Are there big differences among beta-blockers in treating essential hypertension?

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CLINICAL COMMENTARY

Beta-blocker debate may be irrelevant when these drugs are taken with other antihypertensives

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Definitive evidence has demonstrated reduced risk of cardiovascular events with beta-blockers as a primary antihypertensive agent for patients with concurrent coronary heart disease. However, using a beta-blocker as a primary antihypertensive for patients without such compelling indications is now considered controversial. In 2006, the UK's National Institute for Health and Clinical Excellence published a clinical guideline for hypertension (1) in which beta-blockers are no longer preferred as a routine initial therapy for hypertension and are reserved as alternative agents after diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers.

This recommendation was based on results from meta-analyses that suggest beta-blockers, especially atenolol, may not be as cardioprotective as other antihypertensives. This has been confirmed by a 2007 Cochrane analysis. (2) Despite a half-life of only 6 to 7 hours, atenolol is nearly always dosed once daily, while carvedilol and metoprolol have half-lives of 6 to 10 and 3 to 7 hours, respectively, and are dosed at least twice daily. It is possible that the controversy with beta-blockers arises because atenolol should really be a twice-daily drug.

In clinical practice, most patients with hypertension need more than one agent to attain goal blood pressure values. The debate over whether one beta-blocker is better or worse may be clinically irrelevant when beta-blockers are used in combination with another antihypertensive. ❑

EVIDENCE-BASED ANSWER

Yes, a number of beta-blockers are effective in lowering blood pressure (strength of recommendation [SOR]: **A**, multiple, consistent randomized controlled trials [RCTs]). Cardioselective beta-blockers do not alter lung function studies for patients with chronic obstructive pulmonary disease (COPD) or reversible airway disease (SOR: **A**, meta-analysis of RCTs).

Propranolol and timolol have greater risks of causing fatigue as a side effect (SOR: **A**, meta-analysis of RCTs). Recent meta-analyses have stirred debate on the effectiveness of the agents in preventing adverse outcomes. The level of evidence has reached the point where the practice of using beta-blockers as monotherapy should be questioned (SOR: **C**, expert opinion). ❑

EVIDENCE SUMMARY

Numerous trials have shown that beta-blockers lower blood pressure for patients with hypertension. No head-to-head trials of beta-blockers have been conducted that reveal differences in terms of patient-oriented outcomes, such as all-cause mortality, in the treatment of hypertension. ❑

NO EFFECT ON LUNG FUNCTION, BUT FATIGUE IS A FACTOR

A Cochrane review on the cardioselective beta-blockers atenolol (Tenormin), bisoprolol (Zebeta), and metoprolol (Lopressor) found that single-dose and multiple-treatment studies showed no decline in lung function among patients with mild to moderate reversible airway disease or chronic obstructive pulmonary disease. (3,4) The analysis was not able to identify any differential effect of these beta-blockers with or without intrinsic sympathomimetic activity for patients with lung disease.

FAST TRACK

The debate over whether one beta-blocker is better or worse may be irrelevant when beta-blockers are used with another antihypertensive.

That said, beta-blockers do have side effects. One meta-analysis found no difference in the development of depression with beta-blocker therapy; however, first-generation beta-blockers (propranolol and timolol) had higher rates of fatigue than did the later beta-blockers. (5) They reported that the risk of fatigue was only 18 per 1000 patients (95% confidence interval [CI], 5-30) and the risk for sexual dysfunction was 5 per 1000 patients (95% CI, 2-8) for all beta-blockers as a class. Importantly, they also stratified side-effect findings on the basis of lipophilic vs nonlipophilic and found no difference in side effect frequency. ❑

ADVERSE OUTCOMES DATA GIVE REASON TO PAUSE

Two recent meta-analyses (6,7) on beta-blockers have called into question the effectiveness of these agents in preventing adverse outcomes in treating hypertension.

The first meta-analysis (6) reviewed 4 studies that compared atenolol with placebo or no treatment, and 5 that compared atenolol with other antihypertensive drugs. They found no outcome differences between atenolol and placebo in the 4 studies, comprising 6825 patients, followed for a mean of 4.6 years. There was no difference in all-cause mortality (relative risk [RR] = 1.01; 95% CI, 0.89-1.15), cardiovascular mortality (RR = 0.99; 95% CI, 0.83-1.18), or myocardial infarction (RR = 0.99; 95% CI, 0.83-1.19). The risk of stroke appeared to be lower in the atenolol than in the placebo group (RR = 0.85; 95% CI, 0.72-1.01). When atenolol was compared with other antihypertensives, there were no major differences in blood pressure lowering between the treatment arms.

The authors found a significantly higher mortality (RR = 1.13; 95% CI, 1.02-1.25) with atenolol treatment than with other active treatment, in 5 studies comprising 17,671 patients who were followed up for a mean of 4.6 years. Stroke was also more frequent with atenolol in comparison with other agents.

FAST TRACK

A meta-analysis found that beta-blockers reduced major cardiovascular outcomes in younger – but not older – patients.

The second meta-analysis (7) covered 13 randomized controlled trials (n = 105,951) comparing treatment with beta-blockers with other antihypertensive drugs. Seven studies (n = 27,433) were included in a comparison of beta-blockers and placebo or no treatment. The relative risk of stroke was 16% higher for beta-blockers (95% CI, 4%-30%) than for other drugs. No difference was seen for myocardial infarction. When the effect of beta-blockers was compared with that of placebo or no treatment, the relative risk of stroke was reduced by 19% for all beta-blockers (95% CI, 7%-29%). There was no difference for myocardial infarction or mortality. ❑

AN AGE DIVIDE APPEARS WITH ADVERSE EVENTS

A subsequent meta-analysis found that beta-blocker therapy in younger patients (less than 60 years of age) is associated with a significant reduction in cardiovascular morbidity and mortality. (8) Researchers used data from 145,811 participants in 21 hypertension trials, beta-blockers reduced major cardiovascular outcomes in younger patients (risk ratio = 0.86; 95% CI, 0.74-0.99) but not in older patients (risk ratio = 0.89; 95% CI, 0.75-1.05).

In active comparator trials, beta-blockers demonstrated similar reductions in morbidity and mortality to other antihypertensive agents in younger patients (risk ratio = 0.97; 95% CI, 0.88-1.07) but not in older patients (risk ratio = 1.06; 95% CI, 1.01-1.10), with the excess risk being particularly marked for strokes (risk ratio = 1.18; 95% CI, 1.07-1.30). The primary outcome researchers evaluated was a composite of stroke, myocardial infarction, and death. ❑

CALCIUM CHANNEL BLOCKERS BEAT BETA-BLOCKERS IN RECENT REVIEW

Finally, a more recent systematic review found beta blockers to be inferior to calcium channel blockers and renin-angiotensin system inhibitors (ACE inhibitors or ARBs) for major endpoints of all-cause mortality, coronary heart disease, stroke, total cardiovascular events, and cardiovascular mortality. (9) This review found beta-blockers had similar outcomes as diuretics but were less well tolerated than diuretics (RR = 1.80; 95% CI, 1.33-2.42) or renin-angiotensin system inhibitors (RR = 1.41; 1.29-1.54).

Thirteen trials with 91,561 participants, meeting inclusion criteria, compared beta-blockers with placebo (4 trials; n = 23,613), diuretics (5 trials; n = 18,241), calcium-channel

blockers (4 trials; n = 44,825), and renin-angiotensin system inhibitors (3 trials; n = 10,828). Compared with placebo, beta-blockers reduced the risk of stroke (RR = 0.80; 95% CI, 0.66-0.96) with a marginal fall in total cardiovascular events (RR=0.88; 95% CI, 0.79-0.97), but did not affect all-cause mortality (RR = 0.99, 0.88-1.11), coronary heart disease (RR = 0.93, 0.81-1.07), or cardiovascular mortality (RR = 0.93, 0.80-1.09). The effect on stroke was less than that of calcium-channel blockers (RR = 1.24, 1.11-1.40) and renin-angiotensin system inhibitors (RR = 1.30, 1.11-1.53). The effect on total cardiovascular events was less than that of calcium-channel blockers (RR = 1.18, 1.08-1.29). ❑

RECOMMENDATIONS FROM OTHERS

The Joint National Committee on Hypertension (JNC-7) states that excellent clinical trial data demonstrate that lowering blood pressure with beta-blockers (and several other drug classes) will reduce the complications of hypertension. (10)

FAST TRACK

Beta-blockers were inferior to calcium channel blockers, ACE inhibitors, and ARBs for all-cause mortality.

The European Society of Cardiology recommends beta-blockers as the first choice for antihypertensive therapy, alone or in combination, for patients with previous myocardial infarction, ischemic heart disease, arrhythmias or heart failure, asymptomatic left ventricular dysfunction, diabetes, or high risk of coronary disease, based on the efficacy of these drugs in these patient populations. (11) ❑

REFERENCES

1. **Hypertension –** Management of hypertension in adults in primary care. London: *Royal College of Physicians;* June 2006. Available at www.nice.org.uk/CG034. Accessed on March 7, 2007.
2. **Wiysonge C, Bradley H, Mayosi B, et al** – Beta-blockers for hypertension. *Cochrane Database Syst Rev* 2007; (1):CD002003.
3. **Salpeter S, Ormiston T, Salpeter E, Wood-Baker R** – Cardioselective beta-blockers for COPD. *Cochrane Database Syst Rev* 2005; (4):CD003566.
4. **Salpeter S, Ormiston T, Salpeter E** – Cardioselective beta-blockers for reversible airway disease. *Cochrane Database Syst Rev* 2002; (4):CD002992.
5. **Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM** – Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA* 2002; 288:351-357.
6. **Carlberg B, Samuelsson O, Lindholm LH** – Atenolol in hypertension: is it a wise choice? *Lancet* 2004; 364:1684-1689.
7. **Lindholm LH, Carlberg B, Samuelsson O** – Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet* 2005; 366:1545–1553.
8. **Khan N, McAlister FA** – Re-examining the efficacy of beta-blockers for the treatment of hypertension: a meta-analysis. *CMAJ* 2006; 174:1737–1742.
9. **Bradley HA, Wiysonge CS, Volmink JA, et al** – How strong is the evidence for use of beta-blockers as first-line therapy for hypertension? Systematic review and meta-analysis. *J Hypertens* 2006; 24:2131–2141.
10. **Chobanian AV, Bakris GL, Black HR, et al** – Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; 42:1206-1252.
11. **Lopez-Sendon J, Swedberg K, McMurray J, et al** – Expert consensus document on beta-adrenergic receptor blockers. *Eur Heart J* 2004; 25:1341-1362.