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ACE inhibitor and ARB therapy: Practical recommendations

Inhibition of the renin-angiotensin-aldosterone system with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) is widely used in the treatment of heart failure, hypertension, chronic kidney disease, and coronary artery disease with left ventricular dysfunction.

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In this issue, Momoniat et al[1] review the benefits of ACE inhibitors and ARBs and how to manage adverse effects. I would like to add some of my own observations.

ACE inhibitors and ARBs are cornerstones of therapy of cardiovascular disease

ARE ACE INHIBITORS REALLY BETTER THAN ARBs?

ACE inhibitors have been the cornerstone of treatment for patients with heart failure with reduced ejection fraction (HFrEF), in whom their use is associated with reduced rates of morbidity and death.[2,3] The use of ARBs in these patients is also associated with decreased rates of morbidity and death[4,5]; however, in early comparisons, ACE inhibitors were deemed more effective in decreasing the incidence of myocardial infarction, cardiovascular death, and all-cause mortality in patients with hypertension, diabetes, and increased cardiovascular risk,[6] and all-cause mortality in patients with HFrEF.[7]

This presumed superiority of ACE inhibitors over ARBs was thought to be a result of a greater vasodilatory effect caused by inhibiting the degradation of bradykinin and leading to increased levels of nitric oxide and vasoactive prostaglandins.[8] Another proposed explanation was that because ARBs block angiotensin II AT1 receptors but not AT2 receptors, the increased stimulation of markedly upregulated AT2 receptors in atheromatous plaques in response to elevated serum levels of angiotensin II was deleterious.[6] Therefore, ACE inhibitors have been recommended as first-line therapy by most guidelines, whereas ARBs are recommended as second-line therapy, when patients are unable to tolerate ACE inhibitors.

Nevertheless, the much debated differences in outcomes between ACE inhibitors and ARBs do not seem to be real and may have originated from a generational gap in the trials.

The ACE inhibitor trials were performed a decade earlier than the ARB trials. Indirect comparisons of their respective placebo-controlled trials assumed that the placebo groups used for comparison in the 2 sets of trials were similar.[9,10] Actually, the rate of cardiovascular disease decreased nearly 50% between the decades of 1990 to 2000 and 2000 to 2010, the likely result of aggressive primary and secondary prevention strategies in clinical practice, including revascularization and lipid-lowering therapy.[10]

In fact, a meta-regression analysis showed that the differences between ACE inhibitors and ARBs compared with placebo were due to higher event rates in the placebo groups in the ACE inhibitor trials than in the ARB trials for the outcomes of death, cardiovascular death, and myocardial infarction.[11] Sensitivity analyses restricted to trials published after 2000 to control for this generational gap showed similar efficacy with ACE inhibitors vs placebo and with ARBs vs placebo for all clinical outcomes.[11] Moreover, recent studies have shown that ARBs produce a greater

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decrease in cardiovascular events than ACE inhibitors, especially in patients with established cardiovascular disease.[12,13]

An advantage of ARBs over ACE inhibitors is fewer adverse effects: in general, ARBs are better tolerated than ACE inhibitors.[14] There are also ethnic differences in the risks of adverse reactions to these medications. African Americans have a higher risk of developing angioedema with ACE inhibitors compared with the rest of the US population, and Chinese Americans have a higher risk than whites of developing cough with ACE inhibitors.[9,15]

HOW I MANAGE THESE MEDICATIONS

In my medical practice, I try to make sure patients with HFrEF, hypertension, chronic kidney disease, and coronary artery disease with left ventricular dysfunction receive an inhibitor of the renin-angiotensin-aldosterone system.

Which agent?

I prefer ARBs because patients tolerate them better. I continue ACE inhibitors in patients who are already taking them without adverse effects, and I change to ARBs in patients who later become unable to tolerate ACE inhibitors.

Most antihypertensive agents increase the risk of incident gout, except for calcium channel blockers and losartan.[16] Losartan is the only ARB with a uricosuric effect, although a mild one,[17,18] due to inhibition of the urate transporter 1,[19] and therefore I prefer to use it instead of other ARBs or ACE inhibitors in patients who have a concomitant diagnosis of gout.

Which combinations of agents?

The addition of beta-blockers and mineralocorticoid receptor blockers to ACE inhibitors or ARBs is associated with a further decrease in the mortality risk for patients with HFrEF,[20–22] but some patients cannot tolerate these combinations or optimized doses of these medications because of worsening hypotension or increased risk of developing acute kidney injury or hyperkalemia.

In most cases, I try not to combine ACE inhibitors with ARBs. This combination may be useful in nondiabetic patients with proteinuria refractory to maximum treatment with 1 class of these agents, but it is associated with an increased risk of hyperkalemia or acute kidney injury in patients with diabetic nephropathy without improving rates of the clinical outcomes of death or cardiovascular events.[23] I prefer adding a daily low dose of a mineralocorticoid receptor blocker to an ACE inhibitor or an ARB, which is more effective in controlling refractory proteinuria.[24] This regimen is associated with decreased rates of mortality, cardiovascular mortality, and hospitalization for heart failure in patients with HFrEF,[22] although it can lead to a higher frequency of hyperkalemia,[25] and patients on it require frequent dietary education and monitoring of serum potassium.

I avoid combining direct renin inhibitors with ACE inhibitors or ARBs, since this combination has been contraindicated by the US Food and Drug Administration due to lack of reduction in target-organ damage and an associated increased risk of hypotension, hyperkalemia, and kidney failure, and a slight increase in the risk of stroke or death in patients with diabetic nephropathy.[26]

Valsartan-sacubitril

Neprilysin is a membrane-bound endopeptidase that degrades vasoactive peptides, including B-type natriuretic peptide and atrial natriuretic peptide.[27] The combination of the ARB valsartan and the neprilysin inhibitor sacubitril is associated with a 20% further decrease in rates of cardiovascular mortality and hospitalization and a 16% decrease in total mortality for patients with HFrEF compared with an ACE inhibitor, although there can also be more hypotension and angioedema with the combination.[27,28]

An ACE inhibitor cannot be used together with valsartan-sacubitril

Very importantly, an ACE inhibitor cannot be used together with valsartan-sacubitril due to increased risk of angioedema and cough. I change ACE inhibitors or ARBs to valsartan-sacubitril in patients with HFrEF who still have symptoms of heart failure. Interestingly, a network meta-analysis showed that the combination of valsartan-sacubitril plus a mineralocorticoid receptor blocker and a beta-blocker resulted in the greatest mortality reduction in patients with HFrEF.[7] A word

of caution, though: one can also expect an increased risk of hypotension, hyperkalemia, and kidney failure.

Monitoring

It is crucial to monitor blood pressure, serum potassium, and renal function in patients receiving ACE inhibitors, ARBs, mineralocorticoid receptor blockers, valsartan-sacubitril, or combinations of these medications, particularly in elderly patients, who are more susceptible to complications. I use a multidisciplinary approach in my clinic: a patient educator, dietitian, pharmacist, and advanced practice nurse play key roles in educating and monitoring patients for the development of possible complications from this therapy or interactions with other medications.

A recent population-based cohort study found an association of ACE inhibitor use with a 14% relative increase in lung cancer incidence after 10 years of use, compared with ARBs,[29] but this may not represent a large absolute risk (calculated number needed to harm of 2,970 after 10 years of ACE inhibitor use) and should be balanced against the improvement in morbidity and mortality gained with use of an ACE inhibitor. Additional studies with long-term follow-up are needed to investigate this possible association.

TAKE-HOME POINTS

- Blockade of the renin-angiotensin-aldosterone system is a cornerstone in the therapy of cardiovascular disease.
- ARBs are as effective as ACE inhibitors and have a better tolerability profile.
- ACE inhibitors cause more angioedema in African Americans and more cough in Chinese Americans than in the rest of the population.
- ACE inhibitors and most ARBs (except for losartan) increase the risk of gout.
- The combination of beta-blockers and mineralocorticoid receptor blockers with ACE inhibitors or ARBs and, lately, the use of the valsartan-sacubitril combination have been increasingly beneficial for patients with HFrEF.

REFERENCES

1. **Momoniat T, Ilyas D, Bhandari S**. ACE inhibitors and ARBs: managing potassium and renal function. Cleve Clin J Med 2019; 86(9):601–607. doi:10.3949/ccjm.86a.18024
2. **CONSENSUS Trial Study Group**. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987; 316(23):1429–1435. doi:10.1056/NEJM198706043162301
3. **SOLVD Investigators; Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN**. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991; 325(5):293–302. doi:10.1056/NEJM199108013250501
4. **Young JB, Dunlap ME, Pfeffer MA, et al; Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) Investigators and Committees**. Mortality and morbidity reduction with candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. Circulation 2004; 110(17):2618–2626. doi:10.1161/01.CIR.0000146819.43235.A9
5. **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(23):1667–1675. doi:10.1056/NEJMoa010713
6. **Straus MH, Hall AS**. Angiotensin receptor blockers do not reduce risk of myocardial infarction, cardiovascular death, or total mortality: further evidence for the ARB-MI paradox. Circulation 2017; 135(22):2088–2090. doi:10.1161/CIRCULATIONAHA.117.026112
7. **Burnett H, Earley A, Voors AA, et al**. Thirty years of evidence on the efficacy of drug treatments for chronic heart failure with reduced ejection fraction. A network meta-analysis. Circ Heart Fail 2017; 10(1). pii:e003529. doi:10.1161/CIRCHEARTFAILURE.116.003529
8. **Chobanian AV**. Editorial: angiotensin inhibition. N Engl J Med 1974; 291(16):844–845. doi:10.1056/NEJM197410172911611
9. **Messerli FH, Bangalore S, Bavishi C, Rimoldi SF**. Angiotensin-converting enzyme inhibitors in hypertension: to use or not to use? J Am Coll Cardiol 2018; 71(13):1474–1482. doi:10.1016/j.jacc.2018.01.058
10. **Messerli FH, Bangalore S**. Angiotensin receptor blockers reduce cardiovascular events, including the risk of myocardial infarction. Circulation 2017; 135(22):2085–2087. doi:10.1161/CIRCULATIONAHA.116.025950
11. **Bangalore S, Fakheri R, Toklu B, Ogedegbe G, Weintraub H, Messerli FH**. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients without heart failure? Insights from 254,301 patients from randomized trials. Mayo Clin Proc 2016; 91(1):51–60. doi:10.1016/j.mayocp.2015.10.019
12. **Potier L, Roussel R, Elbez Y, et al; REACH Registry Investigators**. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in high vascular risk. Heart 2017; 103(17):1339–1346. doi:10.1136/heartjnl-2016-310705
13. **Bangalore S, Kumar S, Wetterslev J, Messerli FH**. Angiotensin receptor blockers and risk of myocardial infarction: meta-analyses and trial sequential analyses of 147,020 patients from randomized trials. BMJ 2011; 342:d2234. doi:10.1136/bmj.d2234
14. **Saglimbene V, Palmer SC, Ruospo M, et al; Long-Term Impact of RAS Inhibition on Cardiorenal Outcomes (LIRICO) Investigators**. The long-term impact of renin-angiotensin system (RAS) inhibition on cardiorenal outcomes (LIRICO): a randomized, controlled trial. J Am Soc Nephrol 2018; 29(12):2890–2899. doi:10.1681/ASN.2018040443
15. **McDowell SE, Coleman JJ, Ferner RE**. Systematic review and meta-analysis of ethnic differences in risks of adverse reactions to drugs used in cardiovascular medicine. BMJ 2006; 332(7551):1177–1181. doi:10.1136/bmj.38803.528113.55
16. **Choi HK, Soriano LC, Zhang Y, Rodríguez LA**. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. BMJ 2012; 344:d8190. doi:10.1136/bmj.d8190
17. **Wolff ML, Cruz JL, Vanderman AJ, Brown JN**. The effect of angiotensin II receptor blockers on hyperuricemia. Ther Adv Chronic Dis 2015; 6(6):339–346. doi:10.1177/2040622315596119

18. **Schmidt A, Gruber U, Böhmig G, Köller E, Mayer G**. The effect of ACE inhibitor and angiotensin II receptor antagonist therapy on serum uric acid levels and potassium homeostasis in hypertensive renal transplant recipients treated with CsA. Nephrol Dial Transplant 2001; 16(5):1034–1037. pmid:11328912
19. **Hamada T, Ichida K, Hosoyamada M, et al**. Uricosuric action of losartan via the inhibition of urate transporter 1 (URAT1) in hypertensive patients. Am J Hypertens 2008; 21(10):1157–1162. doi:10.1038/ajh.2008.245
20. **Packer M, Coats AJ, Fowler MB, et al; Carvedilol Prospective Randomized Cumulative Survival Study Group**. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001; 344(22):1651–1658. doi:10.1056/NEJM200105313442201
21. **Pitt B, Zannad F, Remme WJ, et al**. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; 341(10):709–717. doi:10.1056/NEJM199909023411001
22. **Zannad F, McMurray JJ, Krum H, et al; EMPHASIS-HF Study Group**. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364(1):11-21. doi: 10.1056/NEJMoa1009492
23. **Fried LF, Emanuele N, Zhang JH, et al**. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med 2011; 364(1):11–21. doi:10.1056/NEJMoa1009492
24. **Chrysostomou A, Pedagogos E, MacGregor L, Becker GJ**. Double-blind, placebo-controlled study on the effect of the aldosterone receptor antagonist spironolactone in patients who have persistent proteinuria and are on long-term angiotensin-converting enzyme inhibitor therapy, with or without an angiotensin II receptor blocker. Clin J Am Soc Nephrol 2006; 1(2):256–262. doi:10.2215/CJN.01040905
25. **Abbas S, Ihle P, Harder S, Schubert I**. Risk of hyperkalemia and combined use of spironolactone and long-term ACE inhibitor/angiotensin receptor blocker therapy in heart failure using real-life data: a population- and insurance-based cohort. Pharmacoepidemiol Drug Saf 2015; 24(4):406–413. doi:10.1002/pds.3748
26. **US Food and Drug Administration**. FDA drug safety communication: new warning and contraindication for blood pressure medicines containing aliskiren (Tekturna). www.fda.gov/Drugs/DrugSafety/ucm300889.htm. Accessed March 8, 2019.
27. **Jhund PS, McMurray JJ**. The neprilysin pathway in heart failure: a review and guide on the use of sacubitril/valsartan. Heart 2016; 102(17):1342–1347. doi:10.1136/heartjnl-2014-306775
28. **McMurray JJ, Packer M, Desai AS, et al; PARADIGM-HF Investigators and Committees**. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014; 371(11):993–1004. doi:10.1056/NEJMoa1409077
29. **Hicks BM, Filion KB, Yin H, Sakr L, Udell JA, Azoulay L**. Angiotensin converting enzyme inhibitors and risk of lung cancer: population based cohort study. BMJ 2018; 363:k4209. doi:10.1136/bmj.k4209

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