

Sripal Bangalore, Franz H. Messerli

St. Luke's-Roosevelt Hospital
and Columbia University,
New York, USA

Beta blockers in hypertension – to use or not to use?

The North-American answer

Summary

Traditionally, beta blockers were used as first line agents in the treatment of uncomplicated hypertension and recommended as a class by national and international guidelines despite paucity of evidence for their cardiovascular benefit. Evidence from recent trials and meta-analyses have questioned the use of beta blocker as the preferred agent. In this article we review the data available from clinical trials to argue that beta blockers are less efficacious compared to other antihypertensive agents currently available for patients with uncomplicated hypertension.

The evidence suggests that beta blockers use in patients with uncomplicated hypertension is associated with little if any cardiovascular morbidity or mortality benefit when compared to other anti-hypertensive agents or even with placebo, whether in the elderly or in the young. In contrast to newer antihypertensives such as calcium antagonists and blockers of the renin angiotensin system, beta blockers have numerous adverse effects. Based on the evidence or lack thereof, we argue that beta blockers should no longer be recommended for the treatment of uncomplicated hypertension.

Key words: beta blockers; cardioprotective; hypertension

Introduction

Recent data suggest that among anti-hypertensive drug classes, beta blockers are not efficacious as first line agents for uncomplicated hypertension. Despite similar reductions in blood pressure, beta blockers have generally demonstrated smaller reductions – or none – in cardiovascular events compared with other antihypertensive classes. However, despite these reports, beta blockers remain extensively used for this indication [1]; according to a report in *New York Times* in 2005, atenolol was the fourth most commonly prescribed drug in the United States, with 44 million prescrip-

tions per year [2]. This review discusses why beta blockers should no longer be considered for treatment of uncomplicated hypertension.

Beta blocker classes and mechanism of action

Beta blockers are a class of drugs widely used for the treatment of various clinical conditions including, but not limited to, hypertension, coronary artery disease, heart failure and arrhythmias. There are three generations of beta blockers that are available for clinical use. The first generation of beta blockers (like propranolol) are non-selective and block both β_1 and β_2 adrenoceptors. The second generation beta blockers (like metoprolol, atenolol or bisoprolol) are more cardioselective and are relatively selective for β_1 adrenoceptors. The third generation beta blockers (eg, labetalol, carvedilol, nebivolol, bucindolol) possess vasodilator actions through blockade of vascular alpha-adrenoceptors and through the release of nitric oxide [3]. The newer (3rd) generation beta blockers differ in their clinical effects and adverse effects from the older generation beta blockers. It must be emphasised that most of the evidence or lack of it for beta blockers in hypertension stems from trials on older generations of beta blockers. Hence, these results cannot and should not be extrapolated to those of newer generation agents such as carvedilol or nebivolol.

The mechanism by which beta blockers exert their antihypertensive effect has not been satisfactorily explained. One proposed mecha-

Franz H. Messerli, MD, has been an ad hoc consultant/speaker for the following organisations: Abbott, GSK, Novartis, Pfizer, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Forest, San-kyo, and Sanofi. Sripal Bangalore, MD, has nothing to disclose.

Correspondence:
Franz H. Messerli, MD, FACC, FACP
Director, Hypertension Program
Division of Cardiology
St. Luke's-Roosevelt Hospital
Columbia University College of Physicians and Surgeons
1000 10th Avenue, Suite 3B-30
New York, NY 10019, USA
E-Mail: fmesserli@aol.com

nism is reduction in cardiac output mediated by inhibition of cardiac adrenoceptors. Many forms of hypertension are associated with an increase in blood volume and cardiac output. Therefore, theoretically, reducing cardiac output by beta-blockade can be an effective treatment for hypertension, especially when used in conjunction with a diuretic. Hypertension in some patients is caused by emotional stress, which causes enhanced sympathetic activity. Beta blockers are useful in this circumstance by reducing sympathetic activity. Beta blockers also inhibit the release of renin by the kidneys (the release of which is partly regulated by β_1 -adrenoceptors in the kidney) which leads to a decrease in angiotensin II and aldosterone, resulting in renal loss of sodium and water, thereby reducing arterial pressure. Other mechanisms such as resetting of baroreceptor levels and reduction of plasma volume have also been suggested. It therefore appears that, theoretically, beta blockers should be efficacious anti-hypertensive agents in the subset of patients with high sympathetic tone and high plasma volume.

Beta blockers in uncomplicated hypertension

Despite the lack of evidence of mortality and morbidity reduction, beta blockers have been repeatedly identified as first line agents in the treatment of hypertension by many national and international guideline committees including the Joint National Commission (JNC) on the prevention, detection, evaluation and treatment of hypertension [4–6]. To the contrary, there is now significant evidence from clinical trials showing that beta blocker therapy may be associated with worse clinical outcomes compared to other currently available agents especially in the elderly.

Older trials

Earlier beta blocker trials showing morbidity and mortality benefits with beta blockers used a combination of beta blockers and diuretics. In the Swedish Trial in Old Patients (STOP) and the Systolic Hypertension in the Elderly Program (SHEP) trials, a beta blocker was given in combination with diuretics and showed a 38% relative risk reduction in all cardiovascular events and 35% risk reduction in strokes respectively [7, 8]. The national and international guidelines were based mostly on

such trials and others like Swedish Trail in Old Patients with hypertension-2 (STOP-2) [9], Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) trial [10], Nordic Diltiazem trial (NORDIL) [11] and Captopril Prevention Project (CAPPP) trial [12]. Although in some of these trials patients were started on a beta blocker, more than $\frac{2}{3}$ ended up on a combination of a beta blocker with a diuretic and no effort was made to separately analyse the morbidity and mortality effects of the beta blocker, the diuretic or the combination of the two. Many subsequent clinical trials have examined the role of beta blocker alone and failed to show similar benefits.

The British Medical Research Council (MRC) study was one of the earliest studies that questioned the use of beta blocker therapy in hypertension [13]. Beta blocker monotherapy was not only ineffective but whenever a beta blocker was added to diuretics the benefits of the anti-hypertensive therapy distinctly diminished [13]. Thus, patients who received the combination of beta blockers and diuretics fared consistently worse than those on diuretics alone, but they did somewhat better than those receiving beta blockers alone [13, 14]. Even in the recent studies like the Anglo Scandinavian Cardiac Outcomes trial (ASCOT), beta blockers were associated with 14% higher risk of coronary events and 23% increase in stroke, compared to a calcium channel blocker based regimen [15]. In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial [16], beta blocker based treatment was associated with a higher incidence of all-cause mortality and stroke compared to an angiotensin receptor blocker based regimen.

Recent data

Recent meta-analyses have further illustrated the lack of cardiovascular morbidity / mortality reduction with beta-blocker [17, 18]. Even when compared to placebo, beta blockers did not result in any significant risk reduction for the end points of all-cause mortality, cardiovascular mortality and non-fatal myocardial infarction [17, 18]. However, they were associated with a 19–20% reduction in the risk of stroke [17, 18]. This risk reduction for stroke is far less than 38% relative risk reduction as seen with other anti-hypertensive agents (compared to placebo) for the same degree of blood pressure control [19]. When compared to

other anti-hypertensive agents [17, 18], beta blockers provided no benefit for the end-points of all-cause mortality, cardiovascular mortality and myocardial infarction with a 16% increased risk of stroke.

Reasons for ineffectiveness

The reasons for lack of cardiovascular morbidity and mortality benefit of beta blockers in the treatment of hypertension could be the result of a number of factors:

Anti-hypertensive efficacy

Beta blockers reduce blood pressure compared to placebo. However, compared to other anti-hypertensive agents, the blood pressure lowering efficacy of beta blockers is suboptimal [18]. In the STOP-1 trial, blood pressure control was only half as effective in the beta blocker arm when compared to patients on a diuretic [8]. Even in more recent trials like the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial [20], blood pressure control was achieved in less than 50% of patients assigned to the beta blocker group and less than 10% of patients remained on beta blocker monotherapy. In the ASCOT-BPLA trial, amlodipine based treatment resulted in a 1.7 mm Hg mean lower systolic pressure and 2.0 mm Hg mean lower diastolic pressure, associated with a 14% lower risk of coronary events and 23% lower risk of stroke compared to atenolol based treatment [15]. In an analysis of 10 trials involving 16164 elderly hypertensive patients assigned to beta blockers or diuretics, hypertension was controlled in 66% of patients assigned to diuretic monotherapy, but was controlled in less than 1/3 of patients on beta blocker monotherapy [21].

Pseudo anti-hypertensive efficacy

Beta blockers are less efficacious at reducing central aortic pressure when compared to renin angiotensin aldosterone system (RAAS) blockers, diuretics and calcium antagonists [22, 23]. In the Conduit Artery Functional Endpoint (CAFÉ) study [24], for the same peripheral blood pressure, a 4.3 mm Hg higher central aortic systolic blood pressure and 3.0 mm Hg higher central aortic pulse pressure was noted with atenolol based treatment compared to the amlodipine based treatment resulting in a 14% higher risk of coronary events and 23% increase in stroke rate [24]. The study suggested that the central aortic systolic blood pressure (measured indirectly by radial artery applanation tonometry) may be more predictive of cardiovascular events, such as stroke

and myocardial infarction, than the traditional peripheral (brachial) blood pressure measurements. Thus, beta blockers (atenolol) have a pseudoantihypertensive effect – they lower brachial blood pressure (as measured by cuff) much better than they lower central aortic pressure.

Metabolic side effects-new onset diabetes

Beta blockers have been shown to increase insulin resistance and predispose patients to diabetes. The Atherosclerosis Risk in Communities (ARIC) study showed that beta blocker use was associated with a 28% greater risk of developing diabetes compared to subjects who took no medication [25]. Similar results were shown in the ASCOT-BPLA study and the INVEST trial, where beta blocker therapy was associated with higher risk (30% and 17% respectively) of developing diabetes compared to the comparison drugs [15, 26]. In a “network meta-analysis” of 22 clinical trials with 143153 participants who did not have diabetes at randomisation, the risk of new onset diabetes was most pronounced with diuretics and beta blockers, more so than with placebo or other classes of antihypertensive agents, implying a negative metabolic effect of these medications [30]. We have shown in a meta-analysis of 12 studies evaluating 94 492 patients, that beta blocker therapy resulted in a 22% increased risk of new onset diabetes compared to non-diuretic antihypertensive agents [27]. The results of our analyses lets us calculate that treatment of 1000 patients with a beta blocker for 4.4 years will result in 14 excess cases of diabetes, 3 excess deaths and 4.7 excess strokes [27] – hardly an acceptable risk benefit ratio! Given that in the United States over 10 million of patients are on beta blockers for hypertension, this translates to 140 000 extra cases of diabetes, 30 000 deaths and 47 000 strokes for the same time period.

Metabolic side effects-dyslipidemia

Dyslipidaemia per se is linked to increased risk for cardiovascular disease. Studies have shown that >50% of patients with hypertension also have concomitant dyslipidaemia [28]. Hence prevention of dyslipidaemia in patients with hypertension is of foremost importance. However, studies have shown that diuretics and beta blockers used for the treatment of hypertension can cause dyslipidaemia. Chronic administration of beta blockers may increase triglyceride levels by 20–50% and decrease HDL-C by 10–20% [29]. However, dyslipidaemia with beta blockers decreases with in-

creasing cardio selectivity and increasing intrinsic sympathomimetic activity.

Decreased compliance

Beta blockers are often not well tolerated and the compliance rate with these medications are dismal. In a meta-analysis of randomised controlled trials, the risk of treatment withdrawal with beta blockers was 80% higher compared to diuretics and 41% higher when compared to RAAS blockers, respectively [30]. Beta blockers as a class have many undesirable adverse effects including drowsiness, lethargy, sleep disturbance, visual hallucinations, depression, blurring of vision, dreams/nightmares, decreased exercise tolerance [31], pulmonary side effects such as increased airway resistance in asthmatics and peripheral vascular side effects such as cold extremities, Raynaud's phenomenon and erectile dysfunction. The MRC study allows us to calculate that for every myocardial infarction or stroke prevented, 3 patients treated with atenolol withdrew from the study secondary to impotence and another 7 withdrew because of fatigue [32].

Cost effectiveness

Patient compliance with medication depends on multiple factors including economic costs of the drugs. Previously, the guideline committees endorsed thiazides and beta blockers as first line agents given the actual cost of medication. However, such an approach does not take into consideration the efficacy and effectiveness of medication. The ideal cost-effectiveness analysis should consider the relative effectiveness of different drugs on clinical outcomes, the direct and indirect cost associated with long term sequelae with the medications (like development of diabetes) and the actual cost of the drug itself.

Such a formal cost-effectiveness analysis was performed by the National Institute for Health and Clinical Excellence (NICE). Based on their economic model they concluded that thiazide diuretics are the most cost-effective agent followed by calcium channel blockers [33]. Beta blockers were the least cost effective option. Given the metabolic adverse effects of beta blockers, its direct and indirect cost, and the direct and indirect cost of increased stroke risk in the elderly, beta blockers are not cost effective for this indication.

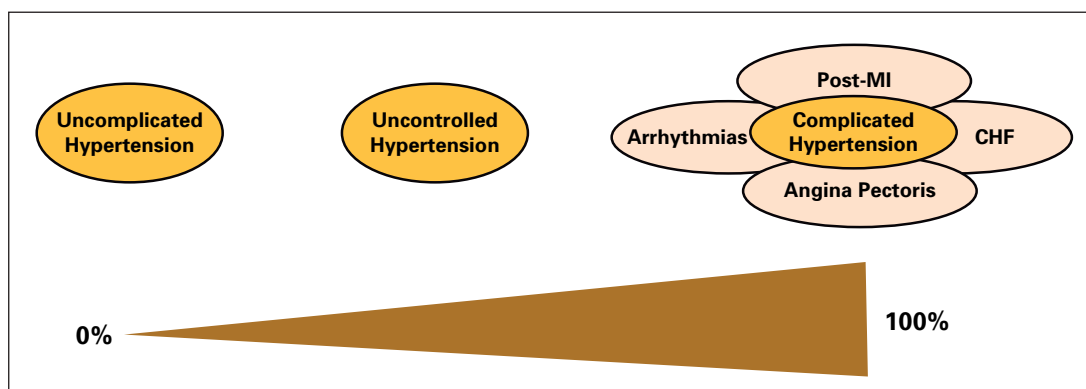
Role in younger patients

Younger patients are seldom included in clinical trials for hypertension so therefore, there is not much evidence to base the treatment of younger patients on. In a meta-analysis by Khan et al. [34], in the cohort of studies on younger patients (mean age <60 years), beta blockers were not associated with any benefit for the end points of all-cause mortality (OR = 0.94; 95% CI = 0.79–1.10), myocardial infarction (OR = 0.85; 95% CI = 0.71–1.03) or stroke (OR = 0.84; 95% CI = 0.65–1.10) when compared against placebo. When compared to other anti-hypertensive agents, though there was no increased risk of stroke (as seen with the elderly cohort), there was no benefit either for the end points of all-cause mortality, myocardial infarction or stroke [34]. Given the deleterious metabolic effects of these medications and the need for chronic treatment, the long term outcomes with these medications in the younger cohort may be far from desirable.

Compelling indications

The use of beta blockers remains appropriate in patients with certain co-morbidities. In patients with known ischaemic heart disease or heart failure, beta blocker treatment is associated with substantial reduction in mortality (fig. 1). In a hypertensive patient with a com-

Figure 1
Proposed use of beta blockers for hypertension. In patients with uncomplicated hypertension beta blockers should not be used as first line agents. However, in patients with uncontrolled hypertension on various other anti-hypertensive agents and in those with complicated hypertension, betablockers should be considered in the armamentarium of treatment.



elling indication for beta-blockade, should the beta blocker be used for both hypertension and the compelling indication (*ie*, to kill two birds with one stone)? Although treating two conditions with one drug certainly is attractive from a cost-effectiveness point-of-view, there is no evidence that such an approach is efficacious. We therefore go one step further than the NICE/British Hypertension Society Guidelines and suggest in such a patient, to use a beta blocker for the compelling cardiac indication *and* to prescribe a BP-lowering agent drug that has been shown to reduce morbidity and mortality for hypertension [1].

Physicians' misperception of beta blocker efficacy in hypertension

Unfortunately physicians still perceive beta blockers as exceedingly efficacious antihypertensive drugs. This is true not only for reduction of blood pressure but also outcome benefits such as decrease in stroke, heart attack and death. In a recent survey [35] in which physicians were asked "Which of the following class of drugs have been proven to reduce the risk of stroke in hypertensive patients?" beta blockers were considered by far the most effective and calcium antagonists the least effective class. Similarly, when asked, "Which of the following classes of drugs have been proven to reduce mortality in hypertensive patients?" beta blockers were rated highest followed by ACE inhibitors, thiazides and calcium antagonists diuretics respectively. These perceptions or misperceptions are unfortunate and obviously must be considered as long lasting repercussions of deceptive marketing by the pharmaceutical industry that beta blockers were "cardioprotective".

Newer beta blockers

The newer vasodilating beta blockers (carvedilol / nebivolol) may have more beneficial cardiovascular effects than the traditional agents. Since these drugs are vasodilating they maintain cardiac output, reduce peripheral resistance and have a lesser effect on heart rate. Not surprisingly, they are some-

what more effective than traditional beta blockers in reducing blood pressure. Additionally, vasodilating beta blockers have a favorable metabolic profile in that they improve insulin sensitivity, oxidative stress, adiponectin levels and decrease plasma soluble P-selectin levels in hypertensive patients [36]. When compared to traditional beta blockers, vasodilating agents have a lesser effect on glycaemia and on dyslipidaemia [37]. Other findings that make them attractive are the release of NO from the endothelium, the reduction of platelet activation [38] and regression of left ventricular hypertrophy [39]. Additionally, vasodilating beta blockers are, in general, better tolerated than the traditional agents [40] and thereby may improve the patient's compliance with the medication. We should remember however, that all of the above features are surrogate endpoints which certainly make these agents more attractive. However, in hypertension there are no morbidity and mortality studies available with vasodilating beta blockers that allow us to conclusively evaluate their efficacy.

Outcome evidence

Of note, the lack of outcome evidence for beta blockers mainly pertains to hypertension. With regard to other cardiovascular disease entities such as congestive heart failure and patients who have suffered an acute myocardial infarction, beta blockers remain a cornerstone in the therapeutic arsenal [41] (table 1).

Conclusion

In patients with primary hypertension there is paucity of evidence to suggest the beneficial effects of beta blocker when used as monotherapy. As discussed above, several studies have indicated that beta blockers as a class are not as effective as other antihypertensive drug classes in the prevention of cardiovascular events and several meta-analyses of major

Table 1
Outcome evidence for beta blockers in cardiovascular disease.

| | surrogate endpoint evidence | outcome evidence |
|---------|-----------------------------|------------------|
| HTN | good | weak to none |
| CHF | weak | good |
| POST MI | good | good |
| HOCM | good | none |
| PERIOP | good | weak |

HTN = hypertension; CHF = chronic heart failure; POST MI = post myocardial infarction; HOCM = hypertrophic obstructive cardiomyopathie; PERIOP = perioperative.

clinical trials in hypertension have concluded that beta blockers should not be used as first-line treatment in primary hypertension. Furthermore, the prevalence of adverse effects and cost associated with beta blocker treatment are too high to use this class of medicine without the evidence of its benefits.

Recently the American Heart Association council for high blood pressure research and the European Society of Hypertension / European Society of Cardiology declared that they too are no longer endorsing beta blockers as first line treatment for uncomplicated hypertension [42, 43].

With the new evidence from the National Institute for Clinical Excellence (NICE) [33], the British guidelines committee was quick to update its recommendations for the pharmacological management of primary hypertension. This was based on analysis of data from clinical trials comparing the different classes of anti-hypertensive medication or their combinations head-to-head. Based on this analysis the guidelines strongly suggest that beta blockers should no longer be used as first, second or third line therapy for uncomplicated hypertension [33]. Thus, there is clearly no evidence supporting the use of beta blockers for first-line therapy in uncomplicated hypertension. However, we maintain that, unfortunately, it will prove to be difficult to remove the physician's security blanket which was founded on the notion that beta blockers will "protect and stabilise the heart of the hypertension patient."

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