



**Lee Green, MD, MPH**

Department of Family Medicine,  
University of Michigan, Ann Arbor; Member,  
Executive Committee, Seventh Joint National  
Committee on Prevention, Detection, Evaluation,  
and Treatment of High Blood Pressure (JNC VII)  
greenla@umich.edu

## Asking the right questions

The Family Physicians Inquiries Network (FPIN) poses and answers a difficult question in the PURL on page 18: What role should beta-blockers play in the treatment of hypertension? It is a hard question to answer, based on the evidence. Certainly, we have plenty of evidence, but not all of it is the right kind. In addition, we haven't always asked the right questions.

### QUESTION #1

#### ■ Why haven't we distinguished between the 2 hypertension?

We use the term "hypertension" in the singular, but it should be plural. There are 2 essential hypertension, and we have not distinguished them in our evidence base or our questions of evidence. Most of the early hypertension trials enrolled middle-aged patients (predominantly male) with diastolic-systolic essential hypertension (DSH). More recent studies have enrolled middle-aged and elderly or solely elderly patients. Elders predominantly have isolated systolic hypertension (ISH). DSH and ISH are different diseases with different pathophysiologies, much like pneumococcal and mycoplasma pneumonia. As such, we must ask the questions of evidence for them separately.

### QUESTION #2

#### ■ Are all beta-blockers created equal?

The Cochrane review<sup>1</sup> cited in this month's PURL concludes with a disclaimer about subgroups of beta-blockers. That caution is well advised. There is evidence that atenolol, specifically, may be the underperformer, not beta-blockers in general.<sup>2</sup> Atenolol differs from other beta-blockers in pharmacologically significant ways; for example, it is strongly hydrophilic, in contrast to other beta-blockers, which are lipophilic. The concern over atenolol's outcome benefits, or lack thereof, is not limited to hypertension. Benefit for heart failure, for example, has been shown for metoprolol, bisoprolol, and carvedilol but not, notably, for atenolol.

#### ■ Looking beyond age to the other issues at play

Khan and McAlister's meta-analysis<sup>3</sup> seems to show beta-blockers to be as effective as any other class of antihypertensive for the middle-aged DSH patient, while they appear ineffective for elders. That is plausible, given the different pathophysiologies of DSH and ISH. However, the trials among middle-aged patients were generally conducted first, and many of them<sup>4-7</sup> used beta-blockers other than atenolol, either entirely or in part.

In contrast, the studies among elders are more recent, and most<sup>8-14</sup> used atenolol exclusively. Even those that did include other beta-blockers<sup>15-17</sup> relied heavily upon atenolol. The effect that Khan and McAlister attribute to an age difference

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may be a difference between DSH and ISH, between atenolol and lipophilic beta-blockers—or quite possibly, both.

### Incomplete data leave us with as many questions as answers

It appears safe to conclude that atenolol is a poor choice for elders with ISH. It may not even be superior to placebo for those patients. It is also clear that lipophilic beta-blockers are effective for middle-aged patients with DSH. They are probably as good as other outcome-improving classes for those patients.

**What about atenolol** for middle-aged patients with DSH? We lack the data to answer this question.

**What about metoprolol or bisoprolol** for elders with ISH? Again, we lack data. Lipophilic beta-blockers are likely superior to placebo, so they may be suitable as additional agents in ISH, but we do not know if they are suitable as first-line agents.

### More research is needed, but no one will fund it

Comparative effectiveness trials would settle these issues, but it is unlikely that anyone will conduct them. The pharmaceutical industry has no interest in funding studies of these very inexpensive, off-patent drugs, and in this era of tightening budgets, the National Institutes of Health is unlikely to do so either. Carefully done studies of medical records may provide the information we need, with due caution to the pitfalls of retrospective observational studies. This is a question that family medicine will likely have to answer for itself from its own data.

Finally, it is worth noting that atenolol is unquestionably quite efficacious at lowering blood pressure, even where it makes no difference in patient outcomes—yet another reminder of the crucial difference between disease-oriented evidence and patient oriented evidence that matters. ■

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#### FAST TRACK

**The effect attributed to age may be due to a difference between diastolic-systolic HTN and isolated systolic HTN, or between atenolol and lipophilic beta-blockers, or both**