Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blockers: Combination Therapy

What We Know

› Angiotensin-converting enzyme (ACE) inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) are medications that are used primarily in the treatment of hypertension (HTN) and heart failure (HF) because they block the formation or action of angiotensin II (Ang II), which is the primary active product of the renin-angiotensin-aldosterone system (RAAS). Blocking Ang II inhibits vasoconstriction and aldosterone secretion, which ultimately lowers blood pressure (BP), increases left ventricular dilatation, and preserves cardiac output (7,18)
  • ACEIs block release of ACE, which catalyzes formation of a precursor to Ang II
  • Although ARBs have neurohormonal and hemodynamic effects that are similar to ACEIs, their mechanism of action is different—they block the effect of Ang II at receptor sites

› Although ACEI/ARB combination therapy has been proposed based on theoretical benefits, there is no evidence that combination therapy (also called dual therapy) reduces the rate of morbidity or death from any cause. In addition, there are no large randomized studies that conclude combination therapy is safe and significantly superior to monotherapy with an ACEI or ARB (2,18)
  • In the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), investigators found that dual therapy reduced systolic BP by an additional 2–3 mm Hg but did not significantly reduce risk for cardiovascular death, myocardial infarction, stroke, or hospitalization for HF in patients with vascular disease or diabetes mellitus (DM) with end-organ damage; dual therapy was associated with higher rates of hyperkalemia, hypotension, syncope, renal insufficiency, with a trend toward an increased risk of renal dysfunction requiring dialysis (9,11)
  – Post hoc analysis of data from ONTARGET and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease (TRANSCEND) did not show evidence to support the use of combination therapy for patients with albuminuria or a low glomerular filtration rate (GFR) (14)
  • Authors of a meta-analysis of 4 large randomized controlled trials (RCTs) involving 17,338 patients showed that compared with ACEI monotherapy, combination therapy was associated with significantly higher rates of adverse event (AE)-related treatment discontinuation, symptomatic hypotension, worsening renal function, and hyperkalemia; hyperkalemia was significantly increased in patients with chronic HF (13)
  • Investigators who conducted a population-based longitudinal analysis of older Canadian patients starting RAAS blockade therapy found that decreased renal function, all-cause death, and hyperkalemia occurred more frequently with dual therapy (12)

› Dual therapy has been studied for use in a number of patient conditions with mixed results (2,9,10,11,18)
  • Atherosclerosis and acute coronary syndrome: Lower rates of cardiovascular death in patients with coronary artery disease who received ACEIs were reported in the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) and Heart Outcomes Prevention Evaluation (HOPE);
However, results of studies in which ARBs were added to ACEIs showed a decrease in BP, but no significant improvement in morbidity or mortality\(^{(11)}\).

– A study of 80,241 patients admitted to a Get With the Guidelines – coronary artery disease program (i.e., program designed to improve the quality of care in patients hospitalized with coronary artery disease by capturing guideline-based recommendation data) found that 1 in 5 patients hospitalized with acute coronary syndrome and eligible for combination ACEI/ARB therapy were not prescribed the therapy upon discharge\(^{(1)}\).

- HTN, including HTN in patients with comorbid DM: ONTARGET study investigators recommended against dual therapy for patients at high risk for vascular events or renal dysfunction because dual therapy did not reduce poor outcomes and there were more drug-related AEs compared with monotherapy\(^{(2,11)}\).

– In patients with nephropathy related to DM type 2 (DM2), dual therapy with lisinopril and irbesartan did not prevent nephropathy progression better than optimal high doses of either agent alone\(^{(3)}\).

– The Eighth Joint National Committee (JNC 8) guidelines, which were issued in 2013, along with the 2013 guidelines issued jointly by the American Society of Hypertension and the European Society of Cardiology (ESC), 2014 guidelines issued jointly by the American Society of Hypertension and the International Society of Hypertension, and the 2006 guidelines issued by the American Association of Clinical Endocrinologists all recommend against the combined use of an ACEI and ARB in the treatment of HTN\(^{(8,10,15,17)}\).

- HF: Authors of a systematic review and meta-analysis of RCTs concluded that the routine use of dual therapy in patients with HF is not supported because of significant AEs without a consistent increase in survival\(^{(9)}\).

– In a clinical trial comparing the addition of telmisartan vs placebo to combination therapy with an ACEI and a β-blocker for patients with chronic HF on dialysis, a significant reduction in all-cause and cardiovascular mortality and significantly fewer hospitalizations for HF in the group receiving telmisartan were observed; hypotension was the only AE that was significantly more frequent in patients receiving telmisartan than those receiving placebo\(^{(4)}\).

– According to guidelines from the American College of Cardiology (ACC)/American Heart Association (AHA), an ARB can be added to a drug regimen that already includes an ACEI and β-blocker in persistently symptomatic patients with reduced left ventricular ejection fraction (LVEF) when an aldosterone antagonist cannot be used. The guidelines point out that dual RAAS inhibition is associated with increased risk for hypotension, renal dysfunction, and hyperkalemia\(^{(18)}\).

- Chronic kidney disease: Evidence from the ONTARGET showed that during the course of the study, laboratory values for proteinuria, which is a marker of renal insufficiency and cardiovascular damage, were reduced in patients with atherosclerotic disease or DM; however, there was an increase in the rates of renal failure and death\(^{(11)}\).

– Authors of a meta-analysis of 6 RCTs involving 109 patients found that dual therapy reduced proteinuria in patients with IgA nephropathy (also called Berger's disease; i.e., a renal disease characterized by buildup of immunoglobulin A in the kidneys) better than either agent alone, although dual therapy did not improve GFRs\(^{(3)}\).

– 1,448 patients with diabetic nephropathy in the VA NEPHRON-D study were randomized to the ARB losartan plus the ACEI lisinopril or placebo group. Study participants were followed for a mean of 2.2 years, and it was found that combination therapy did not significantly improve patient outcomes and was associated with increased risk of adverse events, including hyperkalemia and acute kidney injury\(^{(6)}\).

Preliminary evidence suggests that the addition of a direct renin inhibitor (e.g., aliskiren; which blocks the RAAS at a previous step to those affected by ACEIs and ARBs) to ACEI or ARB therapy may provide superior results to ACEI/ARB combination therapy. Data on the effects of aliskiren combined with an ACEI or ARB on morbidity and mortality are not available\(^{(2)}\).

– As of April 2012, the combination of aliskiren and an ACEI or ARB is contraindicated in patients with DM and is not recommended in patients with moderate to severe renal impairment (i.e., GFR < 60 mL/min) because of the increased incidence of AEs\(^{(16)}\).

– A study analyzing Medicare records of 1,395 patients with HTN found that treatment with aliskiren plus an ARB significantly improved compliance and persistence with prescribed therapy and reduced hospitalizations compared with dual therapy with an ACEI and an ARB\(^{(2)}\).

**What We Can Do**

- Learn about combination therapy using ACEIs and ARBs, including maintaining awareness of current research results regarding their use as monotherapy and dual therapy; share this information with your colleagues.
Emphasize the importance of adhering to the prescribed treatment regimen for combination therapy; verify patient understanding of the desired effects, dosages, and potential AEs of all medications prescribed.

Educate regarding changing positions gradually, reporting severe dizziness or lethargy, and recording weight each morning after voiding and before taking prescribed medications.

Educate regarding the need to make lifestyle modifications to reduce cardiovascular risk, including dietary restriction of sodium, fats, and cholesterol; smoking cessation; and regular exercise.

**Note**

Recent review of the literature has found no updated research evidence on this topic since previous publication on April 29, 2016.
References


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