Canadian Hypertension Guidelines Expressly Warn Against ARB/ACE-Inhibitor Combo--Should Others Follow?

Heart*wire* — a professional news service of WebMD

February 3, 2009 (Washington, DC and Toronto, Ontario) — A Viewpoint online February 2, 2009 in the *Journal of the American College of Cardiology* is calling on physicians to avoid using dual renin-angiotensin system (RAS) blockade--angiotensin-receptor blockers (ARBs) and ACE inhibitors together--in clinical practice [1]. The article, by **Dr Franz Messerli** (St Luke-Roosevelt's Hospital, New York), comes within weeks of an announcement from the **Canadian Hypertension Education Program** (CHEP), urging physicians and patients to stop using the two drugs together. A guideline alert issued simultaneously by the Canadian **Heart and Stroke Foundation** advised patients to see their family physicians as soon as possible to get their treatment changed [2]. According to the foundation, as many as 175 000 Canadians with hypertension may be taking this combination.

Messerli's Viewpoint, as well as the CHEP alert, were spurred by the results of the **Renal Outcomes With Telmisartan, Ramipril, or Both, in People at High Vascular Risk** (ONTARGET) study, which showed the ARB **telmisartan** to be noninferior to the ACE inhibitor **ramipril** but the combination of the two together to be associated with more adverse events and no increased benefit [3]. A separate, prespecified analysis looking at renal outcomes in ONTARGET showed that the ARB/ACE-inhibitor combination was associated with an increased risk of dialysis, doubling of serum creatinine, and death, compared with using either agent alone [4].

"The recent ONTARGET study data have shattered the halo of dual RAS blockade not only for hypertension but also for nephroprotection," Messerli points out in his Viewpoint. "In retrospect, many enticing features of dual RAS blockade were based on surrogate end-point findings and therefore may have represented more wishful thinking rather than solid science. . . . Unless data emerge to the contrary, dual RAS blockade is dead until further notice."

An Enticing Concept

Messerli explains that doctors were attracted to the idea of using both drugs together out of the belief that more complete blockade of the RAS would lead to better blood-pressure control and potentially nephroprotective and cardioprotective effects. "So enticing was the concept of dual RAS blockade that despite a lack of solid evidence on safety and efficacy, it found entrance into recent guidelines," he notes.

The nephroprotective hypothesis grew out of observations that both albuminuria and proteinuria are reduced by dual RAS blockade. But in ONTARGET, despite reducing the increase in albuminuria, the combination of telmisartan and ramipril was associated with a doubling of creatinine and need for dialysis.

"The practice has been ingrained in the physician's mind that one blocker is good, therefore two blockers are better, and so this is used fairly extensively," Messerli told **heart*wire***. "Now we have the outcome data showing that it ain't necessarily so."

One group still being debated is heart-failure patients, largely on the basis of the **CHARM** trial results showing benefits of dual therapy in terms of improvements in LVEF and reduced hospital admissions. But CHARM, as well as subsequent meta-analyses, has shown no improvement in all-cause mortality with dual RAS blockade in HF patients and points to a high discontinuation rate due to renal effects and hypotension. Messerli believes that while the temptation to add another drug in HF patients is powerful, there are not enough data to support dual RAS blockade.

Decisions on Warnings up to Individual Organizations

Contacted by **heart*wire***, a spokesperson for the **American Heart Association** (AHA) pointed out that the AHA guidelines don't currently recommend the use of ACE inhibitors and ARBs together, so the association has no plans to issue an alert similar to the one sent out by the Heart and Stroke Foundation.

Messerli, however, said he thinks that the Canadian guidelines may be leading the way by expressly cautioning against their use. "I think they ought to be commended because they are ahead of the US on this," he said.

Commenting on the alert and Messerli's Viewpoint, **Dr Salim Yusuf** (McMaster University, Hamilton, ON), principal investigator for ONTARGET, told **heart*wire***, "I think it is appropriate not to use combinations in those without severe heart failure," But he added: "Each organization should decide whether or not they want to issue a warning."

1. Messerli FH. The sudden demise of dual renin-angiotensin system blockade or the soft science of the surrogate end point. *J Am Coll Cardiol* 2009; DOI:10.1016/j.jacc.2008.10.036. Available at: http://content.onlinejacc.org.
2. Heart and Stroke Foundation. Guideline alert for blood pressure patients as treatment combo [press release]. January 16, 2009. Available at: http://www.heartandstroke.com/site/apps/nlnet/content2.aspx?c=ikIQLcMWJtE&b=3485819&ct=6501933.
3. Yusuf S, Teo KK, Pogue J, et al for the ONTARGET investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008: 358:1547-1559. Abstract
4. Mann JFE, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both in people at high vascular risk (the ONTARGET study): a multicentre, randomized, double-blind controlled trial. *Lancet* 2008; 372:547-553.Abstract

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