for β-blockers as first-line therapy for hypertension with that for thiazides. β-Blockers were initially introduced for the treatment of angina pectoris. They were subsequently discovered to lower blood pressure in hypertensive patients with angina pectoris. Despite the widespread use of β-blockers in the management of hypertension the precise mechanism for reduction of blood pressure remains unknown.

What is a β-blocker?

β-Blockers are drugs designed to competitively inhibit β-receptors and thus to modulate activity of the sympathetic nervous system. There are 2 main classes of β-receptors, β_1 and β_2. β_1-receptor-blockers (which are cardioselective) have a greater specificity for β_1 receptors than for β_2 receptors. However, this specificity diminishes as the dose of the β-blocker increases. Some β-blockers have partial agonist (intrinsic sympathomimetic) activity. The main effect of a partial agonist is inhibition if the receptors are being stimulated and stimulation if the receptors are quiescent. An important question follows from knowledge of the mechanism of action: Do β-blockers with different mechanisms of action have different benefit–harm ratios in outcome trials? This question is examined here.

What is the evidence that β-blockers reduce cardiovascular morbidity and mortality?

Only 2 randomized trials comparing β-blockers with placebo in the first-line management of hypertension can be assessed.[2,3] Two other trials — Coope and Warrender[4] and the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) trial[5] — are sometimes quoted as providing evidence of the effectiveness of β-blockers. However, these latter studies cannot be used as evidence of the effectiveness of β-blockers as distinct from thiazides. In Coope and Warrender's

study[4] 67% of the active treatment group received bendrofluazide in addition to a β-blocker, and in the STOP-Hypertension trial[5] more than 70% of the active treatment group received hydrochlorothiazide in addition to a β-blocker.

A recent systematic review[6] compared the results of the 2 valid placebo-controlled β-blocker trials with data from 16 placebo-controlled trials in which a thiazide was used as the first-line drug. The thiazides had a statistically significant benefit in terms of all adverse outcomes, whereas the β-blockers had no significant benefit for any of the outcomes (Table 1). However, this finding cannot be taken as definitive evidence that thiazides are better, as it is based on an indirect comparison in different patient populations and the confidence intervals overlap.

Five head-to-head trials have compared first-line thiazides with first-line β-blockers.[6] In these trials there was no statistically significant difference between the two drug classes (Table 2); the data favouring thiazides over β-blockers in terms of total adverse cardiovascular events just failed to reach statistical significance. These trials involved a total of 3 different β-blockers, and it was possible to combine the mortality data for each of these agents. On this basis, the mortality rate was statistically significantly lower with thiazides than with atenolol, but there was no difference between thiazides and propranolol or metoprolol (Table 2).

Two other trials deserve mention. The International Prospective Primary Prevention Study in Hypertension trial[7] randomly assigned hypertensive patients to receive oxprenolol or placebo as first-line therapy and allowed the addition of thiazides, sympatholytic agents and vasodilator drugs as necessary. Seventy percent of the treatment group and 85% of the placebo group required additional therapy of some form. Despite lower mean blood pressure in the oxprenolol group (143.6/88.9 mm Hg) than in the placebo group (147.4/90.1 mm Hg), the addition of a β-blocker was not associated with a significant reduction in clinical events, including sudden death, myocardial infarction (MI) or stroke. The Metoprolol Atherosclerosis Prevention in Hypertensives trial,[8,9] which purportedly showed a benefit of metoprolol over hydrochlorothiazide, cannot be included, as it represents a post hoc extension of the Heart Attack Primary Prevention in Hypertension (HAPPHY) trial, and to include it would constitute double counting.[10,11]

Messerli and colleagues[12] performed a meta-analysis of β-blockers for hypertension in elderly patients and concluded that the lack of evidence of effectiveness was limited to this age group. It is true that most of the evidence of poor outcomes with β-blockers comes from the MRC trial in the elderly,[3] in which atenolol was used. However, a trend toward worse outcomes with atenolol than with thiazides was also seen in the HAPPHY trial (age range 40–64 years),[10] which suggests that the result may be specific to atenolol and unrelated to the age of the patients. However, the evidence does not consistently disfavour atenolol: a recent, relatively small trial compared atenolol with captopril,

Table 2: Adverse outcomes in 5 randomized trials comparing thiazides and β-blockers*

Outcome	Drug; total no. of events / total no. of patients: Thiazide	β-Blocker†	RR‡ (and 95% CI)
Stroke	107/8862	130/8984	0.84 (0.65–1.08)
CAD	285/8862	317/8984	0.91 (0.78–1.07)
Any cardiovascular event	431/8862	495/8984	0.88 (0.78–1.00)
Death			
With atenolol	160/2680	200/2706	0.81 (0.67–0.99)§
With metoprolol	71/1631	57/1647	1.26 (0.89–1.77)
With propranolol	136/4604	130/4684	1.07 (0.85–1.36)
Total	367/8915	387/9037	0.97 (0.84–1.11)

*Data are from Wright and colleagues.[6]
†For outcomes other than death, data for atenolol, metoprolol and propranolol are combined.
‡An RR value less than 1.0 means that the event rate was lower with thiazide than with β-blocker.
§$p < 0.05$

Table 1: Adverse outcomes in placebo-controlled trials with first-line β-blockers or thiazides*

Outcome	Treatment; no. of patients: Thiazide	Placebo	RR (and 95% CI)	Treatment; no. of patients: β-Blocker	Placebo	RR† (and 95% CI)
Stroke	284	584	0.59 (0.51–0.68)‡	98	243	0.80 (0.64–1.01)
CAD	433	703	0.84 (0.75–0.95)‡	183	393	0.92 (0.78–1.10)
Any cardiovascular event§	838	1 512	0.70 (0.64–0.75)‡	297	661	0.89 (0.78–1.02)
Death	742	1 097	0.90 (0.82–0.98)‡	287	568	1.01 (0.88–1.15)
Total no. of patients	12 118	17 233		5505	10 867	

Note: RR = relative risk, CI = confidence interval, CAD = coronary artery disease.
*Data are from Wright and colleagues.[6]
†An RR value less than 1.0 means that the event rate was lower with the drug than with placebo.
‡$p < 0.05$.
§Includes stroke, CAD, congestive heart failure and other significant vascular events (e.g., ruptured aneurysm).

Table 3: Total numbers of deaths after myocardial infarction in placebo-controlled trials of β-blockers*

β-Blocker	Treatment; total no. of events / total no. of patients		RR† (and 95% CI)
	Drug	Placebo	
Nonselective agents			
Propranolol	208/2681	271/2697	0.77 (0.65–0.92)‡
Timolol	98/945	152/939	0.64 (0.51–0.81)‡
Sotalol	64/873	52/583	0.82 (0.55–1.19)
Total	370/4499	475/4219	0.74 (0.65–0.84)‡
Cardioselective agents			
Metoprolol	195/2813	219/2752	0.86 (0.70–1.05)
Atenolol	20/138	20/140	1.02 (0.52–1.98)
Total	215/2951	239/2892	0.87 (0.72–1.05)
Partial agonists			
Acebutolol	17/298	34/309	0.50 (0.28–0.89)‡
Alprenolol	47/430	68/456	0.72 (0.49–1.07)
Oxprenolol	131/1815	102/1642	1.17 (0.90–1.53)
Pindolol	45/263	47/266	0.96 (0.61–1.51)
Total	240/2806	251/2683	0.93 (0.77–1.12)

*Includes all deaths after the β-blocker was started, in all randomized controlled trials continuing for at least 3 months after discharge.
†An RR value less than 1.0 means that the mortality rate was lower with the β-blocker than with placebo.
‡$p < 0.05$

an angiotensin-converting enzyme (ACE) inhibitor, in patients with type 2 diabetes and hypertension.[13] The risk of adverse outcome in the atenolol group relative to the captopril group (relative risk, RR) was as follows: for stroke, RR 0.90 (confidence interval [CI] 0.49–1.69); for coronary artery disease, RR 0.84 (CI 0.59–1.20); for all adverse cardiovascular events, RR 0.78 (CI 0.60–1.00); and for total deaths, RR 0.88 (0.65–1.20). Two recent trials with larger study populations, the Captopril Prevention Project[14] and STOP-Hypertension 2,[15] compared newer therapies with the combination of thiazides and β-blockers, which makes it impossible to distinguish between the benefit conferred by the thiazide or the β-blocker.

There are so few trials of β-blockers in hypertension that not much can be said about differences between drugs within this class. The best evidence of benefit for different β-blockers comes from trials of patients who have had MI. This evidence is probably relevant to hypertension for 2 reasons: a substantial proportion of post-MI patients also have elevated blood pressure, so some of the benefit in these trials could be due to a reduction in blood pressure; and a shared major outcome in antihypertensive trials and post-MI trials is coronary artery disease events, so benefit in preventing this type of event should be common to both types of trials. The data from a systematic review of the randomized placebo-controlled trials in which a β-blocker was administered for at least 3 months are relevant to this issue.[16] In addition, 2 other trials have been published since that review.[17,18] Because several β-blockers, with different actions on receptors, were used in the systematic review[16] it is possible to compare their effectiveness in terms of reduction in mortality rate. Table 3 shows that most of the nons-

Table 4: Dosing and cost of β-blockers for the treatment of hypertension

Drug	Examples of trade names	Usual dosage	Daily cost,* $
Nonselective agents			
Nadolol	Corgard, generic	10–80 mg daily	0.07–0.36
Propranolol	Inderal, generic	10–80 mg bid	0.04–0.12
	Inderal LA	60–160 mg daily	0.44–1.06
Timolol	Blocadren, generic	2.5–20 mg bid	0.17–1.04
Sotalol‡	Sotacor, generic	40–160 mg bid	0.60–1.37
Labetalol†	Trandate	100–400 mg bid	0.50–1.77
Cardioselective agents			
Atenolol	Tenormin, generic	25–100 mg daily	0.19–0.60
Metoprolol	Betaloc, Lopressor, generic	25–100 mg bid	0.13–0.45
	Betaloc SR, Lopressor SR	100–200 mg daily	0.26–0.47
Partial agonists			
Acebutolol	Sectral, Monitan, generic	100–400 mg bid	0.36–1.03
Oxprenolol	Trasicor	20–160 mg bid	0.31–1.66
	Slow Trasicor	80–320 mg daily	0.42–1.65
Pindolol	Visken, generic	2.5–15 mg bid	0.22–1.18

Note: LA = long acting, SR = slow release
*Mean drug cost to Pharmacare BC in 1999; prices may be different in other provinces.
†Also has α-blocking activity.
‡Also has class III antiarrhythmic activity.

elective β-blockers were associated with a statistically significant reduction in mortality rate, whereas almost all of the cardioselective and partial agonist β-blockers were not.

The reasons for these apparent differences are unknown. They could be due to chance alone, given that the 95% CIs overlap, or there might be a real survival advantage associated with blocking the β_2 receptor. However, other factors may be involved, such as the magnitude or duration of β-blockade and lipophilicity (a measure of the ability of the drug to enter the brain). These factors differ between the different drugs, and little or nothing is known about their effects on morbidity and mortality.

How efficacious are β-blockers in lowering blood pressure?

Data from the 5 comparative trials summarized in Table 2 have been used to compare β-blockers with thiazides as first-line therapy in terms of reduction in blood pressure.[6] In these trials, which involved totals of about 9000 patients per group, the mean reduction from baseline was 26.6/15.5 mm Hg with thiazides and 24.3/15.2 mm Hg with β-blockers. The greater reduction in systolic blood pressure with thiazides (2.3 mm Hg) was statistically significant ($p < 0.01$). This difference could be expected to have clinical significance and could explain why there is a trend toward fewer adverse outcomes with thiazide therapy. However, even a greater reduction in blood pressure with β-blockers would not be sufficient reason to choose these drugs, because morbidity and mortality evidence outweighs any surrogate parameters such as reduction in blood pressure. There is no convincing evidence that any drug class or specific β-blocker is better at lowering blood pressure than thiazides, although this issue has not been systematically studied. Different effects on other surrogate markers, such as lipids, glucose and left ventricular hypertrophy, for which there are various relationships to cardiovascular outcomes, likewise do not justify ignoring the morbidity and mortality evidence.

Do β-blockers and other drugs differ in tolerability?

For the 5 comparative trials listed in the article on thiazides[1] it was possible to quantify the rate of withdrawal from studies because of possible or probable adverse drug reactions. The mean withdrawal rate due to adverse drug reactions was 10.3% for β-blockers, significantly higher than for thiazides (7.0%) ($p < 0.01$). This difference was observed even though the trials excluded potential subjects if they had conditions for which a β-blocker might cause serious adverse effects (e.g., asthma, arteriovenous block, sick sinus syndrome or sinus bradycardia [less than 50 beats/min]).

Do β-blockers have advantages in terms of convenience or cost?

Some β–blockers do have a long enough half-life to be effective throughout a 24-h period if given only once daily. The drugs with longer half-life have an advantage in terms of convenience and are easier to titrate to the minimum dose required to achieve the desired blood pressure response. There is no evidence that supramaximal doses have any advantage, and higher doses are associated with a higher frequency of adverse effects. There are considerable differences in cost among the available β-blockers (Table 4). Even the least expensive β-blockers are many times more expensive than the least expensive thiazides.

In which patients with elevated blood pressure is a β-blocker the drug of first choice?

β-Blockers have proven effective in reducing the symptoms of angina pectoris and in reducing morbidity and mortality after MI. Therefore, in patients with elevated blood pressure and MI or angina, a β-blocker would be the drug of first choice. Although evidence is lacking, it may also be reasonable to use a β-blocker as the drug of first choice in patients in whom the drug can be used to treat more than elevated blood pressure (e.g., those with frequent recurrent migraine or hypertrophic obstructive cardiomyopathy).

Conclusion

On the basis of the available evidence of effectiveness, β-blockers are not a first-line choice for most patients with hypertension. When a β-blocker is required, the drug of choice is a nonselective agent. If drug choice is limited to those proven effective in randomized controlled trials, propranolol would be appropriate for treating elevated blood pressure and propranolol or timolol for patients with MI. Twice-daily generic propranolol is significantly less expensive than twice-daily timolol. If it is accepted that the benefits of nonselective β-blockers represent a class effect, the nonselective drug nadolol, given once daily, combines the attributes of convenience, ease of titration and reasonably low cost (Table 4).

Competing interests: None declared.

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