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

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, and that angiotensin receptor blockers (ARBs) are “noninferior” to and better tolerated than ACE inhibitors, causing less angioedema and cough but costing more, 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) 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 phenomenon” (incomplete suppression of angiotensin II) with ACE inhibitor monotherapy. Indeed, studies in rats showed a synergistic effect on blood pressure with an ACE inhibitor combined with an ARB, 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 guidelines 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, 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
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 ran-
donized 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 car-
diovascular 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 ro-
bust clinical benefits. Several studies showed
better renal outcomes, such as fewer patients
needing dialysis with combination therapy
than with an ACE inhibitor or ARB alone.

Reducing proteinuria could be an impor-
tant 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 athero-
sclerotic plaques, which subsequently rupture.
Tissue ACE activity and expression of the an-
giotensin II type 1 receptor are significantly
increased in patients with acute coronary syn-
drome and primarily co-localized to the shoul-
der regions of the plaque. Giving an ACE
inhibitor or an ARB to patients who have un-
stable angina or who have had a myocardial
infarction may decrease the rate of reinfarc-
tion and lessens the inflammatory process in
the atherosclerotic plaque.

Large randomized clinical trials such as
HOPE (Heart Outcomes Prevention Eval-
uation) and EUROPA (European Trial
on Reduction of Cardiac Events With Perin-
dopril in Stable Coronary Artery Disease) 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. (The year after HOPE was
published, the number of prescriptions for
ramipril went up 400%). Interestingly, stud-
ies of ARBs for secondary prevention failed to
show any lowering of the rate of cardiovascu-
lar death or myocardial infarction.

In ONTARGET, although the combina-
tion 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 (rel-
ative 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 (Cande-
sartan in Heart Failure: Assessment of Reduc-
tion in Mortality and Morbidity), VALIANT
(Valsartan in Acute Myocardial Infarction
Trial), and VAL-HeFT (Valsartan Heart
Failure Trial).

CHARM-Added was the only trial that
showed a reduction in cardiovascular deaths
with dual RAS therapy (absolute risk reduc-
tion 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.
Val-HeFT\textsuperscript{16} 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-analysis\textsuperscript{17} 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.

\section*{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,\textsuperscript{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.

\section*{REFERENCES}


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).\textsuperscript{18}

\section*{SURROGATE END POINTS: A CAVEAT}

As defined by Temple,\textsuperscript{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.\textsuperscript{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.
DUAL RAS BLOCKADE


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