Editorial **Asking the right questions** PAGE 6 By Lee Green, MD, MPH, member, JNC

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When *not* to use beta-blockers in seniors with hypertension

FAST TRACK

Meta-analyses of beta-blocker trials show that they are inferior for first-line hypertension treatment in the elderly who do not have heart failure or angina

PURLs methodology
This study was selected and evaluated using FPIN's Priority Updates from the Research Literature (PURL) Surveillance System methodology. The criteria and findings leading to the selection of this study as a PURL can be accessed at www.jfponline.com/purls.

Practice changer

Beta-blockers should not be used to treat hypertension in patients older than age 60 unless they have another compelling indication to use these agents, such as heart failure or ischemic heart disease.[1,2]

Strength of recommendation
A: Based on a well-done meta-analyses

Khan N, McAlister FA. Re-examining the efficacy of beta-blockers for the treatment of hypertension: a meta-analysis. *CMAJ* 2006; 174:1737–1742.[1]

Wiysonge CS, Bradley H, Mayosi BM, et al. Beta-blockers for hypertension. *Cochrane Database Syst Rev* 2007; (1):CD002003.[2]

ILLUSTRATIVE CASE

A 70-year-old man with newly diagnosed hypertension comes to your office. You don't want to prescribe a diuretic due to his history of gout. He has no history of coronary artery disease or heart failure.

What is the best antihypertensive agent for him?

BACKGROUND

Guidelines do not reflect new evidence

Guidelines for the use of beta-blockers in the elderly do not reflect current evidence.

JNC recommendations

The 2003 JNC 7 Report recommended the same antihypertensive medications for adults of all ages.[3] (JNC 7 is the most recent report from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.)

JNC 7 recommends thiazide diuretics for first-line treatment of hypertension, and recommends other drugs—*including beta-blockers*, calcium-channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs)—for first-line therapy if a thiazide is contraindicated, or in combination with thiazides for higher initial blood pressure.

Compelling indications. Beta-blockers are recommended in the JNC 7 Report as first-line therapy in patients with "compelling indications" such as ischemic heart disease and heart failure.

CLINICAL CONTEXT

Seniors taking beta-blockers to their detriment?

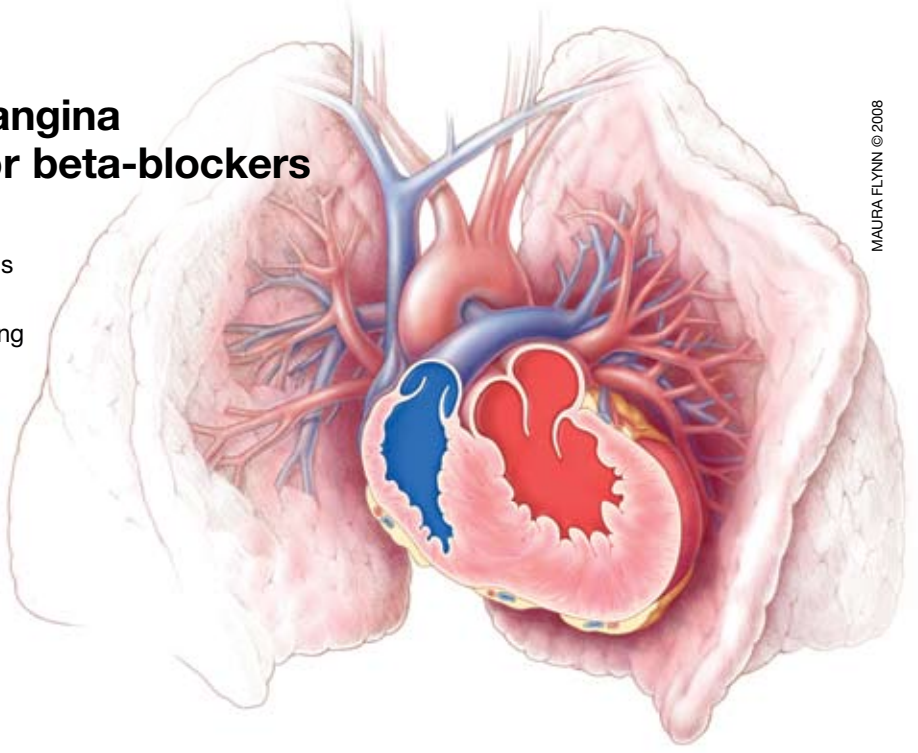
Many elderly patients are on beta-blockers, perhaps to their detriment. Treatment choices for hypertension can have an enormous impact on outcomes among older patients:

Two thirds of US adults 60 years of age and older have hypertension, mostly isolated systolic hypertension.[4,5]

Multiple studies, including the Sys-

Heart failure and angina are indications for beta-blockers

New evidence does not alter the 2003 JNC 7 recommendations to use beta-blockers as first-line therapy in patients with "compelling indications" such as ischemic heart disease and heart failure.



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tolic Hypertension in the Elderly Program and the Systolic Hypertension in Europe, have shown that lowering blood pressure with pharmacologic interventions in older patients can reduce the risk of cardiovascular events and possibly dementia.[6]

Beta-blockers have been a mainstay of hypertension treatment for many decades and we suspect continue to be widely used as first-line therapy in patients for whom the evidence now indicates they are inferior.

STUDY SUMMARIES

Two well-done reviews of beta-blocker trials show that they are inferior for first-line hypertension treatment in the elderly who do not have heart failure or angina.

2007 Cochrane review

The 2007 Cochrane review[2] analyzed randomized trials that compared beta-blockers for hypertension in adults 18 years of age and older to each of the other major classes of antihypertensives.

Conclusion. This meta-analysis showed a "relatively weak effect of beta-blockers to reduce stroke, and the absence of effect on coronary heart disease when compared with placebo or no treatment" and a "trend toward worse outcomes in comparison with calcium channel blockers, renin-angiotensin system inhibitors, and thiazide diuretics."

This meta-analysis included all adults and did not make any conclusions based on age.

2006 *CMAJ* meta-analysis

The Kahn and McAlister meta-analysis[1] pooled data from 21 randomized hypertension trials (including 6 placebo-controlled trials) that evaluated the efficacy of beta-blockers as first-line therapy for hypertension in preventing major cardiovascular outcomes (death, nonfatal MI, or nonfatal stroke).

The results were analyzed by age group: trials enrolling patients with a mean age of 60 years or older at baseline vs trials enrolling patients with a mean age of under 60 years.

Conclusion. They concluded that in trials comparing other antihypertensive medications with beta-blockers, all agents showed similar efficacy in younger patients, while in older patients, beta-blockers were associated

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In older patients, beta-blockers were associated with a higher risk of adverse outcomes

TABLE

Adverse outcomes more likely in seniors taking a beta-blocker vs other antihypertensives[1]

ADVERSE OUTCOME	PATIENTS UNDER AGE 60 ADVERSE OUTCOMES LESS LIKELY WITH A BETA-BLOCKER	PATIENTS AGE 60 AND OVER ADVERSE OUTCOMES MORE LIKELY WITH A BETA-BLOCKER
Composite outcomes (death, stroke, or MI)	RR=0.97 (95% CI, 0.88–1.07)	RR=1.06 (95% CI, 1.01–1.1)
Stroke	RR=0.99 (95% CI, 0.67–1.44)	RR =1.18 (95% CI, 1.07–1.3)

RR, relative risk of adverse outcomes, in randomized clinical trials of hypertensive patients treated with beta-blockers, compared with other antihypertensive drugs.

with a higher risk of both composite events and strokes (**TABLE**).

WHAT'S NEW?

The age distinction

These 2 meta-analyses[1,2] help overturn a long-held belief about the value of beta-blockers for the treatment of hypertension. Beta-blockers may not be a good first-line choice for any hypertensive patient—and the evidence clearly shows they are not a good first-line choice for patients over 60 years old.

Two earlier systematic reviews did raise the concern about using beta-blockers as first-line treatment for hypertension (even when thiazides are not contraindicated).

The first systematic review to raise this concern was a 1998 study of 10 hypertension trials in more than 16,000 patients, ages 60 and older. This review showed that diuretics were superior to beta-blockers in reducing cardiovascular and all-cause mortality—which supports the JNC 7 recommendation to choose a thiazide diuretic as the first-line drug of choice.[7]

The second study, a meta-analysis published in 2005, also concluded that beta-blockers should no longer be considered first-line therapy for hypertension, due to a 16% increase in the relative risk of stroke compared with other agents. This meta-analysis, however, did not report outcomes by patient age.[8]

Beta-blockers are not 1st-line, even if thiazides are contraindicated

What is new about the Kahn and McAlister evidence is that beta-blockers should not be the first-line drug of choice even when thiazide diuretics are contraindicated. Their study included a larger number of trials (21 trials vs 13 in the 2005 meta-analysis), which allowed the investigators to examine outcomes in patients younger than 60 and in those 60 years and older.

CAVEATS

Continue beta-blockers for the right reasons

Patients over 60 with ischemic heart disease or heart failure should still be prescribed beta-blockers for heart failure and angina. Also, in older patients with hypertension who need multiple agents to control their blood pressure, a beta-blocker could be added as a third or fourth agent in addition to a diuretic, ACE inhibitor, ARB, or calcium-channel blocker. Metoprolol is a good choice, as it is inexpensive and proven to reduce mortality in patients with a history of MI or heart failure.

Atenolol may underperform

In a meta-analysis of 31 trials, Freemantle[9] found that after MI, acebutolol, metoprolol, propranolol, and timolol significantly reduced mortality, while there was no mortality reduction with atenolol. Similarly, in

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Changing our beliefs about beta-blockers may be our main challenge

heart failure, only bisoprolol, metoprolol, and carvedilol have evidence to support a reduction in mortality.[10]

Although atenolol is one of the most commonly prescribed beta-blockers due to its low cost and once-daily dosing, it may be the least effective. In a systematic review of 9 hypertension studies, Carlberg[11] showed that atenolol was no more effective than placebo at reducing MI, cardiovascular mortality, or all-cause mortality, and that patients on atenolol had significantly higher mortality than those taking other antihypertensives. Khan and McAlister do not differentiate between atenolol and other beta-blockers in their meta-analysis.[1]

CHALLENGES TO IMPLEMENTATION

Letting go

The evidence supporting this change in practice has been accumulating over time. The change itself represents a significant reversal of long-standing belief in the value of beta-blockers as an antihypertensive agent. For each individual patient, the risk is not dramatic even though the cumulative "harm" from using a beta-blocker compared to other options is potentially staggering because so many people over 60 have hypertension.

We suspect that the main challenge will be changing the beliefs of both physicians and patients. Once doctors are convinced that beta-blockers are not indicated for uncomplicated hypertension in patients over 60, changing medications in the millions of older patients who have been taking a beta-blocker for some time and have become comfortable with it will take tact and excellent communication skills.

Providing patient information may help. Sources for patients are available free or at low cost at www.nhlbi.nih.gov/health/public/heart/index.htm#hbp. These materials explain that diuretics are inexpensive and are the preferred drugs for initial treatment of hypertension. ■

Cost comparison

In patients over 60 who can't tolerate a thiazide, the least expensive option is an ACE inhibitor. For example, in the Target and Walmart discount generic programs, benazepril, captopril, enalapril, and lisinopril are all available for $4 per month.

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FAST TRACK

Atenolol may be the least effective beta-blocker