



EDUCATIONAL OBJECTIVE: Readers will avoid using dual renin-angiotensin system blockade, pending evidence that it is beneficial



BRIEF ANSWERS
TO SPECIFIC
CLINICAL
QUESTIONS

Q: Is an ACE inhibitor plus an ARB more effective than either drug alone?

FRANZ H. MESSERLI, MD*

Division of Cardiology, St. Luke's Roosevelt Hospital Center, New York, NY

MELANA YUZEFPOLSKAYA, MD

Division of Cardiology, St. Luke's Roosevelt Hospital Center, New York, NY

A: No. Although randomized, controlled trials have shown convincingly that angiotensin-converting enzyme (ACE) inhibitors reduce the rates of death, myocardial infarction, stroke, and heart failure in patients with known coronary artery disease or left ventricular dysfunction,¹ and that angiotensin receptor blockers (ARBs) are “noninferior” to and better tolerated than ACE inhibitors, causing less angioedema and cough but costing more,² dual renin-angiotensin system (RAS) blockade—an ACE inhibitor plus an ARB—has never been shown to reduce the rates of morbidity or death from any cause.

In fact, the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET)^{3,4} found that dual RAS blockade was no more beneficial than monotherapy with an ACE inhibitor or an ARB in preventing serious outcomes in patients with known vascular disease or diabetes with end-organ damage. Furthermore, patients on dual RAS blockade had higher rates of renal insufficiency, hyperkalemia, and hypotension.

■ THE RATIONALE FOR DUAL RAS BLOCKADE

Dual RAS blockade was first proposed in the early 1990s as a way to avoid the “escape phe-

nomenon” (incomplete suppression of angiotensin II) with ACE inhibitor monotherapy.⁵ Indeed, studies in rats showed a synergistic effect on blood pressure with an ACE inhibitor combined with an ARB,⁶ and these results were encouraging enough for the medical community to make a remarkably quick transition to adopting dual RAS blockade in clinical practice.

The concept of dual RAS blockade was so appealing that effects on surrogate end points—lower blood pressure, less protein in the urine, and improved endothelial function—were accepted as free passes, obviating the need for evidence of an effect on hard end points such as lower rates of cardiovascular death or kidney failure. Currently, in the United States, about 1.5% of all patients on RAS blockers are currently receiving both an ACE inhibitor and an ARB.

■ CONDITIONS IN WHICH DUAL RAS BLOCKADE WAS THOUGHT BENEFICIAL

Hypertension

The European Society of Cardiology's 2007 clinical practice guidelines⁷ say that treatment with an ACE inhibitor plus an ARB is preferred for hypertensive patients with metabolic syndrome and its major components (eg, abdominal obesity, insulin resistance, frank diabetes).

Dulton et al, in a meta-analysis,⁸ calculated that the combination of an ACE inhibitor and an ARB lowered 24-hour blood pressure by 4/3 mm Hg more than monotherapy did. However, most of the studies were of short duration (6 to 8 weeks) and used submaximal doses or once-daily doses of a short-acting ACE inhibitor. Interestingly, studies that

Trial data so far do not support routine use of dual RAS blockade

*Dr. Messerli has been an ad hoc consultant and speaker for GlaxoSmith-Kline, Novartis, Boehringer Ingelheim, Forest, Daiichi-Sankyo, Sanofi, and Savient Pharmaceuticals, and has received grant support from GlaxoSmith-Kline, Novartis, Forest, Daiichi-Sankyo, and Boehringer Ingelheim.

used a long-acting ACE inhibitor or a larger dose of a short-acting ACE inhibitor generally showed no additive effect on blood pressure when an ARB was added.

Hence, more evidence from larger randomized and appropriately designed studies is needed before we can conclude that dual RAS blockade is safe and significantly superior to monotherapy in blood pressure control.

Proteinuria

Proteinuria is a surrogate end point for cardiovascular death and is a marker as well as a cause of progressive renal insufficiency. It therefore seemed rational that modifying the degree of proteinuria would translate into robust clinical benefits. Several studies⁹ showed better renal outcomes, such as fewer patients needing dialysis with combination therapy than with an ACE inhibitor or ARB alone. However, this has never been proven in an adequately powered trial.

ONTARGET was a perfect opportunity to convert what seemed like reliable mechanistic information into solid outcome data.³ The trial enrolled 25,620 patients with established atherosclerotic disease or with diabetes and evidence of end-organ damage. At baseline, 13.1% had microalbuminuria and 4.0% had macroalbuminuria.³ The amount of protein in the urine increased by a significantly lesser amount in the ARB group and in the dual-therapy group than in the group taking only an ACE inhibitor, but in the dual-therapy group this apparent advantage came at the expense of hard end points: more patients reached the primary composite end point of needing dialysis, doubling of their serum creatinine level, or death.

Reducing proteinuria could be an important benefit, but it certainly does not outweigh the risk of increased rates of renal failure and death.

Atherosclerosis and acute coronary syndrome

The road to myocardial infarction begins with inflammation in the “shoulders” of atherosclerotic plaques, which subsequently rupture. Tissue ACE activity and expression of the angiotensin II type 1 receptor are significantly increased in patients with acute coronary syn-

drome and primarily co-localized to the shoulder regions of the plaque.¹⁰ Giving an ACE inhibitor or an ARB to patients who have unstable angina or who have had a myocardial infarction may decrease the rate of reinfarction and lessens the inflammatory process in the atherosclerotic plaque.

Large randomized clinical trials such as HOPE (Heart Outcomes Prevention Evaluation)¹¹ and EUROPA (European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease)¹² showed a lower rate of cardiovascular death in patients with established coronary artery disease and normal left ventricular function if they received an ACE inhibitor. In the HOPE trial, the rate of cardiovascular death was 25% lower in patients treated with ramipril (Altace) vs placebo.¹¹ (The year after HOPE was published, the number of prescriptions for ramipril went up 400%). Interestingly, studies of ARBs for secondary prevention failed to show any lowering of the rate of cardiovascular death or myocardial infarction.¹³

In ONTARGET,⁴ although the combination of telmisartan (Micardis) and ramipril had a greater effect on blood pressure, it was not significantly better than ramipril alone in terms of the primary outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure (relative risk 0.99).

Heart failure

The bulk of data on dual RAS blockade in heart failure patients comes from three large randomized trials: CHARM-Added (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity),¹⁴ VALIANT (Valsartan in Acute Myocardial Infarction Trial),¹⁵ and VAL-HeFT (Valsartan Heart Failure Trial).¹⁶

CHARM-Added¹⁴ was the only trial that showed a reduction in cardiovascular deaths with dual RAS therapy (absolute risk reduction 3.6%). It also showed a lower rate of hospitalization for heart failure (absolute risk reduction 4%). However, the rate of all-cause mortality was not different between the groups. Of note, more patients receiving dual RAS blockade had to stop taking the study drug because of adverse effects.

**ONTARGET
results:
More adverse
events and
no increased
benefit with
dual RAS
blockade**

Val-HeFT¹⁶ showed, in a post hoc analysis, higher rates of morbidity (cardiac arrest, hospitalization for heart failure, or receipt of intravenous inotropic or vasodilator therapy for at least 4 hours) and death when the ARB valsartan (Diovan) was added to the combination of an ACE inhibitor plus a beta-blocker.

A recent meta-analysis¹⁷ of safety and tolerability of dual RAS blockade compared with an ACE inhibitor alone found a higher risk of discontinuation because of adverse effects such as hyperkalemia, renal dysfunction, and hypotension in patients on dual RAS blockade. The authors concluded that, given the adverse effects and the lack of consistent survival benefit, the available data do not support the routine addition of an ARB to ACE inhibitor therapy in heart failure patients.

■ WHAT ABOUT DIRECT RENIN INHIBITORS?

Another class of RAS blockers is available: direct renin inhibitors. Therefore, dual RAS blockade can be achieved by combining an ACE inhibitor with an ARB, an ACE inhibitor with a direct renin inhibitor, or an ARB with a direct renin inhibitor.

We have some outcome data on the combination of an ACE inhibitor plus an ARB,^{3,4,17} but none for the other two possible dual RAS combinations. Thus far, we know that dual RAS blockade with an ARB and an ACE inhibitor is not beneficial in patients like those in ONTARGET, and that it has questionable benefit in heart failure. However, little is known about combining a direct renin inhibitor with either an ACE inhibitor or an ARB.

■ REFERENCES

1. **Father MD, Yusuf S, Kober L, et al.** Long-term ACE-inhibitor therapy in patients with heart failure or left ventricular dysfunction: a systemic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet* 2000; 355:1575–1581.
2. **Pitt B, Poole-Wilson PA, Segal R, et al.** Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomized trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000; 355:1582–1587.
3. **Mann JF, Schmiede RE, McQueen M, et al; ONTARGET investigators.** 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.
4. **ONTARGET Investigators; Yusuf S, Teo KK, Pogue J, et al.** Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; 358:1547–1559.

Since ARBs and ACE inhibitors both increase plasma renin activity and only partially block the RAS, the argument has been put forward that the addition of a drug such as a direct renin inhibitor, which really decreases plasma renin activity, has the potential to be more beneficial than blockade with either an ACE inhibitor or an ARB. In theory, this is an attractive concept and certainly deserves scrutiny in outcome studies such as ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints).¹⁸

■ SURROGATE END POINTS: A CAVEAT

As defined by Temple,¹⁹ a surrogate end point of a clinical trial is a laboratory measurement or a physical sign used as a substitute for a clinically meaningful end point that measures directly how patients feel or function, or if they survive. Effects on surrogate end points often fail to predict the true clinical effects of an intervention, as the ONTARGET data demonstrated. Among several explanations for this failure is that interventions may affect the clinical outcome by unintended, unanticipated, and unrecognized mechanisms that operate independently of the disease process.²⁰ Nonetheless, surrogate end point cosmetics remains attractive for many clinicians.

The ONTARGET findings indicate that there is no clinically important benefit in adding an ARB for patients with hypertension, proteinuria, heart failure, or coronary artery disease if they are already being treated with an ACE inhibitor. This would indicate that dual RAS blockade should be avoided in clinical practice until we are provided with better evidence. ■

Effects on surrogate end points often fail to predict the true clinical effects

5. **van den Meiracker AH, Man in 't Veld AJ, Admiraal PJ, et al.** Partial escape of angiotensin converting enzyme (ACE) inhibition during prolonged ACE inhibitor treatment: dose it exist and does it affect the antihypertensive response? *J Hypertens* 1992; 10:803–812.
6. **Menard J, Campbell DJ, Azizi M, Gonzales MF.** Synergistic effects of ACE inhibition and Ang II antagonism on blood pressure, cardiac weight, and renin in spontaneously hypertensive rats. *Circulation* 1997; 96:3072–3078.
7. **Mancia G, De Backer G, Dominiczak A, et al; Task Force for the Management of Arterial Hypertension of the European Society of Hypertension; European Society of Hypertension (ESH) and the European Society of Cardiology (ESC).** 2007 guidelines for the management of arterial hypertension. *J Hypertens* 2007; 25:1105–1187.
8. **Dulton TW, He FJ, MacGregor GA.** Systematic review of combined angiotensin-converting enzyme inhibition and angiotensin receptor blockade in hypertension. *Hypertension* 2005; 45:880–886.
9. **Kunz R, Fredrich C, Wolbers M, Mann JF.** Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin

- angiotensin system on proteinuria in renal disease. *Ann Intern Med* 2008; 148:30–48.
10. **Schieffer B, Schieffer E, Hilfiker-Kleiner D, et al.** Expression of angiotensin II and interleukin 6 in human coronary atherosclerotic plaques: potential implications for inflammation and plaque instability. *Circulation* 2000; 101:1372–1378.
 11. **Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G.** Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000; 342:145–153.
 12. **Fox KM; European trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators.** Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomized, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003; 362:782–788.
 13. **Dahlöf B, Devereux RB, Kjeldsen SE, et al; LIFE Study Group.** Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet* 2002; 359:995–1003.
 14. **McMurray JJ, Ostergren J, Swedberg K, et al; CHARM Investigators and Committees.** Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin converting enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003; 362:767–771.
 15. **Pfeffer MA, McMurray JJ, Velquez E, et al; Valsartan in Acute Myocardial Infarction Trial Investigators.** Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; 349:1893–1906.
 16. **Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators.** A randomized trial of the angiotensin receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; 345:1667–1675.
 17. **Lakhdar R, Al-Mallah MH, Lanfear DE.** Safety and tolerability of angiotensin-converting enzyme inhibitor versus the combination of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker in patients with left ventricular dysfunction: a systematic review and meta-analysis of randomized controlled trials. *J Card Fail* 2008; 14:181–188.
 18. **Parving H-H, Brenner BM, McMurray JJV, et al.** Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE): rationale and study design [published online ahead of print January 14, 2009]. *Nephrol Dial Transplant*. doi:10.1093/ndt/gfn721.
 19. **Temple RJ.** A regulatory authority's opinion about surrogate endpoints. In: Nimmo WS, Tucker GT, eds. *Clinical Measurement in Drug Evaluation*. J Wiley: New York, 1995.
 20. **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; 53:468–470.

ADDRESS: Franz H. Messerli, MD, Division of Cardiology, St. Luke's Roosevelt Hospital Center, 1000 10th Avenue, Suite 3B-30, New York, NY 10019; e-mail FMesserli@aol.com.

Back by popular demand—in a new edition!

Proceedings of the 4th Annual Perioperative Medicine Summit

Supplement to
Cleveland Clinic Journal of Medicine
November 2009

Supplement Editor: Amir K. Jaffer, MD, University of Miami School of Medicine

Associate Editors: David L. Hepner, MD, Brigham and Women's Hospital
Franklin A. Michota, MD, Cleveland Clinic

20 full-length articles covering the spectrum of perioperative management
132 pages • CME-certified

Faculty of national and international experts:

- Lee Fleisher on preoperative cardiac risk stratification
- Don Poldermans and P. J. Devereaux debate perioperative beta-blockade
- Gerald Smetana on postoperative pulmonary complications
- Challenging clinical cases from Steven Cohn and BobbieJean Sweitzer
- Many more



Limited supply available.
Order copies at
dunaskk@ccf.org
or 216-444-2661