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Beta-Blockers for Primary Prevention of Heart Failure in Patients With Hypertension

Insights From a Meta-Analysis

Sripal Bangalore, MD, MHA, David Wild, MD, Sanobar Parkar, MD, MPH, Marrick Kukin, MD, FACC, Franz H. Messerli, MD, FACC

New York, New York

Objectives This study sought to evaluate the efficacy of beta-blockers (BBs) for primary prevention of heart failure (HF) in patients with hypertension.

Background The American College of Cardiology/American Heart Association staging for HF classifies patients with hypertension as stage A HF, for which BBs are a treatment option. However, the evidence to support this is unknown.

Methods We conducted a MEDLINE/EMBASE/CENTRAL search of randomized controlled trials that evaluated BB as first-line therapy for hypertension with follow-up for at least 1 year and with data on new-onset HF. The primary outcome was new-onset HF. Secondary outcomes were all-cause mortality, cardiovascular mortality, myocardial infarction, and stroke.

Results Among the 12 randomized controlled trials, which evaluated 112,177 patients with hypertension, BBs reduced blood pressure by 12.6/6.1 mm Hg when compared with placebo, resulting in a 23% (trend) reduction in HF risk ($p = 0.055$). When compared with other agents, the antihypertensive efficacy of BBs was comparable, which resulted in similar but no incremental benefit for HF risk reduction in the overall cohort (risk ratio: 1.00; 95% confidence interval: 0.92 to 1.08), in the elderly (≥60 years) or in the young (<60 years). Analyses of secondary outcomes showed that BBs confirmed similar but no incremental benefit for the outcomes of all-cause mortality, cardiovascular mortality, and myocardial infarction but increased stroke risk by 19% in the elderly.

Conclusions In hypertensive patients, primary prevention of HF is strongly dependent on blood pressure reduction. When compared with other antihypertensive agents, there was similar but no incremental benefit of BBs for the prevention of HF. However, given the increased risk of stroke in the elderly, BBs should not be considered as first-line agents for prevention of HF. (J Am Coll Cardiol 2008;52:1062–72) © 2008 by the American College of Cardiology Foundation

Chronic heart failure (HF) is the only major cardiovascular disease increasing in both incidence and prevalence, with 550,000 new cases diagnosed every year, affecting both genders equally (1). The prevalence in the U.S. is increasing, with 50 HF patients per 1,000 people over the age of 65 years (1). The increase in the incidence and prevalence of HF seem to parallel the increase in incidence and prevalence of hypertension. The Framingham study has shown that hypertension has the greatest influence on the risk of future HF, accounting for 39% of HF in men and 59% in women (2,3). It confers a 2-fold higher risk of HF, carrying the highest population-attributable risk among all risk factors, and this risk increases in a graded continuous fashion with increase in blood pressure (2–4). More than 90% of patients

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with HF have hypertension (3). The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines committee has recognized this important risk factor; patients with hypertension are classified as stage A HF (those with risk factors for HF), and primary prevention of overt HF (stage C HF) is important in this cohort (5).

Although hypertension is an important risk factor, its treatment results in a 49% to 81% reduction in the risk of developing HF (6). The ACC/AHA guidelines (5) state

From the Department of Medicine, Division of Cardiology, St Luke's Roosevelt Hospital and Columbia University College of Physicians and Surgeons, New York, New York. Dr. Kukin is on the Speakers' Bureau of AstraZeneca and Novartis, and has received research grants from Medtronic, Amgen, and Impulse Dynamics. Dr. Messerli is on the Speakers' Bureau of GlaxoSmithKline, Novartis, Pfizer, AstraZeneca, Bayer, Boehringer Ingelheim, Forest, Merck, Sankyo, and Sanofi, and has received research grants from GlaxoSmithKline, Pfizer, Novartis, and CardioVascular Therapeutics.

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that in patients at high risk for developing HF, systolic and diastolic blood pressure should be controlled in accordance with contemporary guidelines, and beta-blockers (BBs) are an option based on the 7th report of the Joint National Committee on hypertension (7). Although BBs are a reasonable option for patients with stage B HF (asymptomatic left ventricular dysfunction) caused by a prior myocardial infarction, its role in patients with stage B HF caused by left ventricular hypertrophy or in hypertensive patients with stage A HF is not well defined.

Messerli et al. (8) had documented nearly a decade earlier that although blood pressure was lowered by BBs, 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) in patients with hypertension. Other meta-analyses (9,10) and reviews (11) have noted similar results, resulting in withdrawal of endorsement for these medications as first-line therapy for hypertension by major national and international guidelines (12,13). Despite this, they remain the fourth-largest selling drug class in the U.S. (14). In a recent survey (15) in which physicians were asked, "Which of the following class of drugs have been proven to reduce the risk of stroke in hypertensive patients?" BBs 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?" BBs were rated highest. These perceptions or misperceptions are unfortunate and probably occur because physicians extrapolate their cardioprotective effects in HF and myocardial infarction to patients with uncomplicated hypertension (16).

The beneficial effect of BBs for primary prevention of HF in patients with hypertension is unknown. The objective of the present analysis was to evaluate the efficacy of BBs for prevention of progression to overt HF in patients with hypertension.

Methods

Search strategy. We conducted a MEDLINE/EMBASE/CENTRAL search of studies using the terms: "beta adrenergic blockers," "adrenergic beta antagonist," "beta-blockers," and "hypertension." We limited our search to studies in human subjects published in journals from 1966 to May 2008. We checked the reference lists of reviewed articles, prior meta-analyses, and original studies identified by the electronic search to find other potentially eligible studies. Trials that were only in abstract form without an article published were not considered for this analysis.

Eligible trials had to fulfill the following criteria to be included in this analysis: 1) randomized controlled trials (RCTs) to be included if they enrolled adult hypertensive patients, both genders, with or without other cardiovascular risk factors, with or without comorbidities but with no established HF; 2) RCTs to be included if they evaluated BBs as first line monotherapy both as intervention (i.e., vs. placebo) or as comparator (i.e., vs. other antihypertensive drugs); 3) follow-up of at least 1 year; and 4) RCTs to be included if they assessed HF as an outcome, being primary or secondary, predefined or analyzed post hoc.

Abbreviations and Acronyms

ACC = American College of Cardiology
ACEI = angiotensin-converting enzyme inhibitor
AHA = American Heart Association
ARB = angiotensin receptor blocker
BB = beta-blocker
CAD = coronary artery disease
CCB = calcium-channel blocker
CI = confidence interval
HF = heart failure
RCT = randomized controlled trial

Selection and quality assessment. Three authors (S.B., M.K., F.H.M) independently assessed trial eligibility and quality. The quality of the trials was assessed based on the following: 1) 0 points for mixed studies and 1 point for nonmixed studies—mixed study indicates studies in which patients could be randomized to either a BB or a diuretic in the BB arm, wherein it is difficult to separate the effects of individual therapy; and 2) 1 point if HF was considered a pre-defined end point and 0 points if not.

Data extraction and synthesis. The primary outcome considered for this analysis was new-onset HF as defined by the trials. Secondary outcomes of interest were all-cause mortality, cardiovascular mortality, myocardial infarction (fatal + nonfatal), and stroke (fatal + nonfatal) considered separately. We extracted the inclusion/exclusion criteria, publication year, the sample size, age, first-line antihypertensive agents used, blood pressure before randomization, blood pressure at the end of the study, length of follow-up, and the outcomes of interest for each of the studies listed earlier. Two authors (S.B., S.P.) independently extracted all trial data in duplicate ($\kappa = 0.96$).

Statistical analysis. Statistical analysis was done using standard software (Stata version 9.0, Stata Corp., College Station, Texas) using the METAN program (17). The pooled effect for each grouping of trials was derived from the point estimate for each separate trial weighted by the inverse of the variance ($1/SE^2$). Heterogeneity was assessed visually using funnel plots, Q (chi-square) statistics, and/or the I^2 statistics (18). If trials were homogeneous ($p > 0.05$), a fixed-effect model was used to calculate pooled effect sizes. Otherwise, a random-effect model of DerSimonian and Laird (19) was applied to calculate overall differences. Publication bias was estimated using the weighted regression test of Egger. A subgroup analysis was performed to evaluate the role of BBs in the elderly versus the young. For this analysis, we defined the younger cohort as studies in which the mean age of the population was <60 years and an elderly cohort as studies in which the mean age of the population was ≥60 years. A sensitivity analysis was performed after excluding mixed BB/diuretic trials in which patients could be randomized to either a BB or a diuretic agent in the BB arm of the trial. A pre-specified post hoc

analysis was conducted to evaluate the effect of different BBs and the age of the study population (young vs. elderly).

Meta-regression analysis. Univariate and multivariate regression analyses were performed to evaluate predictors of new-onset HF in patients on BB. For the univariate analysis the following covariates were considered: systolic and diastolic pressure at entry and end of study, systolic and diastolic pressure difference between the 2 treatment modalities, age, and follow-up duration. The selection criterion for multivariate regression analysis was based on univariate statistical significance and/or clinical judgment. The estimated between-study variance (τ^2) was calculated using an estimate based on restricted maximum likelihood. The p value was considered significant at <0.05.

Power calculation. A power calculation was undertaken to determine whether the individual studies had adequate power to evaluate the beneficial effects of BB for the end point of HF. For a study to have 80% power, at a type I error rate of 5%, to detect a 30% relative risk reduction for HF with BB therapy (a reduction in the incidence of HF from 2.83% to 1.98%), there would need to be 5,099 patients in each arm of a 2-arm trial. The choice of a 2.83% incidence rate was based on the crude proportion from the 3 placebo-controlled trials.

Results

Study selection. We identified 12 RCTs that fulfilled our inclusion criteria (Fig. 1). We excluded the results from the MAPHY (Metoprolol Atherosclerosis in Hypertension) trial (20) because this was a subgroup from the HAPPHY (Heart Attack Primary Prevention in Hypertension) trial (21). There were 5 mixed BB/diuretics trials in which patients could receive either a BB or a diuretic in the BB arm of the trial (22–26). Three trials compared BB with placebo (23,27,28), and 9 trials (10 arms) compared BB with other antihypertensive agents (21,22,24–26,29–32). The antihypertensive agents evaluated in this analysis included diuretics (1 trial), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARBs) (4 trials) and calcium-channel blockers (CCBs) (5 trials). The STOP-2 (Swedish Trial in Old Patients with hypertension-2) trial had 2 comparison arms: 1 comparing BBs with ACEI and the other comparing BBs with CCBs (25). The analysis for publication bias indicated no evidence of bias for any of the analyses (data not shown).

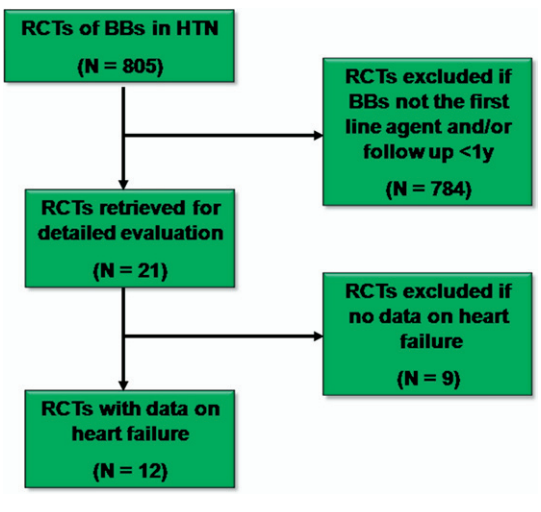


Figure 1 Selection of Studies

BB = beta-blocker; HTN = hypertension; RCT = randomized controlled trial.

Characteristics of the trials. The baseline characteristics, inclusion criteria, and quality assessment are summarized in Tables 1 and 2. The 12 RCTs evaluated 112,177 patients with hypertension, 55,060 (49%) patients randomized to the BB arm, 4,452 (4%) patients randomized to placebo, and 52,665 (47%) patients randomized to other antihypertensive agents. The reported mean age of the patients in the trials ranged from 52 to 76 years, 56% (mean) of the patient population were men, and patients were followed up for a mean of 2.1 to 9 years. The definition of new-onset HF was heterogeneous in these trials.

Blood pressure-lowering effects. The average weighted baseline systolic pressure of included participants was 172 ± 18 mm Hg (range 149 to 197 mm Hg) with the diastolic pressure (weighted) being 96 ± 6 mm Hg (range 86 to 108 mm Hg). When compared with placebo, BBs were more effective at reducing both systolic (weighted mean reduction of 12.6 ± 7.8 mm Hg) and diastolic pressures (weighted mean reduction of 6.1 ± 4.4 mm Hg). When compared with other antihypertensive agents, the antihypertensive effect of BBs was comparable (vs. diuretics 0.0/−1.0 mm Hg; vs. ACEI/ARBs −0.3/−0.6 mm Hg; vs. CCBs −0.1/+0.7 mm Hg; negative numbers indicate that BBs were more efficacious than the comparison agent).

Primary outcome. Among the 112,117 participants in the trials, 2,437 (2.2%) patients developed HF during a mean follow-up (weighted) of 4.4 ± 1.2 years (range 2.1 to 9.0 years): 1,202 (2.2%) patients in the BB group and 1,235 (2.2%) patients in the comparison group (including placebo).

BBs versus placebo. In the 3 trials comparing BBs and placebo (23,27,28), there was trend toward a 23% reduction in the risk of HF in the BB group compared with placebo ($p = 0.055$) (Fig. 2). There was no heterogeneity in this analysis.

BBs versus other antihypertensive agents. In the trials comparing BBs with other antihypertensive agents, the incidence of HF was comparable between the 2 groups (BB vs. others, 2.1% vs. 2.1%; $p = 0.91$), thus failing to show a superiority of BBs over other antihypertensive agents (Fig. 3). In the only trial comparing BBs with diuretics (HAPPHY) (21), there was a reduced incidence of HF in patients on diuretic-based therapy compared with those on BB therapy, but this was not statistically significant (incidence 0.7% vs. 1.0%; $p = 0.18$). In the 4 trials comparing BBs with

Table 1 General Characteristics of Included Trials

Trial	Patient Characteristics	N	Follow-Up	Beta-Blocker	Comparison
Versus placebo					
Coope et al., 1986 (28)	Adults (60–79 yrs) with SBP >170 or DBP >105 mm Hg	884	4.4	Atenolol	Open-control
IPPPSH, 1985 (27)	Adults (40–64 yrs) with HTN and no CAD	6,357	4.0	Oxprenolol	Placebo
STOP, 1991 (23)	Adults (70–84 yrs) with HTN and without prior MI/angina or stroke within prior 12 months	1,627	2.1	Atenolol/metoprolol/pindolol/ HCTZ/amiloride	Placebo
Versus diuretics					
HAPPHY, 1987 (21)	Men (40–64 yrs) with HTN without MI, angina, CVA	6,569	3.8 yrs	Atenolol or metoprolol	BFZ/HCTZ
Versus ACEI/ARBs					
CAPPP, 1999 (26)	Adults (25–66 yrs) with HTN without renal disorders	10,985	6.1	Atenolol or metoprolol/ HCTZ/BFZ	Captopril
LIFE, 2002 (30)	Adults (55–80 yrs) with HTN and LVH without MI or CVA in prior 6 months	9,222	4.8	Atenolol	Losartan
STOP-2, 1999 (25) (ACEI arm)	Adults (70–84 yrs) with HTN without MI or CVA within prior 12 months	4,418	5	Atenolol/metoprolol/pindolol/ HCTZ/amiloride	Enalapril or lisinopril
UKPDS, 1998 (29)	Adults with HTN and DM	758	9	Atenolol	Captopril
Versus CCBs					
ASCOT, 2005 (31)	Adults (40–79 yrs) with HTN and at least one other CV risk factor but no CAD	19,257	5.5	Atenolol	Amlodipine
CONVINCE, 2003 (22)	Adults (≥55 yrs) with HTN and one other CV risk factor (smoking, DM, prior CVD, obesity)	16,476	3.0	Atenolol/HCTZ	Verapamil
INVEST, 2003 (32)	Adults (>50 yrs) with CAD and HTN	22,576	2.7	Atenolol	Verapamil SR
NORDIL, 2000 (24)	Adults (50–59 yrs) with DBP >100 mm Hg	10,881	4.5	Any diuretic/any beta-blocker	Diltiazem
STOP-2, 1999 (25) (CCB arm)	Adults (70–84 yrs) with HTN without MI or CVA within prior 12 months	4,409	5	Atenolol/metoprolol/pindolol/ HCTZ/amiloride	Felodipine/isradipine

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; BFZ = bendrofluazide; BP = blood pressure; CAD = coronary artery disease; CAPPP = Captopril Prevention Project trial; CCB = calcium-channel blocker; CONVINCE = Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; HAPPHY = Heart Attack Primary Prevention in Hypertension trial; HCTZ = hydrochlorothiazide; HTN = hypertension; INVEST = INternational VErapamil SR and Trandolapril Study; IPPPSH = International Prospective Primary Prevention Study in Hypertension; LIFE = Losartan Intervention for Endpoint Reduction trial; LVH = left ventricular hypertrophy; MI = myocardial infarction; NORDIL = Nordic Diltiazem trial; SBP = systolic blood pressure; STOP = Swedish Trial in Old Patients with hypertension; UKPDS = United Kingdom Prospective Diabetes Study.

ACEI/ARBs (25,26,29,30), there was no superiority of BBs for the outcome of HF compared with ACEI/ARBs (incidence 3.3% vs. 3.1%; p = 0.36). Similarly, in the 5 trials comparing BB with CCBs, there was no superiority for the outcome of HF with BBs compared with CCBs (incidence 1.8% vs. 1.9%; p = 0.27) (Fig. 3). There was no heterogeneity in these analyses.

BB type. Among the 9 trials (10 arms) comparing BBs with other antihypertensive agents, 5 trials enrolling 68,260 (66%) patients used atenolol (22,29–32), whereas the remaining 4 trials enrolling 35,049 (44%) patients used mixed BBs (atenolol or metoprolol or pindolol) (21,24–26). Pooled analysis of trials using atenolol failed to show a superiority of atenolol for the prevention of HF compared with other antihypertensive agents (incidence 1.8% vs. 1.7%; p = 0.72) (Fig. 4). There was no heterogeneity in this analysis.

Young versus elderly. Among the 9 trials comparing BBs with other antihypertensive agents, 6 trials enrolling 87,210 (83%) patients were in the elderly cohort (mean age ≥60 years) (22,24,25,30–32), whereas 3 trial enrolling 18,312 (17%) patients were in the younger cohort (mean age <60 years) (21,26,29). There was no superiority of BBs for the primary outcome compared with other antihypertensive agents, both in the elderly (incidence 2.3% vs. 2.3%; p = 0.96) and in the younger cohort (incidence 1.2% vs. 1.2%; p = 0.88) (Fig. 5). There was no heterogeneity in these analyses.

Secondary outcomes. Compared with other antihypertensive agents, BBs did not show any added benefit for any of the secondary end points in the elderly (Fig. 6). In fact, there was a 19% increased risk of stroke when compared with other antihypertensive agents. However, based on 3 trials in the younger cohort (<60 years), there was no increased risk of any of the secondary end points with a 22% decreased risk of stroke with BBs compared with other antihypertensive agents (Fig. 6). There was no heterogeneity in these analyses.

Meta-regression analysis. Univariate meta-regression analysis showed that the relative risk of HF with BB therapy increased with final attained systolic pressure (p = 0.07) (Fig. 7), with systolic pressure difference between the treatment modalities (p = 0.0000004) (Fig. 8), and with length of therapy with BBs (p = 0.0005) (Fig. 9). A multivariate meta-regression analysis identified systolic pressure difference between the 2 treatment modalities as a

Table 2 General Characteristics of Included Trials

Trial	Age	Men, %	Baseline BP (mm Hg)	Study End BP (BB-Placebo/Drug) (mm Hg)	Quality Control	
					Mixed Study/End Point*	Total Points
Versus placebo						
Coope et al. (28)	69	31	196/99	−18.0/−11.0	1/1	2
IPPPSH (27)	52	100	173/108	−3.8/−1.2	1/0	1
STOP (23)	76	37	195/102	−19.5/−8.1	0/1	1
Versus diuretics						
HAPPHY (21)	52	100	166/107	0.0/−1.0	1/0	1
Versus ACEI/ARBs						
CAPPP (26)	53	53	160/99	−1.0/−1.0	0/1	1
LIFE (30)	67	46	174/98	+1.1/−0.2	1/1	2
STOP-2 (25) (ACEI arm)	76	33	194/98	−1.0/0.0	0/1	1
UKPDS (29)	56	54	159/94	−1.0/−1.0	1/1	2
Versus CCBs						
ASCOT (31)	63	77	164/95	+2.7/+1.9	1/1	2
CONVINCE (22)	66	44	150/87	+0.1/+0.7	0/1	1
INVEST (32)	66	48	151/87	<1	1/0	1
NORDIL (24)	60	49	173/106	−3.0/0.0	0/1	1
STOP-2 (25) (CCB arm)	76	33	194/98	−1.0/+1.0	0/1	1

See Table 1 footnote for expansions of trial names. *Mixed study indicates studies in which patients could be randomized to either a beta-blocker (BB) or diuretic in the BB arm: 0 points for mixed studies and 1 point for nonmixed studies. End point indicates whether heart failure was considered a pre-defined end point: 1 point if heart failure was considered an end point and 0 points if not.
Abbreviations as in Table 1.

significant predictor of higher risk of HF with BB therapy (regression coefficient = 0.092; 95% confidence interval [CI]: 0.001 to 0.183; p = 0.04).

Sensitivity analysis. We had 2 a priori hypotheses, the effects of BBs on primary outcome would be further reduced: 1) when studies using mixed BBs/diuretics are excluded (suggesting a dilution effect of these trials); and 2) when only high-quality studies are included.

A sensitivity analysis based on the quality criteria indicated above showed no additional benefit of BBs for the outcome of HF with a trend toward 11% increased risk compared with other antihypertensive agents, confirming our a priori hypothesis (Fig. 10). Similarly, when the analysis was performed excluding mixed BB/diuretic trials, there was no benefit of BBs over other antihypertensive agents for the primary outcome of HF with a trend toward 5% increased risk in patients on BBs. However when only mixed BB/diuretic trials were included, there was a trend toward a 5% decreased risk of HF with BBs, suggesting and confirming our a priori hypothesis of a dilution effect of

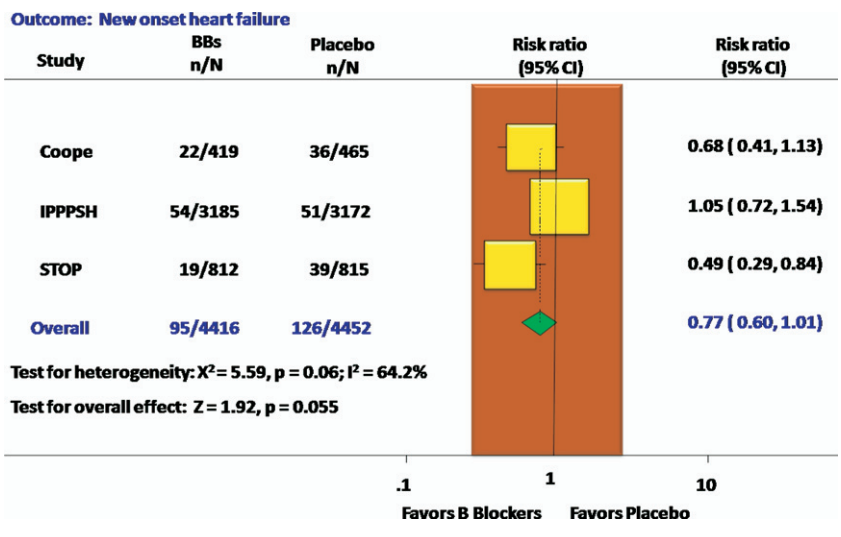


Figure 2 Risk Ratio for Heart Failure When Compared With Placebo

The sizes of the data markers relate to weight of each trial. See Table 1 footnote for expansions of trial names. BB = beta-blocker; CI = confidence interval.

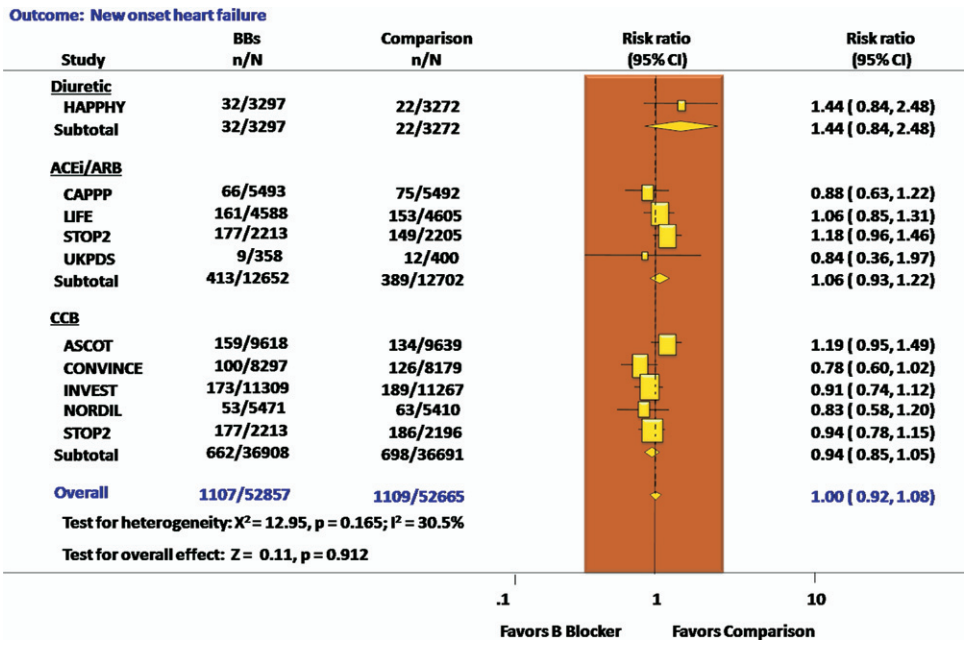


Figure 3 Risk Ratio for Heart Failure When Compared With Other Antihypertensive Agents

The sizes of the data markers relate to weight of each trial. See Table 1 footnote for expansions of trial names.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium-channel blocker; other abbreviations as in Figure 2.

these trials. Similarly, excluding the mixed BB/diuretic trial (STOP) in the comparison with placebo, the trend toward a 23% reduction in the risk of HF was no longer observed (risk ratio [RR]: 0.88; 95% CI: 0.57 to 1.34; p = 0.544) with BBs. A subgroup analysis of high-risk cohorts (patients with left ventricular hypertrophy [30] or known coronary artery disease [CAD] [32] or diabetes [29] or those with ≥1 additional cardiovascular risk factors other than hypertension [22,31]) showed no superiority of BBs for the primary prevention of HF (Fig. 10).

Based on our power calculation, 5,099 patients are required in each arm of a trial for an 80% power and to show

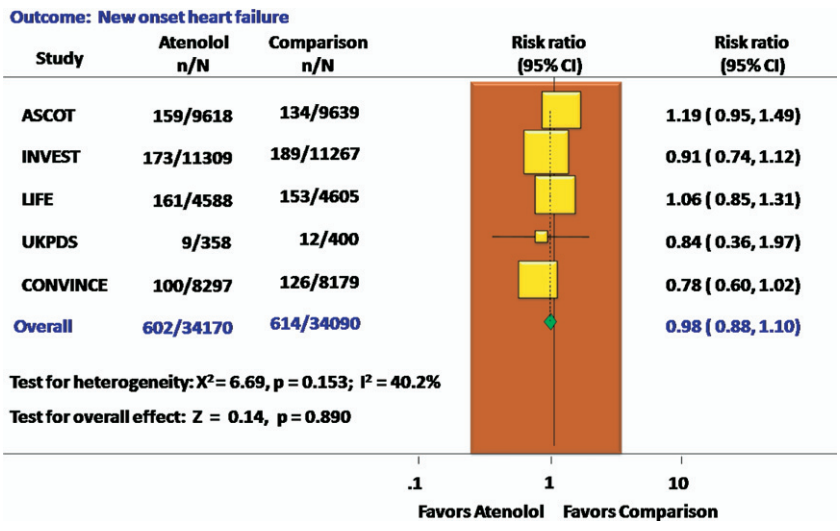


Figure 4 Effect of Atenolol on the Risk of Heart Failure When Compared With Other Antihypertensive Agents

The sizes of the data markers relate to weight of each trial. See Table 1 footnote for expansions of trial names. CI = confidence interval.

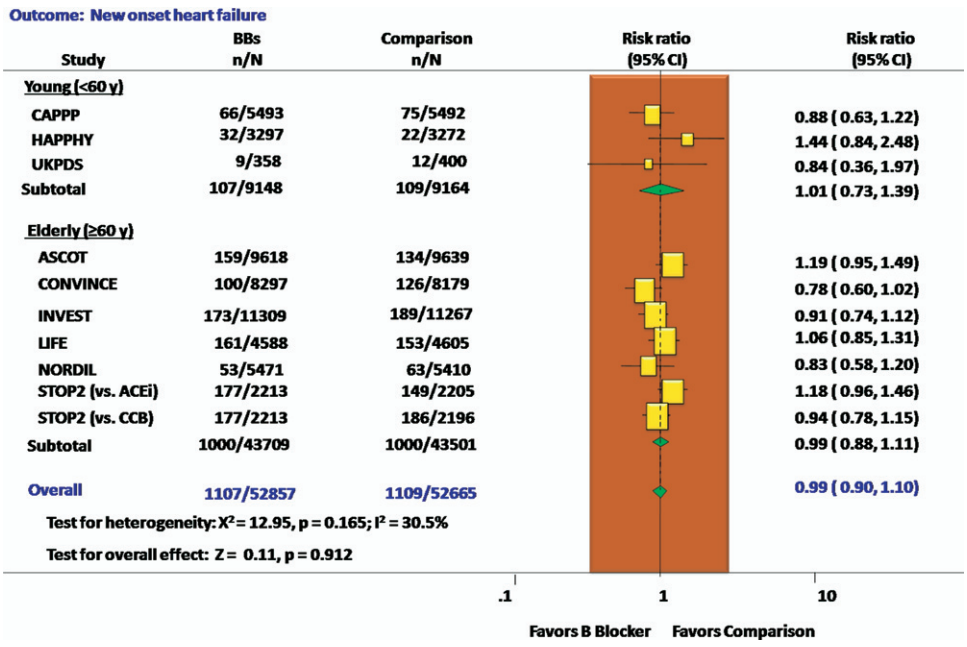


Figure 5 Risk Ratio for Heart Failure When Compared With Other Antihypertensive Agents in Young Versus the Elderly Cohort

The sizes of the data markers relate to weight of each trial. See Table 1 footnote for expansions of trial names. Abbreviations as in Figures 2 and 3.

a 30% relative risk reduction of primary outcome with BB therapy. Based on this criterion, 5 of the 9 trials (nonplacebo) were sufficiently powered. Each of these individual trials failed to show superiority of BBs for the primary outcome over other antihypertensive agents: CAPPP (Captopril Prevention Project) trial (26) (p = 0.445), ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) (31) (p = 0.137), CONVINCE (Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints) (22) (p = 0.065), INVEST (INternational VErapamil SR and Trandolapril Study) (32) (p = 0.377), and NORDIL (Nordic Diltiazem trial) (24) (p = 0.321). Pooled analysis of these trials failed to show a superiority of BBs for the primary outcome over other antihypertensive agents (RR: 0.93; 95% CI: 0.83 to 1.05; p = 0.249).

Discussion

This systematic review of RCTs investigated the efficacy of BBs for the primary prevention of HF in patients with

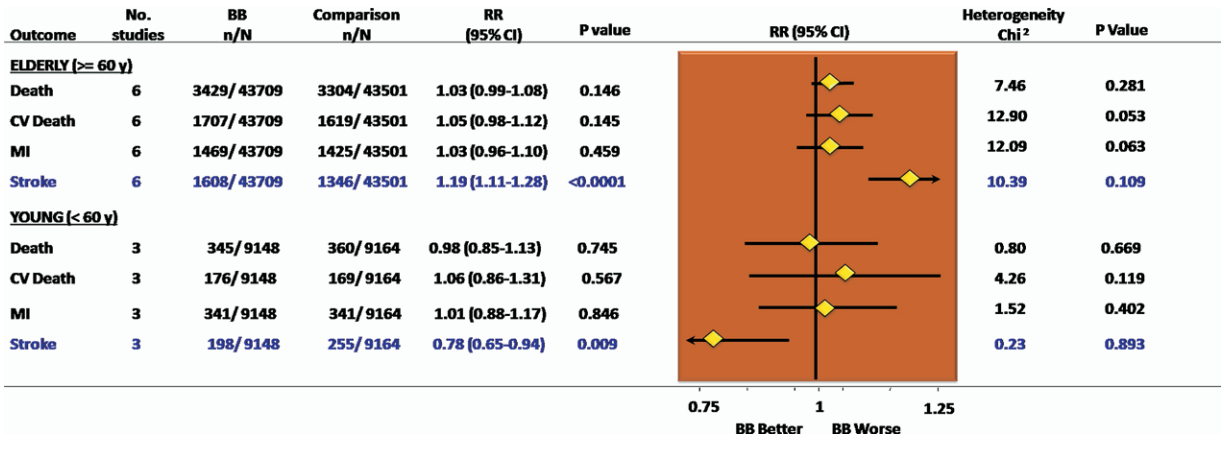


Figure 6 RR for Secondary Outcomes When Compared With Other Antihypertensive Agents

CV = cardiovascular; MI = myocardial infarction; RR = risk ratio; other abbreviations as in Figure 2.

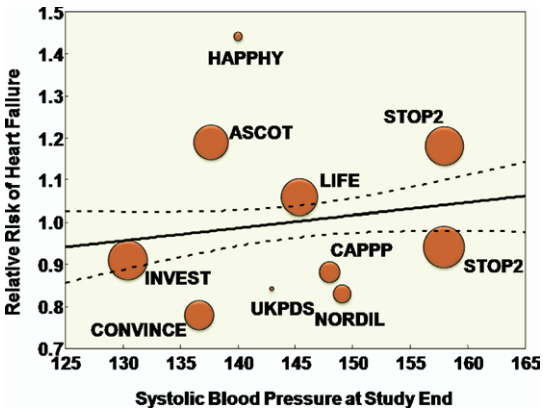


Figure 7 Relative Risk of HF With BB as a Function of SBP at Study End

The sizes of the data markers relate to weight of each trial. See Table 1 footnote for expansions of trial names. BB = beta-blockers; HF = heart failure; SBP = systolic blood pressure.

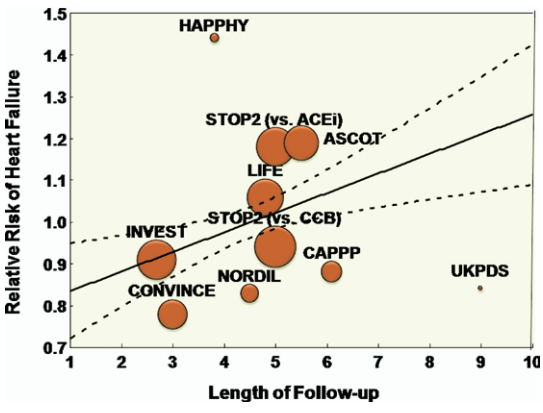


Figure 9 Relative Risk of HF With BB as a Function of Length of Follow-Up

See Table 1 footnote for expansions of trial names. The sizes of the data markers relate to weight of each trial. Abbreviations as in Figures 3 and 7.

hypertension. The results of the present analyses show that BBs provided an incremental benefit for HF risk reduction when compared with placebo (where they were more effective at reducing BP) but not when compared with other antihypertensive agents (where BP reduction was comparable). Similarly, the risk reduction with BBs for secondary outcomes was comparable but with an increased risk of stroke in the elderly.

BBs, blood pressure reduction, and risk of HF. In patients with left ventricular systolic dysfunction, BB therapy has been shown to improve left ventricular systolic function, reduce mortality, and improve exercise tolerance, symptoms and patient well-being (28,33–36). However, it must be emphasized that these beneficial effects are in patients with established HF. There is a tendency among physicians to extrapolate the beneficial effects to primary prevention of HF in patients at high risk. However, no trial to date has shown that monotherapeutic use of BBs in patients with hypertension is associated with reduced cardiovascular mortality and morbidity (8).

In a recent meta-analysis of 105,951 patients, BBs resulted in a 16% higher incidence of stroke and no benefit for the outcome of myocardial infarction in comparison with other antihypertensive agents including thiazide diuretics (9), attesting to and expanding on our observation made almost a decade earlier (8). However, this meta-analysis by Lindholm et al. (9) did not evaluate the end point of HF, and some investigators have speculated that the deleterious effects on stroke prevention could be balanced by better effects on prevention of HF (37) and hence have continued to endorse it.

Blood pressure reduction and risk of HF. The ACC/AHA guidelines emphasize the importance of blood pressure control to reduce the risk of HF. The result of this meta-analysis echoes the importance of blood pressure lowering to reduce the risk of HF. The strongest predictor of increased risk of HF with BBs was a significant blood pressure difference with the comparator agent, i.e., as long as BBs produced an equal reduction in blood pressure, the relative risk reduction for HF was comparable to that of other antihypertensive agents. The BBs were efficacious (trend) when compared with placebo, where they resulted in a significant decrease in blood pressure. However, there was no superiority of BB therapy (comparable efficacy) over other antihypertensive agents for the primary prevention of HF, both in the elderly and in the younger cohort where blood pressure control was comparable. However, does this mean that it does not matter how you lower blood pressure as long as you lower it, to reduce the risk of HF? A closer look at the placebo-controlled studies shows that it may be much more than mere reduction in blood pressure. In the 3

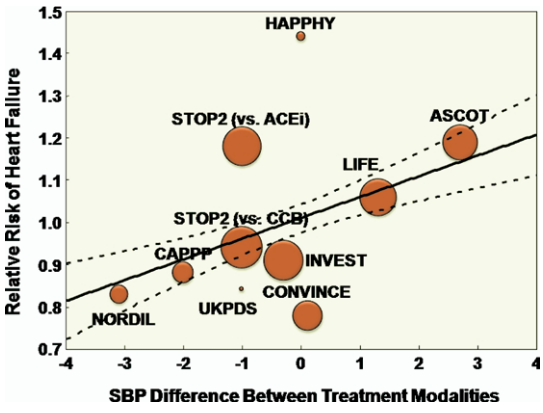


Figure 8 Relative Risk of HF With BB as a Function of SBP Difference Between Treatment Modalities at Study End

The sizes of the data markers relate to weight of each trial. See Table 1 footnote for expansions of trial names. Abbreviations as in Figures 3 and 7.

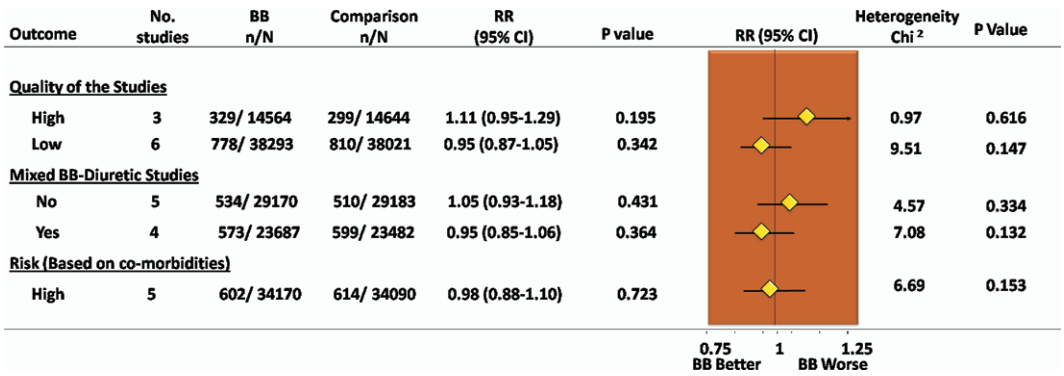


Figure 10 Sensitivity Analysis: Effect of BB on the Risk of Heart Failure When Compared With Other Antihypertensive Agents

See Table 1 footnote for expansions of trial names. RR = risk ratio; other abbreviations as in Figure 2.

placebo-controlled studies (Coope et al. [28], IPPPSH [International Prospective Primary Prevention Study in Hypertension], STOP), BBs resulted in a mean blood pressure decrease of 12.6/6.1 mm Hg compared with placebo, resulting in a trend toward 23% reduction in the risk of HF. However, when the mixed BB/diuretic study (STOP) was excluded from the analysis, BBs resulted in a mean blood pressure reduction of 10.9/6.1 mm Hg compared with placebo, but with no significant reduction in the risk of HF (RR: 0.88; 95% CI: 0.57 to 1.34; p = 0.544) leading one to speculate that the beneficial effect of BBs in the placebo-controlled trial may have been the dilution effect of the mixed BB/diuretic study (STOP).

Blood pressure reduction and risk of stroke. For the similar blood pressure reduction, there was excess stroke risk with BBs compared with other antihypertensive agents, suggesting that for stroke prevention at least, not only lowering blood pressure but also the agent used is important. The BBs differ in their effect on central aortic blood pressure when compared with peripheral brachial pressure (38). When compared with ACEI, diuretics, and CCBs, BBs do not lower central systolic blood pressure (38). For the same peripheral blood pressure, a central aortic systolic blood pressure 4.3 mm Hg higher and a central aortic pulse pressure 3.0 mm Hg higher was noted with atenolol-based treatment compared with the amlodipine-based treatment, resulting in a 14% lower risk of coronary events and 23% lower risk of stroke with CCBs in the CAFE (Conduit Artery Functional Endpoint) trial (39). In our analyses, the excess stroke risk was seen only in the elderly cohort. In the younger cohort, however, BB therapy was associated with a 22% decreased risk of stroke. The result in the younger cohort was heavily weighted by the CAPPP trial (76% weight), which is a mixed BB/diuretic trial, and a dilution effect of this trial thus cannot be ruled out. More over, Khan and McAlister (40) have shown no benefit of BBs for prevention of stroke in the young (RR: 0.99; 95% CI: 0.67 to 1.44). This analysis included the results from the ELSA (European Lacidipine Study on Atherosclerosis) (41) trial and the MRC (Medical Research Council) trial (42), both of which were excluded in the current analysis because they did not report the outcome of HF. Including these 2 trials (for the stroke analysis) and excluding the results of the CAPPP trial (mixed BB/diuretic trial) showed that in the younger cohort, BBs were associated with a nonsignificant 23% increased risk of stroke (RR: 1.23; 95% CI: 0.72 to 2.12; p = 0.450; heterogeneity p = 0.02) using a random-effects model. The beneficial effects of stroke prevention in the young in our analysis should therefore be interpreted with caution.

Prior studies. In the only other meta-analysis that addressed this question (still in abstract form), Elliot (43) in a meta-analysis of 10 RCTs found that CCBs were inferior to diuretic or BBs for the primary prevention of HF in patients with hypertension (RR: 1.32; 95% CI: 1.22 to 1.44; p < 0.0001). However, the study was heavily weighted by the ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial) study, and the analysis included comparison of CCBs against either diuretics or BB. We have shown previously (44) and in this analysis (Fig. 10) that extrapolating the results from mixed BB/diuretic trials to that of BBs is not ideal because these drug classes differ in their effects. The BBs have an increased risk of stroke, whereas the same does not hold true for diuretics.

At first glance, our results contradict the results of the BPLTTC (Blood Pressure Lowering Treatment Trialists Collaboration) trial (45), in which diuretics/BBs were superior to CCBs (RR: 1.33) at preventing HF, with a trend favoring them in the comparison against ACEI (RR: 1.07). However it should be noted that in the analysis by BPLTTC, 6 of the 7 trials in the CCBs comparison groups and 2 of the 3 trials in the ACEI comparison groups were comparisons against diuretic-based therapy, and any meaningful extrapolation of these results to BBs may not be appropriate.

Study limitations. As in other meta-analyses, given the lack of data in each trial, we did not adjust our analyses for dose of medications used nor for compliance to assigned

therapy. In this analysis, similar to analyses by others, we used the mean age of the population to divide them into younger and elderly cohorts. This is not ideal, but given the paucity of data in each of the trials this is probably acceptable. Heart failure was a secondary end point in these trials, and as such the trials may not be sufficiently powered to evaluate this end point. Finally, the definition of new-onset HF varied in these trials. Our search limitations and failure to evaluate/report HF outcomes in many of the RCTs may have introduced publication bias, although this was not evident in the analyses for publication bias. It should be noted that 66% of patients on BBs were on atenolol, hence meaningful extrapolation of these results to those of other BBs cannot be done.

Conclusions

Our results echo the ACC/AHA guideline statement on the importance of blood pressure control to reduce the risk of HF in patients with hypertension in that BBs showed a trend toward risk reduction of HF when compared with placebo, where they resulted in a significant decrease in blood pressure. However, a significant decrease in blood pressure in the placebo-controlled trials, excluding the mixed BB/diuretic trial (STOP), failed to show any beneficial HF risk reduction with BBs, suggesting that a mere reduction in blood pressure may not be sufficient and that the type of medication used to lower it may be important as well.

When compared with other antihypertensive agents, BBs provided comparable but no incremental benefit for the prevention of heart failure. However, given the increased risk of stroke in the elderly patients and lack of any incremental benefit for any of the primary or secondary outcomes, BBs should not be used in the primary prevention of HF, unless compelling circumstances such as prior myocardial infarction were already present (11).

Reprint requests and correspondence: Dr. Franz H. Messerli, 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: messerli.f@gmail.com.

REFERENCES

1. Thom T, Haase N, Rosamond W, et al. Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2006;113:e85–151.
2. Kannel WB, Castelli WP, McNamara PM, McKee PA, Feinleib M. Role of blood pressure in the development of congestive heart failure. The Framingham Study. N Engl J Med 1972;287:781–7.
3. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA 1996;275:1557–62.
4. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Left ventricular mass and incidence of coronary heart disease in an elderly cohort. The Framingham Heart Study. Ann Intern Med 1989;110:101–7.
5. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. J Am Coll Cardiol 2005;46:e1–82.
6. Kostis JB, Davis BR, Cutler J, et al. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. SHEP Cooperative Research Group. JAMA 1997;278:212–6.
7. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560–72.
8. Messerli FH, Grossman E, Goldbourt U. Are beta-blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. JAMA 1998;279:1903–7.
9. Lindholm LH, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. Lancet 2005;366:1545–53.
10. Wiysonge CS, Bradley H, Mayosi BM, et al. Beta-blockers for hypertension. Cochrane Database Syst Rev 2007:CD002003.
11. Bangalore S, Messerli FH, Kostis JB, Pepine CJ. Cardiovascular protection using beta-blockers: a critical review of the evidence. J Am Coll Cardiol 2007;50:563–72.
12. Mancia G, De Backer G, Dominiczak A, et al. 2007 guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2007;28:1462–536.
13. National Collaborating Centre for Chronic Conditions. Hypertension: management of hypertension in adults in primary care: partial update. London: Royal College of Physicians, 2006.
14. Berenson A. Big Drug Makers See Sales Decline With Their Image. New York Times. New York, November 14, 2005.
15. Kaboli PJ, Shivapour DM, Henderson MS, Barnett MJ, Ishani A, Carter BL. Patient and provider perceptions of hypertension treatment: do they agree? J Clin Hypertens 2007;9:416–23.
16. Bangalore S, Messerli FH. Hypertension in the elderly: a compelling contraindication for beta-blockers? J Hum Hypertens 2007;21:259–60.
17. Bradburn MJ DJJADG. Sbe24: metan—an alternative meta-analysis command. Stata Techn Bull Reprints 1998;8:86–100.
18. Galbraith RF. A note on graphical presentation of estimated odds ratios from several clinical trials. Stat Med 1988;7:889–94.
19. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
20. Wikstrand J, Warnold I, Tuomilehto J, et al. Metoprolol versus thiazide diuretics in hypertension. Morbidity results from the MAPHY study. Hypertension 1991;17:579–88.
21. Wilhelmsen L, Berglund G, Elmfeldt D, et al. Beta-blockers versus diuretics in hypertensive men: main results from the HAPPHY trial. J Hypertens 1987;5:561–72.
22. Black HR, Elliott WJ, Grandits G, et al. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. JAMA 2003;289:2073–82.
23. Dahlof B, Lindholm LH, Hansson L, Schersten B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). Lancet 1991;338:1281–5.
24. Hansson L, Hedner T, Lund-Johansen P, et al. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. Lancet 2000;356:359–65.
25. Hansson L, Lindholm LH, Ekbom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. Lancet 1999;354:1751–6.
26. Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril

Prevention Project (CAPPP) randomised trial. Lancet 1999;353: 611–6.
27. Cardiovascular risk and risk factors in a randomized trial of treatment based on the beta-blocker oxprenolol: the International Prospective Primary Prevention Study in Hypertension (IPPPSH). The IPPPSH Collaborative Group. J Hypertens 1985;3:379–92.
28. Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. Br Med J (Clin Res Ed) 1986;293:1145–51.
29. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. BMJ 1998;317:713–20.
30. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:995–1003.
31. Dahlof B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005;366:895–906.
32. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA 2003;290:2805–16.
33. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353:9–13.
34. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001–7.
35. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651–8.
36. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation 2002;106:2194–9.
37. Nilsson PM, Berglund G. Beta-receptor blockers in primary prevention for cardiovascular disease: forgotten benefits? J Hum Hypertens 2006;20:719–21.
38. Poulter NR, Wedel H, Dahlof B, et al. Role of blood pressure and other variables in the differential cardiovascular event rates noted in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA). Lancet 2005;366:907–13.
39. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation 2006;113:1213–25.
40. Khan N, McAlister FA. Re-examining the efficacy of beta-blockers for the treatment of hypertension: a meta-analysis. CMAJ 2006;174: 1737–42.
41. Zanchetti A, Bond MG, Hennig M, et al. Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: principal results of the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double-blind, long-term trial. Circulation 2002;106:2422–7.
42. MRC trial of treatment of mild hypertension: principal results. Medical Research Council Working Party. Br Med J (Clin Res Ed) 1985;291:97–104.
43. Elliott W. Cardiovascular events during antihypertensive therapy with either a calcium antagonist or a diuretic/beta-blocker: meta-analysis of 7 clinical trials (abstr). Am Soc Hypertens 2003;16:9A.
44. Messerli FH. Antihypertensive therapy: beta-blockers and diuretics-why do physicians not always follow guidelines? Proc Bayl Univ Med Cent 2000;13:128–31.
45. Turnbull F. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet 2003;362:1527–35.

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