Editorial

James V. Felicetta, MD
Editor-in-Chief

ACEIs and ARBs: Use 'Em Both if You Need To!

I detest it when clinical trials are misquoted or misinterpreted. It's especially disturbing when it's a trial in which I served as an investigator, because I know the data very well. In this case, the trial I'm referring to is the ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint) study. It turns out that many folks are unfortunately way off target in their understanding of this important trial.

What's gotten me riled this time around relates to the management of proteinuria, both in patients with and without diabetes. We've known for some time that proteinuria is an indicator of future vascular trouble ahead, such as a possible heart attack or a stroke. The thinking is that the urine can serve as a poor man's biopsy of the endothelial vasculature. We know that protein showing up in the urine means there are sizable holes in the capillary allowing endothelium the protein to slide through, which correlates with endothelial damage throughout the vascular system. And we know from a number of studies—such as IDNT (Irbesartan Diabetic Nephropathy Trial) and RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan)—that antihypertensive agents which reduce proteinuria will delay the development of end-stage renal failure compared with antihypertensive agents which reduce blood pressure to the same degree but do not reduce proteinuria.

A trend also exists toward fewer cardiovascular events with these proteinuria-reducing angiotensin receptor blockers (ARBs) in these studies, but they did not reach statistical significance. We also know from a multitude of studies dating back to the late 1980s that our old friends, the angiotensin converting enzyme inhibitors (ACEIs), are also very effective at reducing proteinuria and slowing the rate of progression to end-stage renal disease. At least 1 study, Candesartan and Lisinopril Microalbuminuria (CALM), suggested that the relative efficacy of ACEIs and ARBs in reducing proteinuria was pretty much the same.

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All right. So we all agree that ACEIs and ARBs are both effective at reducing proteinuria, and that this is a laudable goal in patients spilling significant amounts of protein in their urine. But, what happens if you use both agents together in someone whose proteinuria has not been adequately controlled on 1 class alone? It turns out that the effects are indeed additive, such that the proteinuria reduction is significantly greater on the 2 together than on either 1 class by itself.

Mind you, we don't yet have definitive evidence that reducing proteinuria to a greater extent will give us better outcomes, either in terms of reducing the rate of progression to renal failure or, even better, in reducing the number of cardiovascular events. But it remains a very appealing hypothesis, particularly because there was a dose-response effect seen with irbesartan in IDNT, such that a higher dose of the drug was more effective than a smaller dose in reducing the risk of end-stage renal disease.

So, then, what's the problem? Everyone agrees that it's a reasonable approach to combine an ACEI with an ARB in a patient with persistent proteinuria, right? Unfortunately, no. The problem is that some well-meaning, but misinformed, folks have misinterpreted the ONTARGET trial as showing that the combination of the 2 agents produces more adverse effects than either alone, without any improvement at all in outcomes. But the issue here is that we're talking apples and oranges.

The ONTARGET trial was not a study of proteinuria at all. Rather, it was a follow-on to the much-ballyhooed Heart Outcomes Prevention Evaluation (HOPE) trial, which appeared to demonstrate that higher-risk patients had fewer cardiovascular events when given the ACEI ramipril, compared with placebo. (George Bakris, MD, a leading nephrologist, routinely calls it the HYPE trial because he believes that

the reduction in events was primarily an antihypertensive effect rather than any uniquely protective effect of ACEIs.) At any rate, ONTARGET was designed to compare ARBs and ACEIs in a very similar cohort of higher-risk patients. These patients were randomized to either the same ACEI as in HOPE, namely ramipril, or to telmisartan, an ARB, or to the combination of the ACEI and the ARB.

Yes, there was definitely an increase in adverse effects with the combination, primarily increases in the serum creatinine level and in the potassium level, both predictable effects from agents that block the renin-angiotensin-aldosterone system. It is definitely true that the combination was no more effective than either agent alone in reducing the total number of cardiovascular events.

The critical factor to note, however, is that this trial was not conducted in subjects with proteinuria! Thus, this trial cannot—and should not—be cited as important evidence against the idea of combining ACEIs and ARBs in the treatment of proteinuria. We will need to wait for the results of another ongoing trial, the VA NEPHRON-D (Diabetes iN Nephropathy Study), to find out if the greater reduction in proteinuria with the combination of the 2 drugs is more effective than just 1 alone. NEPHRON-D is a multicenter VA Cooperative Trial in patients with significant diabetic proteinuria comparing the ARB losartan alone with the combination of losartan and the ACEI lisinopril. Funding limitations precluded including another line with the ACEI alone but, nonetheless, the results should be very informative when they finally emerge.

So until the results of NEPHRON-D are known, don't let anyone tell you it's a bad idea to combine ACEIs and ARBs in patients with heavy proteinuria. It's a very reasonable thing to do on the basis of what we know today, as long as we remember that it has not yet been proven to be of long-term benefit. ●