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ACE inhibitors and ARBs: One or the other—not both—for high-risk patients

The combination of an ACE inhibitor and an ARB reduces proteinuria, but leads to worse renal outcomes

Practice changer

Avoid prescribing an angiotensin-converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) for patients at high risk of vascular events or renal dysfunction. The combination does not reduce poor outcomes, and leads to more adverse drug-related events than an ACE inhibitor or ARB alone.[1]

Strength of recommendation

B: 1 large, high-quality randomized controlled trial (RCT).

The ONTARGET investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med.* 2008;358:1547-1559.

PODCAST

To hear author **James J. Stevermer, MD, MSPH**, discuss the highlights of this study, go to **www.jfponline.com**, click on this article, and then click on the podcast link.

ILLUSTRATIVE CASE

A 56-year-old patient with well-controlled type 2 diabetes and hypertension comes to see you for routine follow up. His blood pressure is controlled with lisinopril 40 mg/d. But his albumin-to-creatinine ratio is 75 mg/g, and your records reveal that his albuminuria is getting progressively worse.

You're aware of the potential benefits of a dual angiotensin blockade, and are considering adding an angiotensin receptor blocker (ARB) to your patient's medication regimen. You wonder whether the combination of an angiotensin-converting enzyme (ACE) inhibitor and an ARB will slow the decline of renal function. You also wonder whether the combination will reduce your patient's cardiovascular risk.

ACE inhibitors are known to reduce cardiovascular morbidity and mortality, as well as proteinuria in patients with vascular disease or diabetes, whether or not they have heart failure.[2] But few studies have compared the effects of ACE inhibitors and ARBs in high-risk patients without heart failure. Nor has there been a definitive study of the effects of an ACE inhibitor–ARB combination on proteinuria and cardiovascular risk.

Are 2 drugs better than 1?

In a recent meta-analysis, researchers reported that combination therapy had a beneficial effect on proteinuria.[3] But that observation was based on a small number of patients (N=309 from 10 studies),

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Key findings

The ONTARGET study:

- established that telmisartan, an ARB, is not inferior to ramipril, an ACE inhibitor, in reducing cardiovascular and renal events in high-risk patients without heart failure.
- found that either drug alone is more effective than combination therapy for this patient population.
- cast fresh doubt on the assumption that proteinuria is an accurate surrogate marker for progressive renal dysfunction.

short follow up, and a lack of data on key clinical end points such as decline of the glomerular filtration rate (GFR) and the onset of dialysis.

Other evidence comes from a study of 199 patients with diabetes and microalbuminuria, in which the ACE inhibitor–ARB combination reduced proteinuria more than either agent alone.[4] And in a study of 336 patients with nondiabetic nephropathy, the 2-drug combination slowed the decline in renal function more than monotherapy.[5]

Small studies raise hopes. These preliminary findings, along with the theoretical benefits of dual angiotensin blockade, suggested that the benefits of taking both agents together could be significant. A large, well-done randomized controlled trial (RCT) was needed to determine the following: (1) whether an ARB is as effective as an ACE inhibitor in reducing morbidity and mortality in high-risk patients who don't have heart failure, and (2) whether the ACE inhibitor–ARB combination is better than monotherapy for patients at high risk.

STUDY SUMMARY

Vascular outcomes same for ACE inhibitors, ARBs

The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET), a multiyear study of thousands of patients, addressed both of those questions. The researchers compared the effects of both telmisartan (Micardis, an ARB) alone and a telmisartan + ramipril (Altace, an ACE inhibitor) combination with the effects of the ACE inhibitor alone in patients ≥55 years of age with established atherosclerotic vascular disease or diabetes with end-organ damage.[1] Exclusion criteria included major renal artery stenosis, uncorrected volume or sodium depletion, a serum creatinine concentration of ≥3 mg/dL, and uncontrolled hypertension (>160 mm Hg systolic or >100 mm Hg diastolic).

After a 3-week run-in period to eliminate those who were unable to tolerate either medication or were nonadherent, a total of 25,620 patients remained. They were randomly assigned to take

FAST TRACK

Patients on the combination had lower blood pressure but more side effects—and no improvement in key outcomes

ramipril 10 mg/d, telmisartan 80 mg/d, or both the ACE inhibitor and the ARB. The researchers followed the patients for a median of 56 months.

The primary composite outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure;[1] the main renal outcome was a composite of first dialysis, doubling of serum creatinine, or death.[6]

The percentage of patients with the primary outcome was the same in all 3 groups (~16.5%). This finding was somewhat surprising because the blood pressure of patients in the combination therapy group was 2 to 3 mm Hg lower overall (both systolic and diastolic) than the blood pressure of patients on monotherapy—a difference that in other studies has been associated with an estimated 4% to 5% reduction in risk.[1,2] Patients in the combination group had more hypotensive symptoms compared with those in the ramipril group (4.8% vs 1.7%, number needed to harm [NNH]=32, *P*<.001).

Renal dysfunction was highest in dual therapy group

Patients in the combination therapy group had higher rates of renal dysfunction than either the ramipril group (13.5% vs 10.2%, NNH=30, *P*<.001) or the telmisartan group (10.6%), despite a decrease in proteinuria among those on dual therapy. Patients taking the 2-drug combination also had higher rates of hyperkalemia.

While telmisartan proved to be equal to ramipril in reducing vascular events in high-risk patients, patients taking the ACE inhibitor experienced more cough (NNH=32, *P*<.001) and angioedema (NNH=500, *P*=.01). In both monotherapy groups, the rates of adverse drug reactions were probably lower than what we typically see in clinical practice because after the run-in period, only patients who were better able to tolerate both medications remained.

FAST TRACK

The reduction in proteinuria in combination therapy patients came at a cost of increased renal impairment

PURLs methodology

This study was selected and evaluated using FPIN's Priority Updates from the Research Literature (PURL) Surveillance System methodology. The criteria and findings leading to the selection of this study as a PURL can be accessed at www.jfponline.com/purls.

WHAT'S NEW

Combination causes renal impairment

This study established that telmisartan, an ARB, is not inferior to ramipril, an ACE inhibitor, in reducing cardiovascular and renal events in patients without heart failure. In addition, as the largest RCT to explore the effects of a dual blockade of the renin-angiotensin system with an ACE inhibitor and an ARB, it casts fresh doubt on the assumption that proteinuria is an accurate surrogate marker for progressive renal dysfunction. The reduction in proteinuria seen in patients in the combination therapy group came at a cost of increased renal impairment.

CAVEATS

Findings do not apply to heart failure patients

More than 11% of potential subjects were excluded from this study during the run-in period. This suggests that physicians in practice are likely to find a significant number of patients who are unable to tolerate (or fail to adhere to) monotherapy with ACE inhibitors or ARBs.

At baseline, only a small subgroup—13%—had overt diabetic nephropathy, the hallmark for a substantial continuous decline of GFR. However, 38% of the study group had diabetes, and almost 30% of these diabetes patients had microalbuminuria. Subgroup analysis found results consistent with the overall group, and the large sample size reduces the likelihood that these findings were due to low power. The overall rate of dialysis and doubling of serum creatinine was low, but still statistically significant, due to the large size of this study.

In determining treatment for high-risk patients with vascular disease or diabetes, it is important to keep the study population in mind. Studies of patients with poorly controlled congestive heart failure (CHF) have shown potential benefits from an ACE inhibitor–ARB combination.[7] The ONTARGET trial specifically

excluded individuals with CHF, and its findings—and recommendations to avoid combination therapy—should not be applied to heart failure patients.

CHALLENGES TO IMPLEMENTATION

Best microalbuminuria Tx remains elusive

Although albuminuria has been considered an early sign of the onset of diabetic nephropathy, the ONTARGET study demonstrated that combination therapy may cause further reduction in albuminuria but still adversely affect renal function. Thus, this study raises important questions about the best treatment for patients with diabetes who have microalbuminuria and are already on either an ACE inhibitor or an ARB. We wonder, too, whether we should continue to test for microalbuminuria in patients who are taking one of these agents, given the lack of guidance regarding further treatment. ■

Acknowledgements

The PURLs Surveillance System is supported in part by Grant Number UL1RR024999 from the National Center for Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

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