

Practice Pointers

Use of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blocking Agents

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Should ACEIs/ARBs be given to all diabetic patients?

The current guidelines are for angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blocking agents (ARBs) to be given to all diabetic patients without a contraindication if there is albuminuria, regardless of the presence of hypertension and independently of GFR. A diagnosis of diabetes without evidence of renal injury and in the absence of microalbuminuria and hypertension is not of itself an indication for ACEIs/ARBs. In other words, there is no evidence to support ACEIs/ARBs for the primary prevention of microalbuminuria. If hypertension and microalbuminuria are present, ACEIs/ARBs should be used as first-line therapy. The target dose of ACEIs/ARBs is unknown, but in normotensive patients, titrating the dose to the maximum tolerated level seems reasonable, given the known benefits. The target BP should be less than 130/80 mm Hg. Also important are hemoglobin A_{1c} level less than 6.5 percent, total cholesterol less than 175 mg/dL, triglyceride less than 150 mg/dL, smoking cessation, and weight reduction (1–3).

Is an ACEI/ARB combination superior to either agent alone?

Intuitively, combination therapy to maximally block the renal angiotensin aldosterone system makes sense, given the demonstrated renal protective and cardiovascular beneficial effects. This issue was controversially addressed in the now withdrawn COOPERATE study, which reported outcome benefits in terms of renal protection in nondiabetic patients with chronic kidney disease (CKD) who received a combination of ACEIs and ARBs versus either alone (4).

The CALM study looked at candesartan and lisinopril combination endpoints in terms of BP control and proteinuria and showed a benefit (5). However, the benefits did not extrapolate to mortality and disease outcomes. The OnTarget study looked at cardiovascular outcomes in diabetic patients with cardiovascular risk who received ACEIs and ARBs alone or in combination, but when the renal outcomes were analyzed, the combination group had worse renal function and adverse outcomes compared with the group who received a single agent (6). Now the NEPHRON D study has reported that combination therapy with ACEIs and ARBs is associated with an increased risk of adverse events among patients with diabetic nephropathy (7). Although these results are puzzling to those who believe in the benefits of renal angiotensin aldosterone system blockade, for purposes of clinical practice we are left with the use of either ACEIs or ARBs to achieve the desired endpoints.

Should we discontinue ACEIs/ARBs in patients with late-stage CKD?

The use of angiotensin blockade in late-stage CKD was addressed by Hou et al (8) in a study of 400 nondiabetic CKD patients published in the *New England Journal of Medicine* in 2006. In this study, patients with late-stage CKD creatinine levels of 1.5

to 3.0 mg% in group 1 and 3.1 to 5 mg% in group 2 treated with Benzapril 20 mg a day versus placebo had a marked reduction in risk to primary endpoint (doubling of serum creatinine, ESRD, or death) in both groups, and this benefit was not felt to be due to blood pressure control alone. Meanwhile, Ahmed et al. (9) in a small study of elderly patients with stage 5 CKD, evaluated in a clinic in Sheffield, England, for patients with low estimated GFR who had demonstrated progressive CKD, showed that discontinuation of ACEI delayed the initiation of dialysis



by significantly slowing the rate of decline in CKD function. So although ACEIs appear to be beneficial through stage IV CKD, discontinuing ACEI in stage V CKD might delay progression to ESRD and allow for the option to extend medical management of stage V CKD, at least for a while. Whether or not to discontinue ACEI in late-stage disease should depend on the patient's preference; in those who prefer medical management over dialysis, the option of discontinuing ACEI would be a consideration.

Is there a role for ACEI use in transplant patients?

Transplant patients by the nature of their presentation have a reduced nephron mass, and protection against hyperfiltration injury therefore seems intuitive. For transplant patients with greater than 1 g of proteinuria, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend ACEIs/ARBs as first-line treatment (20). That said, renal physiology in transplantation is skewed by the use of calcineurin inhibitors and by impedance of tonic afferent arteriole vasodilation. A meta-analysis of studies reviewing the management of hypertension in renal transplantation and comparisons between calcium channel blockers, ACEIs, and placebo suggested that calcium channel blockers may be preferred as first-line agents for hypertensive kidney transplant recipients (10). In retrospective reviews of patients receiving ACEIs/ARBs after kidney transplantation, the use of these agents has been associated with, and not associated with, improved

graft survival. More importantly, patient survival was reported improved in these studies (11, 12). Therefore, following the KDIGO guidelines, if the transplant recipient has proteinuria, ACEIs/ARBs are a reasonable choice. If the patient has hypertension and no proteinuria, then a calcium channel blocker seems logical.

Should we stop ACEIs/ARBs in the context of major surgery for purposes of renoprotection?

This is a controversial subject. Studies of continuing versus discontinuing ACEIs/ARBs before major surgery have observed increased intraoperative hypotension in patients who continued ACEIs/ARBs and increased postoperative hypertension in those in whom the indication for ACEIs/ARBs was hypertension. The inclination of many nephrologists is to hold ACEIs/ARBs perioperatively to maintain GFR, assuming adverse renal hemodynamics with the patient under anesthesia, but data from small studies have shown preserved and improved renal function and less acute kidney injury when ACEIs/ARBs were continued (12–14). Data in cardiac surgery patients show both increased and decreased acute kidney injury when ACEIs or ARBs are given perioperatively (15, 16). As a result, decision making should be on a case-by-case basis. In patients who are taking ACEIs/ARBs primarily for renal benefit, short-term discontinuation seems reasonable; if the indication is hypertension or myopathic heart disease, it may be preferable to continue.

How should we manage hyperkalemia in patients taking ACEIs/ARBs?

Hyperkalemia is a problem in many patients for whom ACEIs/ARBs are indicated and is the reason these agents cannot be used in some cases. Some predictors suggest which patients will be prone to hyperkalemia: those taking potassium-sparing diuretics, those with type IV renal tubular acidosis, and those taking diuretics whose potassium levels are above 4.5 mEq/L before starting ACEIs/ARBs. (17).

Whether to tolerate mild hyperkalemia is a clinical decision based on many factors, including the ability to closely follow up the patient. Certainly, dietary potassium restriction can be helpful in this setting. Reducing the ACEI/ARB dose is also indicated. Loop diuretics to increase renal potassium wasting and oral bicarbonate to correct metabolic acidosis can be used. In patients who become hyperkalemic, a repeated laboratory test should be done in 5 to 7 days. If the potassium level does not return to baseline during the next 2 to 4 weeks despite these interventions, a decision about discontinuing therapy with ACEIs/ARBs should be made (1). Of note, long-term exposure to sodium polystyrene sulfonate (Kayexalate) carries the inherent risk of gastrointestinal necrosis and should be avoided but recently released results from the HARMONIZE Trial that evaluated ZS-9 (sodium zirconium cyclosilicate), a cation that exchanges potassium in the intesti-

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nal tract for sodium and hydrogen, and the OPAL-HK trial that evaluated Patiromer, a non-absorbed polymer that binds potassium in exchange for calcium, show effective alternatives that will hopefully be available in the near future. (18,19) ●

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