

STATE-OF-THE-ART PAPER

# Cardiovascular Protection Using Beta-Blockers

## A Critical Review of the Evidence

Sripal Bangalore, MD, MHA,\* Franz H. Messerli, MD,\* John B. Kostis, MD,† Carl J. Pepine, MD‡  
*New York, New York; New Brunswick, New Jersey; and Gainesville, Florida*

For more than 3 decades, beta-blockers have been widely used in the treatment of hypertension and are still recommended as first-line agents by national and international guidelines. Recent meta-analyses indicate that, in patients with uncomplicated hypertension, compared with other antihypertensive agents, first-line therapy with beta-blockers was associated with an increased risk of stroke, especially in the elderly cohort with no benefit for the end points of all-cause mortality, cardiovascular morbidity, and mortality. In this review, we critically analyze the evidence supporting the use of beta-blockers in patients with hypertension and evaluate evidence for its role in other indications. The review of the currently available literature shows that in patients with uncomplicated hypertension, there is a paucity of data or absence of evidence to support use of beta-blockers as monotherapy or as first-line agents. Given the increased risk of stroke, their "pseudo-antihypertensive" efficacy (failure to lower central aortic pressure), lack of effect on regression of target end organ effects like left ventricular hypertrophy and endothelial dysfunction, and numerous adverse effects, the risk benefit ratio for beta-blockers is not acceptable for this indication. However, beta-blockers remain very efficacious agents for the treatment of heart failure, certain types of arrhythmia, hypertropic obstructive cardiomyopathy, and in patients with prior myocardial infarction. (*J Am Coll Cardiol* 2007; 50:563-72) © 2007 by the American College of Cardiology Foundation

On November 14, 2005, the *New York Times* reported that beta-blockers (atenolol) were the fourth most-prescribed drug in the U.S., with 44 million prescriptions yearly (1). Clearly, most of these prescriptions were for hypertension and, during the past decade, national and international guidelines have promoted beta-blockers to be used on an equal footing with thiazide diuretics, calcium antagonists, or renin angiotensin aldosterone system (RAAS) blockers for initial therapy of hypertension (2-4). According to authoritative sources who drafted these guidelines, this preferred status was supposedly based on evidence documenting reduction in morbidity and mortality with beta-blockers in hypertension. A closer look at the available evidence has cast serious doubt on efficacy and safety of beta-blockers for hypertensive cardiovascular disease.

From \*St. Luke's-Roosevelt Hospital and Columbia University, New York, New York; †University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, New Brunswick, New Jersey; and the ‡University of Florida College of Medicine, Gainesville, Florida. Dr. Messerli is on the Speakers' Bureau of Abbott, GlaxoSmithKline, Novartis, Pfizer, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Forest, Sankyo, and Sanofi and has received research/grants from GlaxoSmithKline, Pfizer, Novartis, and CardioVascular Therapeutics. Dr. Kostis has received grants from Pfizer. He is an advisor/consultant to Pfizer, Schering-Plough, Berlex, and Taisho and is on the Speaker's Bureau of Pfizer, Merck, and Bristol-Myers Squibb. Dr. Pepine has consulted for Abbott Laboratories and CV Therapeutics and received grants from Abbott Laboratories, AstraZeneca, Berlex Laboratories Inc., CV Therapeutics, GlaxoSmithKline, King Pharmaceuticals Inc., Millennium Pharmaceuticals, Inc., Monarch Pharmaceuticals, Pfizer, Sanofi-Aventis, Schering-Plough, and Wyeth-Ayerst Laboratories.

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In a recent editorial, Beevers (5) notes that many national guideline committees should rethink their stand on beta-blockers as reasonable first-line medications for treatment of hypertension. As a consequence, headlines suggesting the end of the beta-blocker era have suddenly appeared in the medical literature (5). Before we throw out the baby with the bathing water, it seems reasonable to critically analyze the evidence. How strong are the data on which the widespread use of beta-blockers in cardiovascular disease is based?

### Beta-Blockers in Hypertension

For more than 3 decades, beta-blockers have been widely used in the treatment of hypertension and are still recommended as first-line agents by national and international guidelines (2,3). However, ever since the Veterans Administration study in the 1970s (6), multiple, prospective randomized trials have documented that diuretic-based antihypertensive therapy reduces risk of stroke and, to a lesser extent, the risk of myocardial infarction and cardiovascular morbidity and mortality. However, the data are much less convincing for beta-blockers (7).

**Effects on morbidity and mortality.** It is somewhat ironic that after 3 decades of using beta-blockers for hypertension, no study has shown that their monotherapeutic use has reduced morbidity or mortality in hypertensive patients even when compared with the use of placebo.

In some of the early trials like the British Medical Research Council study in the elderly, beta-blocker mono-

**Abbreviations and Acronyms**

**ACC/AHA** = American College of Cardiology/  
 American Heart Association  
**CI** = confidence interval  
**HR** = hazard ratio  
**JNC** = Joint National Committee  
**LVH** = left ventricular hypertrophy  
**MI** = myocardial infarction  
**NNH** = number needed to harm  
**RAAS** = renin angiotensin aldosterone system

therapy was not only ineffective, but whenever a beta-blocker was added to diuretics, the benefits of the antihypertensive therapy distinctly diminished (8). 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 (8,9). Even in the more recent trials like the ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm) study of 19,257 patients with hypertension and at least 3 other coronary risk factors but no

clinically overt coronary artery disease, atenolol-based treatment resulted in a 14% greater risk of coronary events and 23% greater risk of stroke when compared with an amlodipine-based regimen (10).

Recent meta-analyses have shown that beta-blockers do not provide benefit for the end points of all-cause mortality and myocardial infarction even when compared with placebo, both in the elderly and in the younger cohort

(Table 1). Pooled analysis report that beta-blockers reduce the risk of stroke by 16% to 22% when compared with placebo. However, this risk reduction is suboptimal compared with 38% reduction for the same degree of blood pressure reduction observed with the use of other antihypertensive agents (11). When compared with other antihypertensive agents (12–18), beta-blockers provide no benefit for the end points of all-cause mortality, cardiovascular mortality, and myocardial infarction, with a 16% to 30% increased risk of stroke (Table 1). This was the case when all beta-blockers were analyzed together and when atenolol was analyzed separately as a subgroup (15). Other meta-analyses since then have shown similar results with 24% and 30% greater risk of stroke compared with calcium antagonists and RAAS blockers, respectively (12), with the risk being greater in the elderly patients compared to younger patients (14). We (7) had similarly documented, nearly a decade earlier, that although blood pressure was lowered with beta-blockers, these drugs were ineffective in preventing coronary artery disease, cardiovascular events, and all-cause mortality (odds ratios 1.01, 0.98, and 1.05, respectively) Our meta-analysis showed that diuretic therapy was superior to beta-blockers with regard to all outcomes (fatal and nonfatal strokes, cardiovascular events, and all-cause mortality) (7).

**Where did we go wrong?** Given this state-of-the-art paper, one may appropriately inquire about the evidence on

**Table 1 Overview of Major Meta-Analyses of Randomized Controlled Trials of Beta-Blockers in Patients With Hypertension**

Meta-Analysis	Parameter	No. of Trials	Mortality	Myocardial Infarction	Stroke
<b>vs. placebo</b>					
Cochrane, 2007 (18)	Overall	4	0.99 (0.88–1.11)	0.93 (0.81–1.07)	0.80 (0.66–0.96)
Bradley et al., 2006 (12)	Overall	4	0.99 (0.88–1.11)	0.93 (0.81–1.07)	0.80 (0.66–0.96)
Khan et al., 2006 (14)	Younger	2	0.94 (0.79–1.10)	0.85 (0.71–1.03)	0.84 (0.65–1.10)
Khan et al., 2006 (14)	Elderly	5	0.91 (0.74–1.12)	0.98 (0.83–1.16)	0.78 (0.63–0.98)
Lindholm et al., 2005 (15)	Overall	7	0.95 (0.86–1.04)	0.93 (0.83–1.05)	0.81 (0.71–0.93)
Carlberg et al., 2004 (13) (atenolol)	Overall	4	1.01 (0.89–1.15)	0.99 (0.83–1.19)	0.85 (0.72–1.01)
<b>vs. other antihypertensive agents</b>					
Khan et al., 2006 (14)	Younger	5	0.97 (0.83–1.14)	0.97 (0.86–1.10)	0.99 (0.67–1.44)
Khan et al., 2006 (14)	Elderly	7	1.05 (0.99–1.11)	1.06 (0.94–1.20)	1.18 (1.07–1.30)
Lindholm et al., 2005 (15)	Overall	13	1.03 (0.99–1.08)	1.02 (0.93–1.12)	1.16 (1.04–1.30)
Carlberg et al., 2004 (13) (atenolol)	Overall	5	1.13 (0.97–1.33)	1.04 (0.89–1.20)	1.30 (1.12–1.50)
<b>vs. diuretics</b>					
Cochrane, 2007 (18)	Overall	4	1.04 (0.91–1.19)	1.12 (0.82–1.54)	1.17 (0.65–2.09)
Bradley et al., 2006 (12)	Overall	5	1.04 (0.91–1.19)	1.12 (0.82–1.54)	1.17 (0.65–2.09)
Psaty et al., 2003 (16)	Overall	Network	1.01 (0.93–1.10)	1.15 (0.97–1.35)	1.11 (0.94–1.31)
<b>vs. calcium antagonists</b>					
Cochrane, 2007 (18)	Overall	4	1.07 (1.00–1.14)	1.05 (0.96–1.15)	1.24 (1.11–1.40)
Bradley et al., 2006 (12)	Overall	4	1.07 (1.00–1.14)	1.05 (0.96–1.15)	1.24 (1.11–1.40)
BPLTTC, 2003* (17)	Overall	9	1.01 (0.96–1.05)	0.99 (0.93–1.06)	1.07 (1.00–1.16)
<b>vs. RAAS blockers</b>					
Cochrane, 2007 (18)	Overall	3	1.10 (0.98–1.24)	0.90 (0.76–1.06)	1.30 (1.11–1.53)
Bradley et al., 2006 (12)	Overall	3	1.08 (0.95–1.23)	0.90 (0.76–1.06)	1.30 (1.11–1.53)
BPLTTC, 2003 (17)	Overall	9	1.00 (0.95–1.05)	1.02 (0.95–1.10)	0.92 (0.85–1.00)

Numbers represent hazard ratio (95% confidence interval).

BPLTTC = Blood Pressure Lowering Treatment Trialists' Collaboration; RAAS = renin angiotensin aldosterone system.

which the seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 7) is based (3). It appears that the guidelines were based mostly on trials like the STOP-2 (Swedish Trial in Old Patients with hypertension-2) trial (19), the CONVINCe (Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints) trial (20), the NORDIL (Nordic Diltiazem) trial (21), the CAPPP (Captopril Prevention Project) trial (22), and most of all the meta-analysis by Psaty et al. (23) published in 1997. Although in some of these trials patients were started on a beta-blocker, more than two-thirds ended up on a combination of a beta-blocker with a diuretic, and no effort was made to separately analyze the morbidity and mortality effects of the beta-blocker, the diuretic, or the combination of the two. We (24) had earlier suggested that it would be erroneous to conclude from the results of these mixed trials that there was cardiovascular morbidity and mortality benefit of beta-blockers. To illustrate the inappropriate use of including these studies as beta-blocker studies, we used an analogy model of the effects of gin and tonic on hepatic cirrhosis. One would hardly conclude that the tonic water caused cirrhosis based on a study in which two-thirds of patients were on gin and tonic and one-third on tonic water alone, and no attempt had been made to separately assess the effects (24).

To further illustrate the “dilution” effect of these trials, in the meta-analysis by Lindholm et al. (15), in the studies comparing beta-blockers to placebo, beta-blockers resulted in a 19% reduction in stroke. However, when a sensitivity analysis was performed using only mixed beta-blocker/diuretics studies versus placebo, the beta-blocker arm suddenly became more efficacious, with a 45% reduction in the risk of stroke. Similarly, in the comparison of beta-blockers with other antihypertensive agents, a sensitivity analysis of only the mixed beta-blocker/diuretics studies failed to show the 16% increased risk of stroke observed when all studies were included (15). It therefore appears that most of the beneficial effects/nonharmful effects of these trials may be the result of the diuretics and hence these studies should not be used as evidence to suggest the beneficial effect of beta-blockers.

**Effects on blood pressure.** Beta-blockers reduce blood pressure compared with placebo. However, compared with other antihypertensive 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 with patients on a diuretic (25). Even in more recent trials like the LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) trial (26), 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 with atenolol-based treatment (10). In an analysis of 10 trials involving 16,164 elderly hypertensive patients assigned to beta-blocker or diuretics, hypertension was controlled in 66% of patients assigned to diuretics monotherapy but was controlled in less than one-third of patients on beta-blocker monotherapy (7).

**Pseudo-antihypertensive efficacy.** Beta-blockers are not only less efficacious at reducing peripheral blood pressure but also have a lesser effect on perhaps the more important central aortic pressure when compared with RAAS blockers, diuretics, and calcium antagonists (27,28). In the CAFE (Conduit Artery Functional Endpoint) study (29), for the same peripheral blood pressure, a 4.3 mm Hg greater central aortic systolic blood pressure and 3.0 mm Hg greater central aortic pulse pressure was noted with atenolol based treatment compared with the amlodipine-based treatment (29). The study results also strongly suggest that the central aortic systolic blood pressure may be more predictive of cardiovascular events, such as stroke and myocardial infarction, than the traditional peripheral (brachial) blood pressure measurements. Given this discrepancy between cuff and central aortic pressure, the antihypertensive efficacy of beta-blockers can be best described as a “pseudo antihypertensive” efficacy.

**Beta-blockers: side effects.** Beta-blockers often are not well tolerated, and the compliance rate with these medications are dismal. In a meta-analysis of randomized controlled trials, the risk of treatment withdrawal was 80% and 41% greater with beta-blockers compared with diuretics and RAAS blockers, respectively (12).

**New-onset diabetes mellitus.** Since the 1960s, the metabolic side effects of beta-blockers have been widely studied. Beta-blockers have been shown to increase insulin resistance and predispose patients to diabetes. In a “network meta-analysis” of 22 clinical trials with 143,153 participants who did not have diabetes at randomization, 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).

Whether this new-onset diabetes induced by beta-blockers has deleterious consequences is debatable. After a median of 6 years, the risk of cardiovascular events with new-onset diabetes was found to be similar to the risk in patients with established diabetes and hypertension at baseline (31). Similarly, in the 18-year follow-up of the MRFIT (Multiple Risk Factor Intervention Trial), patients who had developed diabetes during treatment had greater mortality rates than those without diabetes (32). Alderman et al. (33), in a follow-up of 6,886 hypertensive patients, found a significant greater incidence of cardiovascular events in individuals with in-treatment blood glucose levels of 139.5 mg/dl or greater. Similarly, in a population-based cohort study of 1,860 men followed up for 17.4 years, increased blood glucose during treatment for hypertension (mainly by thiazides and beta-blockers) was an independent risk factor

for myocardial infarction (31). However, only in one study so far, SHEP (Systolic Hypertension in the Elderly Program), patients with diabetes at baseline had worse prognosis (adjusted hazard ratio [HR] 1.66, 95% confidence interval [CI] 1.41 to 1.95), patients with new-onset diabetes while on placebo had worse prognosis (adjusted HR 1.56, 95% CI 1.12 to 2.18), but patients with new-onset diabetes while receiving chlorthalidone had no excess cardiovascular morbidity or mortality (adjusted HR 1.04, 95% CI 0.74 to 1.46) after a follow-up of 14.3 years (34), leading some investigators to conclude that new-onset diabetes caused by these medications might not be harmful.

Given the data from previous studies showing detrimental effects of new-onset diabetes, the long-term atherogenic potential of diabetes, whether primary or secondary (to medications), cannot and should not be ignored. Nevertheless, the economic consequences of management of a chronic condition like diabetes and its long-term micro- and macrovascular complications added on to an asymptomatic and chronic condition like hypertension would be enormous.

Potential mechanisms by which beta-blockers may contribute to development of diabetes include weight gain, attenuation of the beta-receptor-mediated release of insulin from pancreatic beta cells (35), and decreased bloodflow through the microcirculation in skeletal-muscle tissue, leading to decreased insulin sensitivity (36). The usefulness of beta-blockers in patients at risk for diabetes (like those with advanced age, family history of diabetes, impaired glucose tolerance, elevated fasting glucose levels, obesity, and metabolic syndrome) is thus questionable.

However, in the GEMINI (Glycemic Effects in Diabetes Mellitus Carvedilol-Metoprolol Comparison in Hypertensives) trial (35), treatment of diabetics with metoprolol resulted in an increase in hemoglobin A1c whereas treatment with carvedilol (a newer nonselective beta-blocker) did not, attesting to the fact that not all beta-blockers are created equal.

**Effects on left ventricular hypertrophy (LVH) regression.** Left ventricular hypertrophy is a strong predictor of cardiovascular mortality and morbidity and its regression lowers the risk, independent of blood pressure lowering effect (37). In patients with hypertension, medications that regress LVH are therefore desirable. In the LIFE study, antihypertensive treatment with losartan-based therapy resulted in greater LVH regression than conventional atenolol-based therapy (26). In a meta-analysis of 104 studies comparing various antihypertension strategies on LVH regression, beta-blocker based therapy produced the least LVH regression compared with RAAS blockers, calcium antagonists, and diuretics (38). Beta-blockers, unlike RAAS blockers, do not decrease collagen content in the myocardium and hence are not efficacious in LVH regression (39). The usefulness of beta-blockers in patients with LVH is therefore questionable.

**Vascular effects.** Hypertension stems from and results in structural and functional changes in the resistance vessels.

Medications that improve endothelial function can therefore not only improve blood pressure control but also result in substantial reduction in the cardiovascular end points of stroke and myocardial infarction. Beta-blockers have no effect on resistance blood vessels and endothelial function compared with other antihypertensive agents. In a prospective study of 19 untreated hypertensive patients randomized to beta-blocker (atenolol) or calcium antagonist (amlodipine), after 1 year of treatment, for the same blood pressure control, amlodipine resulted in correction of altered resistance artery structure (on gluteal resistance vessels) and tended to improve endothelial function, whereas similar good control of blood pressure with the beta-blocker did not (40). Furthermore, in another study, switching the medication from beta-blocker to the AT1 receptor antagonist irbesartan resulted in correction of previously persistently altered vascular structure and endothelial dysfunction suggesting a structural and endothelial protective effect of AT1 receptor antagonists (41). Improvement in endothelial function also has been demonstrated with other antihypertensive agents like RAAS blockers (41,42). This effect on endothelial function is thus independent of blood pressure control and seems to be an intrinsic property of these antihypertensive agents (calcium antagonists/RAAS blockers). Therefore, conceivably, the lack of cardioprotective effects of beta-blockers in patients with essential hypertension maybe due to its failure to improve endothelial function and LVH.

**Weight gain.** All hypertension management guidelines recommend weight loss and/or avoidance of medications that cause weight gain in obese hypertensive patients. Beta-blocker use, however, has been associated with small-but-systematic weight gain. In the few hypertension studies that reported weight status, beta-blocker use resulted in a weight gain by as much as 1.2 kg (43). The weight gain secondary to beta-blockers has been attributed to its effect on decreasing metabolic activity by as much as 10% and also on other effects on energy metabolism (43). Compared with patients who maintain the same weight or lose weight, patients who gain weight have a 2- to 3-fold greater risk of developing diabetes (44). The usefulness of beta-blockers in obese patients or patients with risk factors for diabetes is thus questionable. In the GEMINI trial (45), patients on metoprolol had a significant weight gain, but patients on carvedilol did not, again attesting the fact that not all beta-blockers are the same.

**Beta-blockers and exercise endurance.** Exercise endurance in a healthy person depends, in part, on a properly functioning sympathetic nervous system. Beta-blockers, by antagonizing this effect, may hamper exercise capacity. In fact, studies conducted half a century earlier have shown that surgical sympathetic denervation of the heart hinders exercise performance in dogs (46). Epstein et al. (47) 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 and those with hypertension (48). Many other studies since have shown a clear reduction in exercise endurance in young healthy test subjects and trained sportsmen. In sharp contrast, in patients with coronary artery disease, an improvement in exercise tolerance with beta-blocker therapy has been shown (49). This discrepancy between the 2 groups has been attributed to differing behavior of the cardiovascular system in health and in disease states.

The mechanism of reduced exercise tolerance in subjects on a beta-blocker is in part secondary to hemodynamic effects (i.e., decrease in heart rate, cardiac output, mean arterial pressure) and also due to its effect on glucose and lipid metabolism. The usefulness of beta-blockers in young/physically active patients is thus questionable.

**Others.** Beta-blockers as a class have many undesirable adverse effects, including drowsiness, lethargy, sleep disturbance, visual hallucinations, depression, blurring of vision, dreams/nightmares, pulmonary side effects such as increased airway resistance in asthmatics, and peripheral vascular side effects such as cold extremities, Raynaud's phenomenon, erectile, and orgasmic dysfunction. The Medical Research Council 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 (50). For an asymptomatic disorder such as mild hypertension, this risk/benefit ratio is hardly an acceptable one.

**Risk/benefit ratio.** Compared with other antihypertensive agents, the number needed to harm (NNH) for beta-blockers based on meta-analysis by Lindholm et al. (15) is 2,500 patients, (i.e., treatment of 2,500 patients with beta-blockers for 1 year results in 1 excess stroke). However, when only nonmixed beta-blockers/diuretic studies are considered, the results are dismal for beta-blockers with NNH of 909 patients/year of treatment. These data are worse when patients are treated with atenolol, with NNH of 714 patients/year of treatment. Using the same dataset, the NNH for elderly patients is 625 patients/year of treatment (after excluding the mixed beta-blocker/diuretic studies). Given that 52 million patients have hypertension, beta-blocker therapy could potentially result in about 208,000 needless strokes per year compared with other antihypertensive agents. As always, the NNH should be weighed against the potential benefits. However, because no study to date has shown the beneficial effects of beta-blockers for all-cause mortality, cardiovascular morbidity, and mortality when used as monotherapy for hypertension, their use for this indication clearly violates the principle of *primum non nocere*.

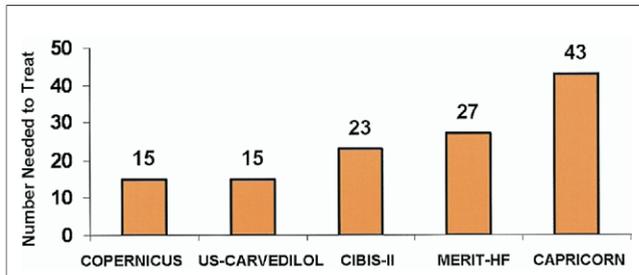
**Joint National Committee.** Beta-blockers along with diuretics were regarded as the preferred first line of treatment from 1984 to 1997 (JNC III to VI), although there was a consistent paucity or even absence of data to show the beneficial effects of beta-blockers as first-line agents for hypertension. The JNC VII recommends beta-blockers for

"compelling" indications on an equal basis with calcium antagonists, RAAS blockers (3). However, in patients with "compelling" indication for beta-blocker, it is unknown if the beneficial effect of beta-blockers is secondary to its blood pressure-lowering effects. Should the beta-blocker be used both for hypertension and the compelling indication (two-for-one "twofer")? Although the twofer certainly is attractive from a pharmacoeconomic point of view, there is no evidence that such an approach is efficacious or safe. We therefore suggest in such a patient to use a beta-blocker for the compelling indication and to use a drug that has been shown to reduce morbidity and mortality for hypertension (51).

**Chronic heart failure.** Beta-blockers traditionally were considered contraindicated in patients with heart failure because of their initial transient negative inotropic effects. However, many studies have consistently shown a substantial reduction in the rate of mortality (~30%) and morbidity with the use of beta-blocker therapy, as well as an improvement in symptoms and the patient's well-being (52-54). Treatment of 15 to 43 patients with heart failure prevents 1 death and, thus, beta-blockers are very effective in patients with heart failure (Fig. 1). Multiple meta-analyses have echoed this observation, showing mortality benefit in the overall cohort (55,56), in the elderly or the young (57), in men or women (58), in diabetics (59) or nondiabetics (60), in patients with ejection fraction <25% or ≥25% (61), and in patients on or not on background RAAS blocker therapy (62) (Fig. 2). Present American College of Cardiology/American Heart Association (ACC/AHA) guidelines rightly recommend beta-blockers in patients with systolic heart failure (63).

The reason for the difference in the efficacy of beta-blockers in these 2 conditions are that, in patients with heart failure, the adrenergic system is activated (initially as a compensatory mechanism) with up-regulation of adrenergic receptors on the myocardium which over a long run results in myocardial remodeling and fibrosis. Beta-blockers probably act to protect the heart from these harmful effects of norepinephrine and epinephrine. Consequently, beta-blockers have been, are, and will remain a cornerstone for the treatment of heart failure. However, hypertension in the elderly is characterized by decreased cardiac output, heart rate, elevated systemic vascular resistance, decreased arterial compliance, and decreased beta-adrenergic responsiveness and, hence, beta-blockers are not effective in this subgroup of patients.

**Coronary artery disease.** The ACC/AHA committee recommends beta-blockers as the first-line therapy for chronic stable angina (64) based on 2 pieces of evidence: first, the evidence of improved mortality with beta-blockers in post-myocardial infarction (MI) patients, and, second, by extrapolation from the supposed effects of these agents in hypertension, where the guidelines believe that beta-blockers reduce mortality. The first statement is reasonable, but extrapolating this evidence to patients with stable angina but

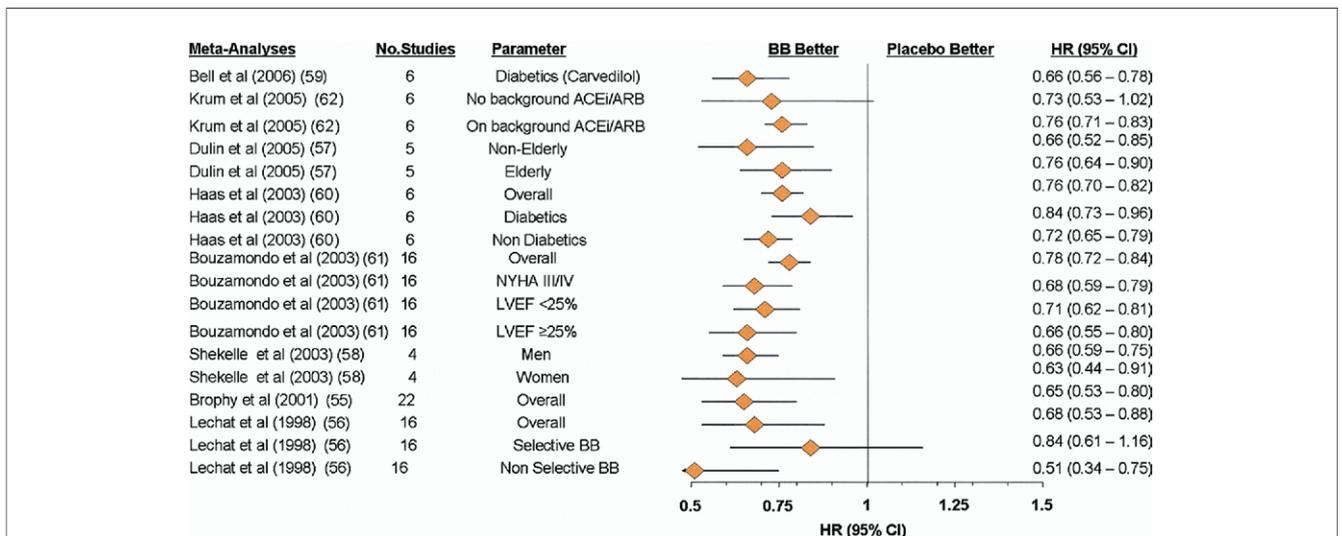


**Figure 1** Number Needed to Treat in Major Randomized Controlled Trials of Beta-Blockers for Heart Failure

Treatment of 15 to 43 patients with heart failure prevents 1 death and, thus, beta-blockers are very effective in patients with heart failure. CAPRICORN = CARvedilol Post infaRction Survival COntrol in left ventricular dysfunction; CIBIS = Cardiac Insufficiency Bisoprolol Study; COPERNICUS = Carvedilol ProspEctive RaNdomized CUMulative Survival Trial; MERIT-HF = METoprolol CR/XL Randomized Intervention Trial in chronic Heart Failure.

no prior MI may be erroneous. We now have sufficient data to support the fact that beta-blockers used as monotherapy or as first-line agents for hypertension have no mortality benefits and increase the risk for stroke. Opie (65) recently suggested that, in patients with stable angina and no prior MI, a calcium antagonist may be as beneficial without the adverse effects of insulin resistance, weight gain, decreased exercise tolerance, and sexual dysfunction associated with beta-blockers. In patients with stable angina, when compared with beta-blockers, long-acting calcium channel blockers were noninferior for the end points of death/myocardial infarction, frequency of anginal episodes, or nitroglycerine usage (66) and, hence, may be an acceptable alternative.

**Acute coronary syndromes.** In the MIAMI (Metoprolol in Acute Myocardial Infarction) study, early initiation of intravenous beta-blockade with metoprolol resulted in a 13% trend toward decreased mortality compared with placebo (67). Patients in the beta-blocker arm had lower incidence of ventricular and supra ventricular arrhythmias (67). In the ISIS-1 (International Study of Infarct Survival) trial, early initiation of intravenous beta-blockade resulted in a 15% trend toward decreased vascular mortality compared with placebo (68). The TIMI (Thrombolysis In Myocardial Infarction)-2B study also demonstrated superiority of early intravenous beta-blocker therapy for patients with acute ST-segment elevation MI (69). However, not all studies have consistently demonstrated benefit of early intravenous beta-blocker therapy: in the GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial, early beta-blockade resulted in a 30% increased risk of death, with a greater incidence of heart failure, shock, and pacemaker use (70). In the recently concluded COMMIT (CLOpidogrel and Metoprolol in Myocardial Infarction) trial, early beta-blocker therapy in acute MI reduced the risks of reinfarction and ventricular fibrillation but increased the risk of cardiogenic shock by 30%, especially during the first day or so after admission (71). The risk of cardiogenic shock was greatest in patients >70 years, in those with systolic blood pressure <120 mm Hg, heart rate >110 beats/min, and those presenting with Killip III heart failure (71). Acute beta-blockade should therefore be deferred in patients with acute coronary syndrome until hemodynamic stability is achieved. Further studies are needed to appropriately evaluate the role of intravenous beta-blockers in patients with acute MI.



**Figure 2** Overview of Major Meta-Analyses of Randomized Controlled Trials of Beta-Blockers in Patients With Heart Failure

In patients with heart failure, beta-blockers are efficacious agents for the prevention of cardiovascular events. ACEi = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; BB = beta-blocker; CI = confidence interval; HR = hazard ratio; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

**Post-MI.** Since it was first reported in 1965 that administration of propranolol after acute MI reduced mortality, there is now increasing evidence that beta-blockers reduce mortality in patients with prior MI, coming both from meta-analyses of randomized trials (72) and from observational studies (73). These studies have shown that beta-blockers reduce mortality by approximately 23% in prospective trials and up to 40% in observational studies (72,73). Treatment of 84 patients for 1 year prevents 1 death, and treatment of 107 patients with beta-blockers for 1 year avoids 1 nonfatal reinfarction (74) and the benefit is stronger with long-term use rather than the short term. The number needed to treat to achieve mortality reduction is much fewer for beta-blockers when compared with antiplatelet agents or statins use after MI (74). The evidence for beta-blockers in post-MI patient is thus strong, and patients should not be denied the benefits from beta-blockade where and when appropriate. However, most of these trials were performed in the era of medical management of MI, and it is largely unknown whether the benefits hold true in the era of reperfusion, RAAS blockers, statins, and aspirin.

Furthermore, beta-blockers often are not well tolerated, and their ability to control blood pressure, particularly in elderly patients, is limited. In an analysis of 55,315 patients who survived an acute MI and were prescribed a beta-blocker, a RAAS blocker, and a statin, 74% of patients were still receiving a RAAS blocker, 82% a statin, but only 58% a beta-blocker after 5 years of follow-up (75).

Alternative treatment strategies are therefore needed to improve compliance. In a recent analysis of the INVEST (International Verapamil-SR Trandolapril) study, we showed that, in patients with prior MI, a heart rate-lowering calcium antagonists-based strategy (verapamil-SR) was equivalent to a beta-blocker (atenolol)-based strategy for the primary outcome (composite of all-cause mortality, myocardial infarction, and stroke; HR 0.94, 95% CI 0.83 to 1.06) with a trend toward 29% reduction in the risk of nonfatal stroke (HR 0.71, 95% CI 0.49 to 1.01) in the group on Verapamil-SR when compared with the group on beta-blockers (76).

**Perioperative beta-blockers.** Perioperative beta-blockers during noncardiac surgery have been shown to be useful in preventing postoperative cardiac complications. The mechanisms by which beta-blockers exert their perioperative cardioprotective effect are multifactorial. Beta-blockers decrease myocardial oxygen demand by reduction of heart rate and myocardial contractility and reduce adrenergic activity resulting in reduced levels of free fatty acid thereby causing a shift in the myocardial metabolism towards glucose uptake.

In a meta-analysis of 1,077 patients, perioperative beta-blocker therapy was associated with a 56% reduction in the risk of perioperative MI and 67% reduction in the risk of perioperative MI or cardiac death when compared with placebo (77). Treatment of 32 patients with beta-blocker is associated with 1 less perioperative MI (77), and the benefit

is greater in patients undergoing high-risk surgery. Consequently, the ACC/AHA guidelines on perioperative cardiovascular evaluation for noncardiac surgery recommends beta-blockers in those already on therapy or who are undergoing vascular surgery and have ischemia on preoperative testing (Class I) and for those undergoing vascular surgery or intermediate or high-risk nonvascular surgery with high risk for coronary disease or those with established disease (Class II) (78).

However, in the recently concluded MaVS (Metoprolol in Vascular Surgery) trial, which had a sample size greater than twice that of any study used by the guideline committee to make the recommendations, metoprolol was not effective in reducing the 30-day and 6-month postoperative cardiac event rates when compared with placebo (79). Similarly, in the DIPOM (Diabetic Postoperative Mortality and Morbidity) trial, metoprolol treatment before noncardiac surgery was not associated with decreased cardiac events rates when compared with placebo (80). Other large randomized trials have similarly failed to show a cardiovascular benefit of beta-blockade in patients undergoing noncardiac surgery (80).

**Hypertrophic obstructive cardiomyopathy.** Beta-blockers are also efficacious in patients with hypertrophic obstructive cardiomyopathy, both for the reduction of symptoms and preventing sudden cardiac death (81). However, in patients with mild or moderate hypertrophic cardiomyopathy, treatment with beta-blocker (nadolol) resulted in a greater decrease in peak exercise work load compared with a verapamil strategy (82).

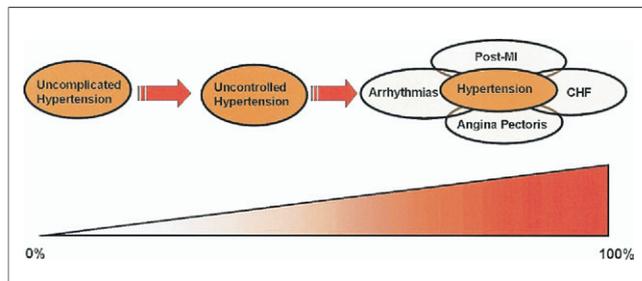
**Other indications.** Beta-blockers have been shown to reduce tachycardia and arrhythmias of everyday stress in pilots undergoing simulated flights (83), public speaking (84), race car drivers (85), and so on, and are also efficacious in the treatment of supraventricular arrhythmias and effective in the control of ventricular arrhythmias related to sympathetic activation and prevents sudden cardiac death (86).

**Physicians' misperception of beta-blockers in the management of hypertension.** Unfortunately, physicians still perceive beta-blockers as exceedingly efficacious antihypertensive drugs. In a recent survey (87) in which physicians were asked "Which of the following class of drugs have been

**Table 2** Strength of Evidence for the Use of Beta-Blockers in Cardiovascular Disease

Conditions	Weak to None	Some Evidence	Strong Evidence
Hypertension (uncomplicated)	✓		
Heart failure			✓
Acute coronary syndrome		✓	
Postmyocardial infarction			✓
Stable angina without MI		✓	
Perioperative (noncardiac surgery)		✓	
HOCM		✓	

HOCM = hypertrophic obstructive cardiomyopathy; MI = myocardial infarction.



**Figure 3** 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 antihypertensive agents and in those with complicated hypertension, beta-blockers should be considered in the armamentarium of treatment. CHF = chronic heart failure; MI = myocardial infarction.

proven to reduce the risk of stroke in hypertensive patients?” beta-blockers were by far considered the most 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. 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.”

### Conclusions

The strength of evidence supporting the use of beta-blockers in certain cardiovascular conditions is summarized in Table 2. In 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 agents. Given the risk of stroke, lack of cardiovascular morbidity and mortality benefit, numerous adverse effects, lack of regression of target end-organ effects of hypertension like LVH, and endothelial dysfunction, the risk benefit ratio for beta-blockers is not acceptable for this indication. Guideline committees should revise recommendations for beta-blockers as first-line therapy for uncomplicated hypertension. It is worthwhile to note that the British Hypertension Society has withdrawn its endorsement of beta-blockers as first-line treatment for patients with uncomplicated hypertension (88). In patients with uncontrolled or complicated hypertension, beta-blockers can be considered in the armamentarium of treatment (Fig. 3).

However, it must be clearly emphasized that all outcomes studies showing no benefit in hypertension were conducted with traditional beta-blockers such as atenolol and metoprolol. Whether the newer vasodilating agents such as nebivolol and carvedilol, which have a more favorable hemodynamic and metabolic profile, will be more efficacious in reducing morbidity and mortality, remains to be determined.

Beta-blockers, however, have been, are, and will remain the cornerstone for the treatment of heart failure. For patients with previous MI and hypertrophic obstructive cardiomyopathy,

there is strong evidence to suggest its beneficial effects, provided patients can tolerate these medications. However, the evidence supporting its use perioperatively for noncardiac surgery is now been called into question.

At the time of writing this article, the AHA Council for High Blood Pressure Research and the European Society of Hypertension/European Society of Cardiology are no longer endorsing beta-blockers as first-line treatment for uncomplicated hypertension (89,90).

**Reprint requests and correspondence:** Dr. Franz H. Messerli, 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, New York 10019. E-mail: fmesserli@chpnet.org.

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