Do ß-blockers have a role in treating hypertension?

YES

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The 2006 Canadian Hypertension Education Program recommendations[1] continue to list ß-blockers as appropriate first-line therapy for uncomplicated hypertension in those younger than 60 years (but not for those older than 60). A recent, widely publicized meta-analysis, however, reported that ß-blocker use was associated with increased risk of stroke,[2] sparking great controversy about the role of these agents in treating hypertension. Many family physicians are now facing the following questions.

1. Do ß-blockers have any role in treatment of hypertension?
2. If patients are stable and well controlled on ß-blocker therapy, should their therapy be changed?

Pathophysiology of hypertension

Efficacy of ß-blockers might differ by age, given the differences in the pathophysiology of hypertension in younger and older patients. Younger patients tend to develop hypertension with high sympathetic drive and cardiac output but normal arterial compliance—a state attenuated by ß-adrenergic blockade. Older patients generally have systolic hypertension with increased arterial stiffness. Thus, agents having little effect on arterial compliance, such as ß-blockers, would be expected to be less beneficial for older patients.

Clinical trial evidence

These differences in efficacy according to age have largely been borne out in clinical trials. Messerli et al published a meta-analysis of hypertension trials that evaluated ß-blockers in patients older than 60.[3] From a pooled analysis of 10 trials published before 1999 (N=16 164), they found that ß-blockers were not significantly different from placebo in reducing cardiovascular mortality and all-cause mortality. Because of these data, the Canadian hypertension guidelines[1] have recommended that ß-blockers not be used as initial monotherapy for uncomplicated hypertension among the elderly. The guidelines have continued, however, to endorse ß-blockers for elderly patients with congestive heart failure

NO

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When your heart's on fire, you must realize, smoke gets in your eyes.

The Platters, Smoke Gets in Your Eyes

In 1996, a colleague and I wrote in the hypertension chapter of a textbook, "[ß-blockers] have proven efficacy in reducing morbidity and mortality"[1] (M&M). In hindsight, the only way we could have thought this was true was to ignore the results of almost all the large ß-blocker hypertension trials.

Table 1 summarizes the available evidence from placebo-controlled trials looking at the effect of ß-blockers on M&M when used for hypertension.[2] Five of 7 trials were unable to demonstrate that ß-blockers had any effect on individual end points of stroke, myocardial infarction (MI), or overall mortality when compared with placebo. In the 2 trials that did show significant differences, approximately 60% of subjects were taking thiazides, which might have contributed to the observed benefit. Lindholm et al recently published these results as a meta-analysis.[2] Compared with placebo, ß-blockers produced no statistically significant effect on coronary artery disease or mortality, but there was a 19% relative

Table 1. Summary of ß-blocker vs placebo or open control data*

YEAR	TRIAL NAME	N	DRUG STUDIED	STROKE	MI	DEATH
1985	MRC	13 057	Propranolol	NSS	NSS	NSS
1985	IPPPSH	6357	Oxprenolol	NSS	NSS	NSS
1986	HEP	720†	Atenolol	SS	NSS	NSS
1991	STOP	1627†	Atenolol, metoprolol, pindolol	SS	NSS	SS
1992	MRC Old	3315	Atenolol	NSS	NSS	NSS
1993	Dutch TIA	874	Atenolol	NSS	NSS	NSS
1995	TEST	1471	Atenolol	NSS	NSS	NSS

Dutch TIA—Dutch Transient Ischemic Attack trial, HEP—Hypertension in Elderly Patients trial, IPPPSH—International Prospective Primary Prevention Study in Hypertension, MI—myocardial infarction, MRC—Medical Research Council trial of mild hypertension, NSS—end points not statistically different between ß-blocker and placebo groups, SS—end points statistically different between ß-blocker and placebo or open control groups, STOP—Swedish Trial in Old Patients with hypertension, TEST—Tenormin after Stroke and Transient ischemic attack trial.

*Data from Lindholm et al.[2]

†Approximately 60% of subjects were taking thiazides.

YES

or a history of myocardial infarction (MI) or symptomatic angina and as second- or third-line agents for patients with uncontrolled hypertension.

In their meta-analysis, Lindholm et al pooled together 18 trials (N = 106 460) evaluating ß-blocker use regardless of patient age.[2] In this analysis, there was no difference in risk of MI or death. While ß-blockers were associated with reduced risk of stroke (reduced relative risk [RR] 19%, 95% confidence interval [CI] 7% to 29%) in placebo-controlled trials, this was less than the 32% reduction seen with other antihypertensive agents in placebo-controlled trials.[4] In trials comparing one antihypertensive agent with another, patients assigned ß-blockers had a 16% higher risk of stroke than patients taking other antihypertensives did.

Given the plausible differences in ß-blocker efficacy according to age, however, we re-analyzed all ß-blocker hypertension trials according to age of participants.[5] In trials where the average age was older than 60, ß-blockers were associated with increased risk of stroke, MI, or death compared with other antihypertensives (RR 1.07, 95% CI 1.00-1.14), largely driven by an 18% increase (95% CI 7%-30%) in risk of stroke. Among trials where the average age of patients was younger than 60, there was no difference in the composite outcome of stroke, MI, or death between patients taking ß-blockers and those taking other agents (RR 0.97, 95% CI 0.88-1.07).

Tolerability and side effect profile

Like all antihypertensive agents, ß-blockers can have adverse effects. Contrary to popular belief, however, ß-blockers are generally well tolerated and do not impair quality of life.[6] They do have several contraindications, including moderate or severe asthma, but they appear to be safe for patients with chronic obstructive pulmonary disease with minor airway reversibility and those with sick sinus syndrome or high-degree atrioventricular block. While studies demonstrate adverse effects on insulin resistance and lipid profile, newer ß-blockers with vasodilatory effects, such as carvedilol, have neutral effects on insulin sensitivity and lipid profile.[7] Meta-analyses also report no significant increases in depressive symptoms[8] or in exacerbation of claudication for patients with peripheral arterial disease.[9] Although ß-blockers are associated with fatigue and sexual dysfunction, the absolute risks are fairly small (fatigue, 18 per 1000 patients; sexual dysfunction, 5 per 1000).

Conclusion

Do ß-blockers have any role in the treatment of hypertension? Although ß-blockers should not be used for first-line monotherapy in elderly patients with hypertension, they remain reasonable first-line treatment for patients younger than 60 with uncomplicated

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reduction (<0.5% absolute reduction) in stroke. This is half of what is typically seen with other antihypertensives. Looking only at the trials that compared atenolol with placebo, no statistically significant reduction in any end point was found.

These findings are not new. Earlier meta-analyses[3,4] questioned the use of ß-blockers for hypertension, especially among the elderly. Given this uncertainty, one would expect the use of ß-blockers (especially atenolol) in the elderly to be minimal. Nothing could be further from the truth. British Columbia pharmacare data showed the number of atenolol prescriptions in British Columbia for patients older than 65 had increased each year from 2003 to 2005. It was the most prescribed ß-blocker in both 2004 and 2005, and now sits at ¼ million prescriptions a year.

In a more recent meta-analysis,[5] the authors split the ß-blocker studies into those that looked at either younger (<60) or older (≥60) patients. In patients younger than 60, using a composite outcome of MI, stroke, and mortality, the authors calculated a risk ratio of 0.86, with the upper limit of the 95% confidence interval just sneaking (0.99) under the magical 1. Using their estimates, ß-blockers produced a whopping 0.5% absolute reduction (over 5 years) in this composite outcome. This led the authors to state that "in younger patients ß-blockers are associated with a significant reduction in cardiovascular morbidity and mortality."[5] Interestingly, the main study used to support this statement was the Medical Research Council trial of mild hypertension,[6] which reported that "cardiovascular events [were] not reduced by … smokers taking propranolol" and that "all cause mortality was reduced in men on active treatment [thiazide or ß-blockers] but increased in women." Space precludes a detailed critique of this meta-analysis, but one of the problems with retrospective analysis of data is that, if one looks at enough end points, something statistically significant can show up, including the things the MRC mentioned.

So why, in the mid-1990s, did my colleague and I state that ß-blockers had been shown to reduce M&M associated with hypertension? In hindsight, I believe we erred in the following ways:

- by talking about thiazides and ß-blockers as a group rather than looking at individual agents,
- by not questioning the link between surrogate markers (blood pressure) and M&M,
- by not requiring solid evidence from randomized controlled trials to make recommendations, and
- by selecting ß-blockers for post-MI therapy or for patients who also had angina, migraine, or essential tremour and thinking we were getting "2-fers."

We were not the only ones making these statements. For example, the 1993 report from the Canadian

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hypertension or for patients of any age with heart failure, symptomatic angina, or MI within the previous 2 years, and they remain reasonable add-on agents for patients with uncontrolled hypertension.

If patients are stable and well controlled on ß-blocker therapy, should their therapy be changed? While no trial data directly answer this question, hypertension studies collectively demonstrate that the most important factor in improving outcomes is achieving good blood pressure control; choice of agent is less important.[10]

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Acknowledgment

Dr Khan *is a GENESIS (Canadian Institutes of Health Research [CIHR] and Heart and Stroke Foundation of Canada) young investigator, a CIHR New Investigator, and a St Paul's Hospital Foundation New Investigator.* **Dr McAlister** *is supported by the Alberta Heritage Foundation for Medical Research, CIHR, and the University of Alberta/Merck Frosst/Aventis Chair in Patient Health Management.*

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NO

Hypertension Society stated, "since 1988 three studies…have confirmed the efficacy…of diuretics and ß-blockers and have shown a marked and significant reduction in the risk of [cerebrovascular accident]."[7] The 3 studies referenced don't support that conclusion with regard to ß-blockers.

The 2004 Canadian Hypertension Education Program guidelines recommended that ß-blockers be among 5 first-line drugs for initial therapy. The 2005 and 2006 guidelines were similar, but said ß-blockers should be used only for those younger than 60.

So after 42 years of using these agents, what do we know about the effects of ß-blockers on the M&M associated with hypertension?

- Studies of patients 60 and older have not shown a benefit.
- Studies using atenolol have not shown a benefit.
- Studies of patients younger than 60 have not shown a benefit in individual cardiovascular end points.
- If one retrospectively searches for statistically significant differences, a 0.5% absolute reduction in a composite cardiovascular end point is possible in patients younger than 60.
- A recent meta-analysis[2] showed that ß-blockers had less effect on some end points (particularly stroke) than other antihypertensive agents did.

In my opinion, these data do not justify a first-line recommendation for ß-blockers in hypertension. But so as to not be roundly criticized for throwing out the baby with the bath water, I strongly believe that for younger, male, non-smoking, hypertensive patients, who wish to reduce their cardiovascular risk by upwards of 0.5% and who have been shown to be intolerant (when appropriately dosed) of every other available first-line class of antihypertensives, ß-blockers would clearly be a solid first-line choice (except for atenolol, that is).

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KEY POINTS

- ß-Blockers are appropriate first-line treatment for patients younger than 60 with uncomplicated hypertension or for patients of any age with heart failure, symptomatic angina, or myocardial infarction within the previous 2 years.
- ß-Blockers are reasonable add-on agents for patients with uncontrolled hypertension.
- Hypertension studies collectively demonstrate that the most important factor in improving outcomes is achieving good blood pressure control; choice of agent is less important.

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KEY POINTS

- Only minimal evidence suggests ß-blockers reduce the morbidity and mortality associated with hypertension, especially among the elderly.
- Clinicians must be sceptical of using drugs for which only surrogate marker evidence is available.
- All patients 60 and older who are taking ß-blockers for hypertension alone should be reassessed because ß-blockers are not in a class of agents that reduces morbidity and mortality.
- Even among patients younger than 60, in my opinion, ß-blockers should not be first-line agents.