

Shades of Opinion: What is Prudent?

Notions differ regarding the “prudent” approach to the use of calcium channel blockers. On one hand, the merits of calcium channel blockers have been widely demonstrated in clinical practice, especially in



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treating patients with hypertension. On the other hand, there are the recently voiced concerns about the long-term efficacy and safety of these drugs; the lack of large-scale, long-term, prospective, randomized trials designed to assess the effects of calcium channel blockers on hard morbidity and mortality endpoints; and the recommendations of the JNC-V, in particular, their designation of beta-blockers and diuretics as “preferred” first-line drugs for anti-hypertensive therapy.

Suzanne Oparil, MD, and Barry Massie, MD, provide two different opinions on this matter. Dr. Oparil’s remarks were made in an interview during the AHA meeting in November. Dr. Massie’s comments were presented in a talk given at the symposium “Current Cardiac Therapies and a Glimpse into the 21st Century,” held as a satellite symposium to the AHA sessions.

Dr. Oparil, immediate past-president of the American Heart Association, said

that experience in a large practice has taught her that “many of the older classes of antihypertensive drugs are poorly tolerated. Diuretics are associated with a high incidence of impotence in our patient population, and beta-blockers can cause depression, lassitude, and problems with potency. Asymptomatic patients will not take a drug for 30 years that makes them feel sick. So the newer classes of agents—the angiotensin converting enzyme (ACE) inhibitors, the angiotensin-II receptor blockers, the α_1 -blockers, and the calcium channel blockers—are needed, because they seem to be better tolerated.”

Although not a complete surrogate for preventing coronary heart disease, lowering blood pressure is helpful, and “certainly so in conjunction with lipid lowering,” said Dr. Oparil. Whatever difficulties may exist with the use of calcium channel blockers in patients with established coronary heart disease, “for people with uncomplicated hypertension who are at low risk for atherosclerosis, calcium channel blockers have a plus side. To throw them all away on the basis of inadequate cross-sectional data that can be questioned would be a big error.”

Dr. Oparil said she “has not changed [her] practice at all.” She considers calcium channel blockers, ACE inhibitors, and the new angiotensin-II blockers to be “treatments of choice for initial therapy because of better tolerability than the diuretics and beta-blockers.” If these do not control the hypertension, she adds a drug from one of the other classes or a low-dose diuretic. “I do not believe in the diuretic/beta-blocker preferred

treatment scheme of the JNC-V, because so many of our patients cannot tolerate it."

Because her practice in Alabama includes many African Americans, elderly persons, and obese patients, and because the diets of her patients tend to be high in sodium and low in calcium, potassium, and magnesium, Dr. Oparil finds that most of her patients need more than one drug. "Calcium channel blockers work well in patients with low-renin, volume-expanded hypertension, which is common among older persons and African Americans. That is another reason why their benefits cannot be ignored," said Dr. Oparil.

Dr. Oparil acknowledged that treatment is more complex for a patient who is hypertensive and also has angina, or for one who has coronary heart disease and is normotensive. For the patient with uncomplicated hypertension, however, one of the newer drugs would be her first choice. "Most physicians' first choices for patients with uncomplicated hypertension are either an ACE inhibitor or a calcium channel blocker," said Dr. Oparil. That is as it should be, she believes. "I think physicians should not race to change their prescribing practices until we have more evidence, except that they should use rapidly acting dihydropyridines, such as capsular nifedipine, with great caution, particularly in patients with active coronary artery disease—unstable angina or recent myocardial infarction."

Dr. Massie, a member of the Food and Drug Administration Advisory Committee on Cardiorenal Drugs, takes a somewhat more conservative position. His sense of what is prudent is more in line with the views of Furberg, Yusuf, and others and the recommendations of the JNC-V.

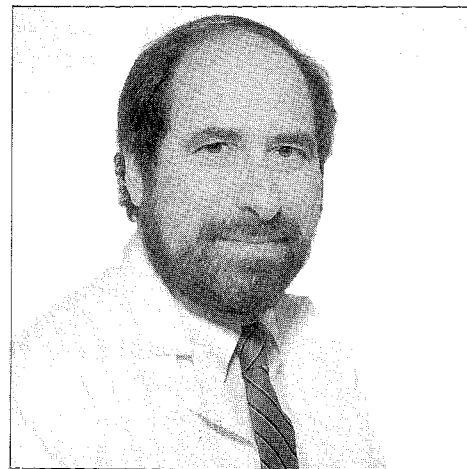
Dr. Massie addressed the question of whether physicians should modify their use of calcium channel blockers on the basis of recently publicized evidence of their possible harmfulness. He reviewed the case control study of Psaty et al¹ and the meta-analysis of Furberg et al² and

referred as well to the earlier (1989) meta-analysis of Held et al,³ which covered a similar set of trials and showed slightly unfavorable effects from dihydropyridine calcium channel blockers in patients with acute myocardial infarction and unstable angina, but neutral for diltiazem and slightly favorable for verapamil.

With obvious eagerness to weigh both sides of the issue carefully, Dr. Massie pointed alternately to the shortcomings in these retrospective studies, imprecisions in the authors' interpretations of their data, and other published work that offsets the data and the interpretations. He then turned to the soundness of some of the analysts' arguments, the importance of the studies for having brought unresolved issues to light, and the high caliber of the Psaty and Furberg groups' work in case control studies and meta-analyses.

"When we integrate the data of the second meta-analysis with the rest of what we know about calcium channel blockers, we can draw a few conclusions," Dr. Massie said with regard to uses in patients with coronary artery disease. "Nifedipine may increase the risk of events in these patients. If so, the excess risk appears to be limited to the use of short-acting formulations of nifedipine. There is no a priori reason to extrapolate these data to long-acting dihydropyridines, although one cannot assume their safety either. However, the data with sustained-release preparations of the nondihydropyridine calcium channel blockers verapamil and diltiazem give no hint of risk."

In this connection, Dr. Massie cited a paper that other participants in the re-



Barry Massie, MD

cent controversy have not mentioned. In 1991, in the *American Journal of Cardiology*,⁴ the MDPIT investigators isolated approximately 700 patients in that study who had hypertension when they had their index myocardial infarction. The greatest benefit of diltiazem compared with placebo was found in this hypertensive subgroup. At the conclusion of Dr. Massie's talk, William Boden, MD, the principal investigator in MDPIT, added that, in the group of 1,325 post-myocardial infarction patients with hypertension identified in and pooled from the

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MDPIT and DAVIT populations, the combined adverse outcomes of death plus reinfarction were 26% less common among those treated with either of the heart-rate-lowering calcium channel blockers verapamil or diltiazem compared with those who received placebo. This difference was statistically significant ($P = 0.001$).

With regard to the management of hypertension alone, Dr. Massie said, notwithstanding the aforementioned studies' deficiencies and those of the case control study in particular, he "would not ignore the results." They demonstrate the need for prospective trials. The JNC-V recommended diuretics and beta-blockers as preferred agents because they have been shown to reduce morbidity and mortality in prospective, controlled trials. "Although trials are under way now, no such data exist for the calcium channel blockers or ACE inhibitors." However, Dr. Massie continued, "calcium channel blockers have been shown to lower blood pressure most consistently and, in some populations, to a greater extent than do other antihypertensive agents." Evidence from a variety of sources, including the VA Cooperative Study and the TOMHS study, supports this.

Dr. Massie said that the Psaty et al¹ and Furberg et al² studies do not taint calcium channel blockers enough to remove them from clinical use. He maintained that valid conclusions cannot easily be drawn from these retrospective analyses. Nevertheless, he said, "I have allowed the information to affect my practice to some extent. I have stopped using high doses of calcium channel blockers as monotherapy in patients with hypertension. When I use a calcium channel blocker, I now use it in a lower dose and in combination with other drugs. Is this logical? I can't answer that. But I consider it a prudent approach until good data are in."

Dr. Massie concluded that calcium channel blockers are not first-choice agents for patients with acute coronary syndromes and, except for vasospastic angina, they are not indicated for these conditions. They are indicated for and are highly effective in patients with hypertension and chronic stable angina pectoris, "and there they should be chosen selectively."

In his opinion, the JNC-V is correct. "Before you use a calcium channel blocker for any individual patient," Dr. Massie counseled his colleagues, "think about why you are about to use it. There are many good reasons to select a calcium channel blocker—the magnitude of blood pressure response you can expect, the patient's demographic characteristics and associated diseases, and so on. When you sort through these potential reasons, there will be a certain percentage of your patients for whom a calcium channel blocker is probably the best agent. But that does not mean a calcium channel blocker should be first-line therapy for all hypertensive patients."

According to Dr. Massie, outcome data are needed so that selective therapeutic decisions can be made in the most educated manner. "The Psaty and Furberg papers have jump-started us into realizing that these data are needed, and we will have them in a few years. Until then, a prudent approach is in order."

During a question-and-answer period, Dr. Massie agreed with the view of a member of the HINT research group that it was regrettable that calcium channel blockers and ACE inhibitors had been swept into first-line therapy for hypertension "by analogy," that is, because they decrease blood pressure. To this day, Dr. Massie said, the Food and Drug Administration is dissatisfied that "hypertension remains one of the few non-outcome-driven indications for drug therapy." At the same time, "we should recall that even beta-blockers and diuretics were approved for hypertension without the appropriate outcome data. All that came later," Dr. Massie said.

In a larger view, Dr. Massie observed that clinicians often must make selective therapeutic decisions without adequate evidence. Consider the post-myocardial infarction patient. Some evidence supports the use of a calcium channel blocker as a first-choice agent in some of these patients. At this point, however, the more likely first option for

post-myocardial infarction patients who cannot tolerate a beta-blocker might be an ACE inhibitor. "But there is no evidence that long-term treatment with an ACE inhibitor prevents events in low-risk post-myocardial infarction patients, such as those with normal left ventricular function." Prescribing an ACE inhibitor might prove to be "another instance of practicing without adequate evidence."

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