

# How useful are $\beta$ -blockers in cardiovascular disease?

## *Kardiyovasküler hastalıklarda $\beta$ -blokerler ne kadar yararlı?*

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### ABSTRACT

Recent studies have shown that  $\beta$ -blockers in patients with hypertension is associated with an increased risk of cardiovascular events, in particular stroke, leading to headlines speculating the end of the  $\beta$ -blocker era. The objective of this review is to critically examine the usefulness of  $\beta$ -blockers in cardiovascular diseases. We reviewed the currently available evidence for the usefulness of  $\beta$ -blockers in patients with hypertension and also assessed the efficacy of its use for other indications, like, chronic heart failure, stable angina, myocardial infarction, arrhythmias etc. The review of the currently available literature shows that for patients with uncomplicated hypertension, there is paucity of data or absence of evidence to support use of  $\beta$ -blockers as monotherapy or as first line agent. Given the risk of stroke and numerous unacceptable adverse effects, the risk benefit ratio for  $\beta$ -blockers is not acceptable for this indication. However,  $\beta$ -blockers are very efficacious agents for the treatment of heart failure, certain types of arrhythmia, and post myocardial infarction. The various guideline committees should seriously reconsider their decision about their endorsement of  $\beta$ -blockers as first line therapy for uncomplicated hypertension. However, this is applicable for hypertension and  $\beta$ -blockers continue to be efficacious for other indications. (*Anadolu Kardiyol Derg 2006; 6: 358-63*)

**Key words:**  $\beta$ -blockers, cardiovascular disease, hypertension

### ÖZET

Son zamanlarda yayınlanan çalışmalar hipertansiyonu olan hastalarda beta-blokerlerin kardiyovasküler olaylar ve özellikle inmenin riskini artırdığını göstermiş ve böylece "beta-blokerlerin dönemi sona erdi" gibi spekülatif başlıklara yol açmışlar. Bu derlemenin amacı, kardiyovasküler hastalıklarda beta-blokerlerin yararlarını kritik olarak değerlendirmektir. Biz, hipertansiyon tanısı olan hastalarda beta-blokerlerin yararları ile ilgili şu anda mevcut olan kanıtları derledik ve aynı zamanda bu ilaçların başka endikasyonlarını, kronik kalp yetersizliği, stabil anjina, miyokard infarktüsü ve aritmiler gibi nedenler ile kullanımda faydalarını da değerlendirdik. Mevcut kaynakların derlemesi komplikasyonsuz hipertansif hastalarda beta-blokerlerin monoterapi veya birincil ajanı olarak kullanımını destekleyen kanıtların olmadığını ve bu konuda veri yetersizliği olduğunu gösterdi. İnme ve kabul edilmesi mümkün olmayan birçok yan etkileri göz önüne alındığında, bu endikasyon için beta-blokerlerin risk/yarar oranı kabul edilemez. Ancak, beta-blokerler miyokard infarktüsü sonrası, belli aritmilerin tedavisinde ve kalp yetersizliği tedavisinde çok yararlı ajanlardır. Farklı kılavuz komiteleri, beta-blokerlerin komplikasyonsuz hipertansiyonda birincil ajan olarak onaylanması hakkındaki kararlarını ciddi olarak yeniden incelemelidir. Ancak bu hipertansiyon için geçerlidir ve beta-blokerlerin başka endikasyonlar için yararları devam etmektedir. (*Anadolu Kardiyol Derg 2006; 6: 358-63*)

**Anahtar kelimeler:**  $\beta$ -blokerler, kardiyovasküler hastalığı, hipertansiyon

### Introduction

From a medication originally developed for ischemic heart disease,  $\beta$ -blockers now have a wide range of indications, from hypertension to heart failure and are the fourth largest selling medication in the United States (1). However, recent analyses (2,3) has shown that in patients with hypertension and no known coronary artery disease,  $\beta$ -blockers as first line antihypertensive therapy was associated with high risk of stroke and the authors conclude that  $\beta$ -blockers should not be recommended as first-choice agents in the treatment of hypertension or be used as reference drugs in future randomized controlled trials of hypertension; an observation which we made more than half a

decade earlier in elderly hypertensive patients (4). In his editorial, Beevers (5) notes that many national guidelines committee should rethink their stand on  $\beta$ -blockers as reasonable first-line medication for treatment of hypertension and the NHLBI may have to rethink its proposal to include  $\beta$ -blockers in long term outcome studies. Does this mark the end of the  $\beta$ -blocker era? (5) How solid are the data on which is based the widespread use of  $\beta$ -blockers in cardiovascular disease?

### $\beta$ -Blockers in Hypertension

For three decades,  $\beta$ -blockers have been widely used in the treatment of hypertension and are still recommended as first line

agents by most national and international guidelines. However, ever since the Veterans Administration study in the 1970s, multiple and prospective randomized trials have documented that diuretic-based therapy reduces the risk of stroke and, to a lesser extent, of myocardial infarction and cardiovascular morbidity and mortality. However, the data are much less convincing for  $\beta$ -blockers. In fact, no trial has shown that lowering blood pressure with a  $\beta$ -blocker reduces the risk of heart attack, stroke or other cardiovascular events in patients with hypertension compared with placebo.

### Effects on Morbidity and Mortality

It is somewhat ironic that after 3 decades of using  $\beta$ -blocker for hypertension, no study has shown that their monotherapeutic use has reduced morbidity or mortality in elderly hypertensive patients compared with placebo.

In the British Medical Research Council (MRC) study in the elderly published in 1992,  $\beta$ -blocker monotherapy was not only ineffective but, interestingly enough, whenever a  $\beta$ -blocker was added to diuretics, the benefits of the antihypertensive therapy distinctly diminished (6). 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 on  $\beta$ -blockers alone (6).

Thirteen years later, in the Anglo-Scandinavian Cardiac Outcomes Trial- Blood Pressure Lowering Arm (ASCOT-BPLA) study of 19,257 patients with hypertension and at least 3 other coronary risk factors but no coronary artery disease (CAD),  $\beta$ -blocker (atenolol) based treatment resulted in a 14% higher risk of coronary events and 23% increase in stroke rate compared to calcium antagonist (amlodipine) based regimen (7).

Back in 1998, we had documented that although blood pressure was lowered significantly by  $\beta$ -blockers, these drugs were ineffective in preventing coronary artery disease and cardiovascular and all-cause mortality (odds ratio, 1.01, 0.98, and 1.05, respectively) (4). Our meta-analysis showed that diuretic therapy was superior to  $\beta$ -blockers with regards to all endpoints (fatal and nonfatal strokes, cardiovascular events, and cardiovascular and all-cause mortality) (4).

Seven years later, in a meta-analysis of 134,000 patients on antihypertensive therapy, Lindholm et al showed that  $\beta$ -blocker treatment was associated with a 16% higher incidence of stroke compared to other hypertensive treatment, confirming and extending our observation (3). This was the case when all  $\beta$ -blockers were analyzed together and when atenolol was analyzed separately as a subgroup (3).

Similarly, in a meta-analysis of 6825 patients, who were followed up for a mean of 4.6 years there was no outcome difference on all-cause mortality, cardiovascular mortality and myocardial infarction (MI) between treatment strategy with atenolol when compared to placebo (8). When compared to other hypertensive therapy, atenolol treatment resulted in higher all-cause mortality, trend towards higher cardiovascular mortality and stroke (8).

In a meta-analysis of 42 clinical trial involving 192,478 patients, treatment with a diuretic was found to be the most effective first line agent for preventing the occurrence of cardiovascular morbidity and mortality. Compared with low-dose diuretics,  $\beta$ -blockers were associated with a 11% increased risk of cardiovascular disease events (9).

### Effects on Blood Pressure

Prior studies have shown that the blood pressure lowering effects of  $\beta$ -blockers are not different from that of other antihypertensive agents. However, in our analysis of patients who received  $\beta$ -blocker as a first line drug, less than a third were controlled on monotherapy and about two thirds required a diuretic as a supplement (4). In the Swedish Trial in Old Patients with hypertension-1 (STOP-1) study, blood pressure control was only half as good in the  $\beta$ -blocker arm when compared to patients on a diuretic (10). In the ASCOT-BPLA trial amlodipine based treatment resulted in a 1.7 mm Hg mean lower systolic blood pressure and 2.0 mm Hg mean lower diastolic blood pressure, resulting in a 14% lower risk of coronary events and 23% decrease in stroke rate compared to  $\beta$ -blocker (atenolol) based treatment (7). In fact, a 5-6 mm Hg blood pressure reduction reduces coronary heart disease risk by 16% and stroke risk by 38% (11).

However, a separate analysis of the ASCOT trial found that adjusting for differences in weight, heart rate, metabolic variables and even blood pressure explained only about 50% and 40% of differences in coronary and stroke events respectively (12). The authors hypothesized that the rest of the difference may be secondary to the effect of the drug itself (atenolol) - such as its effect on central blood pressure (12). In fact,  $\beta$ -blockers differ in their effect on central aortic blood pressure when compared to peripheral brachial pressure. When compared to Angiotensin Converting Enzyme Inhibitors (ACEi), diuretics and Calcium Channel Blockers (CCBs),  $\beta$ -blockers do not lower central systolic blood pressure. The results of the Conduit Artery Functional Endpoint (CAFE) (13) study suggests that a CCB based treatment is much more effective at reducing central aortic blood pressure than a conventional atenolol-based ( $\beta$ -blocker) regimen. 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 (13). The study also strongly suggests that the central aortic blood pressure may be more predictive of cardiovascular events, such as stroke and heart attack, than traditional peripheral (brachial) blood pressure measurements.

### Effects on Heart Rate

$\beta$ -blockers reduce heart rate. Prior epidemiological studies have shown that increased heart rate is an independent risk factor for all-cause and cardiovascular mortality, independent of other risk factors for atherosclerosis and in subjects with or without co-morbidities (including hypertension) (14). It is also a well known fact that well trained athletes' have a low resting heart rate. However, it is yet to be determined if increased heart rate is a mere marker of patients overall cardiovascular condition and disease progression (indicator of systolic/diastolic heart failure, high sympathetic tone etc) rather than a risk factor per se. Other than in patients with acute myocardial infarction, no study to date has shown that reducing heart rate using  $\beta$ -blocker reduces cardiovascular events in patients with uncomplicated hypertension. It is interesting to note that, in the meta-analyses on patients with hypertension, there was no cardiovascular benefit for a  $\beta$ -blocker when compared to agents which does not affect heart rate (like ACEi, diuretics and non dihydropyridine CCBs) (3,4,8). In patients with heart failure, though both dihydropyridine

CCBs and β-blockers reduce heart rate, their efficacy for reducing cardiovascular end points is not similar. Thus reducing heart rate per se (other than aerobic training) with medications in patients without acute MI may not translate to reduced cardiovascular events. Given this controversy, there are no clear cut guidelines for heart rate reduction in patients with uncomplicated hypertension, unless patient is tachycardic or is symptomatic from the increased heart rate (14).

#### β -Blockers: Adverse Effects

**1. New Onset Diabetes:** Since 1960s, the metabolic side effects of β-blockers have been widely studied. β-blockers have been shown to increase insulin resistance. In a meta-analysis of 10 studies involving 76949 patients, a significantly higher incidence of diabetes in patients randomly assigned to β-blockers or thiazides was found (15). The authors rightfully conclude that “the routine combined use of a thiazide with a β-blocker should be questioned in the early management of hypertension, particularly in patients who are at increased risk of developing new-onset diabetes. In such patients, the increased risk of developing diabetes may exceed the benefit of blood pressure lowering” (15). The Atherosclerosis Risk in Communities (ARIC) study, analyzed 12,550 patients without diabetes, on antihypertensive therapy. The results, showed that risk of diabetes was 28% greater among those who were on β-blockers than among those who were on no medication (16). In the ASCOT-BPLA study, there was a 30% increased incidence of new onset diabetes in the β-blocker (atenolol) arm when compared to the amlodipine arm (7). In the International Verapamil-SR Trandolapril Study (INVEST), a β-blocker (atenolol) based strategy was associated with a 17% risk of new onset diabetes compared to a verapamil strategy (17).

Potential mechanisms by which β-blockers may contribute to the development of diabetes include weight gain, attenuation of the β-receptor-mediated release of insulin from pancreatic β-cells, decreased blood flow through the microcirculation in skeletal-muscle tissue, leading to decreased insulin sensitivity (18). Of note however, not all β-blockers are created equal with regard to insulin sensitivity. In the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial, glucose metabolism was not affected when carvedilol was added in diabetic hypertensive patients, whereas it significantly deteriorated when metoprolol was added (19).

#### 2. Effects on Left Ventricular Hypertrophy (LVH) Regression:

Left ventricular hypertrophy is a strong predictor of cardiovascular mortality and morbidity. Left ventricular hypertrophy regression lowers the likelihood of cardiovascular morbidity and mortality, independent of blood pressure lowering effects. In the Losartan Intervention for Endpoint reduction (LIFE) study, antihypertensive treatment with losartan based therapy resulted in greater LVH regression in patients with electrocardiographic LVH than conventional β-blocker (atenolol)-based treatment (20). In a meta-analysis of 104 studies comparing the effects of various anti-hypertension strategies on LVH regression, β-blocker based therapy produced the least LVH regression compared to ACEi, CCB and diuretics (21). Unlike β-blockers, ACEi/ARBs has been shown to decrease collagen content in the myocardium and hence a beneficial effect on LVH regression (22).

#### 3. Weight Gain: All hypertension management guidelines re-

commend weight loss as the first line management in obese hypertensive patients. β-blockers have however been shown to cause a small but systematic weight gain. In the few hypertension studies, which do report the weight status, β-blockers results in a weight gain by as much as 1.2 kg (23). The weight gain secondary to β-blockers have been attributed to the effect of β-blockers on decreasing the metabolic activity by as much as 10% and also on other effects on energy metabolism (23). Studies have shown that compared to patients who maintain the same weight or lose weight, patients who gain weight have a 2-3 folds higher risk of developing diabetes (24). The usefulness of β-blockers in obese patients or patients with risk factors for diabetes is thus questionable. Of note, in GEMINI there was no weight gain with carvedilol; where as patients on metoprolol gained 1.3 kg after only 6 months (19).

**4. β -Blockers and Exercise Endurance.** Exercise endurance in a healthy person depends in part on a properly functioning sympathetic nervous system. β-blockers by antagonizing this effect may hamper exercise capacity (25). In fact studies done nearly half a century earlier, have shown that surgical sympathetic denervation of heart hinders exercise performance in dogs (26). The mechanism of reduced exercise tolerance in subjects on β-blockers in part is secondary to the hemodynamic effects, i.e., decrease in heart rate, cardiac output and mean arterial pressure. β-blockers also affect the glucose and lipid metabolism and this is hypothesized as one of the mechanism for reduced exercise tolerance. In 1965, Braunwald et al (27) observed that propranolol in healthy volunteers reduced the exercise endurance by 40% along with significant reduction in heart rate, cardiac output, mean arterial pressure, left ventricular minute work and central venous pressure. The results were similar in patients with heart disease. In patients with hypertension on β-blockers, a reduction in exercise tolerance in part could be attributable to be secondary to β-blockers (28). Many other studies since then have shown a clear reduction in exercise endurance in young healthy test subjects and trained sportsmen (29). In sharp contrast, in patients with coronary artery disease an improvement in exercise tolerance with β-blocker therapy has been shown (30). This discrepancy between the two groups has been attributed to differing behavior of the cardiovascular system in health and in disease states.

**5. Others.** β-blockers have a long list of adverse effects including lethargy, sleep disturbance, visual hallucinations, depression, blurring of vision, troublesome dreams, pulmonary effects such as increased airway resistance in asthmatics and peripheral vascular effects such as cold extremities, Raynaud's phenomenon, erectile dysfunction etc. The MRC study allows us to calculate that for every heart attack or stroke prevented, 3 patients withdrew from the study secondary to impotence and another 7 withdrew because of fatigue (31). For a completely asymptomatic disease such as mild hypertension, this is hardly an acceptable risk/ benefit ratio.

#### Risk Benefit Ratio

There are now at least 3 to 4 meta-analyses showing an increased incidence of stroke in patient treated with β-blockers as first line therapy. In extrapolating this data, it appears that the number needed to harm (NNH) based on this is 476 patients. The data is worse with atenolol with NNH ranging from 79 to 133, i.e.,

treating 79 patients with  $\beta$ -blockers results in 1 stroke. Given that 52 million patients have hypertension, this would account for about 520,000 strokes (taking an average NNH of 100). As always the NNH should be weighed against the benefits of this medication. However, since no study has shown the benefits of  $\beta$ -blockers for all-cause mortality or cardiovascular mortality when used as monotherapy for hypertension, their use for this indication clearly violates the principle of *primum non nocere*.

#### Joint National Committee

Since the conceptualization of the Joint National Committee for evaluation and treatment of hypertension (JNC) in the United States, the definition of a normal blood pressure has been brought down lower and lower.  $\beta$ -blockers along with diuretics were regarded as the preferred first line of treatment from 1984 to 1993 (JNC III to VI), though there was a consistent paucity or even absence of data to show the beneficial effects of  $\beta$ -blockers as first line agents for hypertension. The JNC VII recommends diuretics as the first line and  $\beta$ -blockers can be used for "compelling" indications, an indication, which should be further emphasized in future JNC recommendations as well as recommendations from other bodies (32). However, in patients with "compelling" indication for  $\beta$ -blocker, it is unknown if the beneficial effect of  $\beta$ -blockers is secondary to blood pressure lowering effects. In such patients, addition of a non  $\beta$ -blockers agent for hypertension and  $\beta$ -blockers for the compelling indication may be justifiable (33).

#### Congestive Heart Failure

Because of their initial transient negative inotropic effects,  $\beta$ -blockers were traditionally considered contraindicated in patients with heart failure (HF). However, many studies have shown that  $\beta$ -blockers bring about a substantial reduction in mortality (~30%) and morbidity, improvement in symptoms and the patient's well-being (34-37). Treatment of 15 to 43 patients with HF prevents one death and thus  $\beta$ -blockers are very effective in patients with HF. Present American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend that in patients with systolic HF, an ACE inhibitor should be used first, and a  $\beta$ -blocker should be started at low doses and gradually increased over 12 weeks (38).  $\beta$ -blockers probably act to protect the heart from the harmful effects of norepinephrine and epinephrine. Consequently,  $\beta$ -blockers along with ACEi form the cornerstone for the treatment of heart failure in patients who can tolerate the medication.

#### Coronary Artery Disease

The ACC/AHA Committee recommends  $\beta$ -blocking agents as first line therapy for chronic stable angina (39). This is based on two pieces of evidence: first, the evidence of improved mortality with  $\beta$ -blockers in post MI patients, and, second, by extrapolation from the supposed effects of these agents in hypertension, where the guidelines believe that  $\beta$ -blockers reduce mortality (40). The first statement is reasonable but extrapolating this evidence to patients with stable angina but no prior MI may be erroneous. However, we now have sufficient data to support the fact that  $\beta$ -blockers either used as monotherapy or as first line

agents for hypertension have no mortality benefits and increases the risk for stroke. Others have suggested that in patients with stable angina and no prior MI, a CCB may be as beneficial without the adverse effects of insulin resistance, weight gain, decreased exercise tolerance and sexual dysfunction associated with  $\beta$ -blockers (40).

#### Post MI

Since it was first reported in 1965 that administration of propranolol after acute MI reduced mortality (41), there is now an increasing evidence that  $\beta$ -blockers reduce mortality, coming both from meta-analyses of randomized trials (42) and from observational studies (43). These studies have shown that  $\beta$ -blockers reduce mortality by about 23% in prospective trials and up to 40% in observational studies (42,43). Treatment of 84 patients for 1 year prevents one death and treatment of 107 patients with  $\beta$ -blockers for 1 year avoids one non-fatal reinfarction and the benefit is stronger with long term use rather than short term (44). The number needed to treat to achieve mortality reduction is much less for  $\beta$ -blockers when compared to antiplatelet agents or statins use post MI (44). The evidence for  $\beta$ -blockers in post MI patient is thus strong and patients should not be denied the benefits from  $\beta$ -blockade where appropriate. However, most of these trials were done in the era of medical management of MI and it is largely unknown if the benefits holds true in the era of open artery (45).

#### Other Indications

$\beta$ -blockers have been shown to reduce tachycardia and arrhythmias of everyday stress in pilots undergoing simulated flights, public speaking, racing car drivers etc (46).  $\beta$ -blockers are efficacious in the treatment of supraventricular arrhythmias (47) and effective in the control of ventricular arrhythmias related to sympathetic activation and prevents sudden cardiac death (43).

$\beta$ -blockers are also efficacious in patients with hypertrophic cardiomyopathy, both for the reduction of symptoms and preventing sudden cardiac death (48). However, in patients with mild to moderate hypertrophic cardiomyopathy, treatment with  $\beta$ -blocker (nadolol) resulted in a greater decrease in peak exercise work load compared to a verapamil strategy (49).

$\beta$ -blockers are used pre operatively in patients undergoing non cardiac surgery to prevent ischemic events and arrhythmias (50).

#### Summary

For patients with uncomplicated hypertension, there is consistent paucity of data or even absence of evidence to support the use of  $\beta$ -blockers as monotherapy. Given the risk of stroke and the various other unacceptable adverse effects, the risk-benefit ratio for  $\beta$ -blockers is far from being favorable. The various guideline committees should seriously reconsider their decision about their endorsement of  $\beta$ -blockers as first line therapy for uncomplicated hypertension.

However, it must be clearly emphasized that all outcome studies showing no benefit in hypertension were carried out with traditional  $\beta$ -blockers, such as atenolol and metoprolol. It may

thus be prudent not to extrapolate these results to the newer vasodilating agents such as nebivolol, lisoprolol and carvedilol, which have more favorable hemodynamic profile. Before we throw out the "baby with the bathing water", it should also be emphasized that the adverse results with β-blockers are in patients with uncomplicated hypertension. There is data to support the use of β-blockers for other indications like heart failure, supraventricular arrhythmias, hypertrophic cardiomyopathy etc and hence these results should not be extrapolated for such indications.

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