

Journal View

ACEIs/ARBs Show Renoprotective Effect in Stage 5 CKD Linked to Increased Cancer Risk

In patients with advanced predialysis chronic kidney disease (CKD) and stable hypertension, treatment with a renin-angiotensin-aldosterone system blocker reduces the risk of long-term dialysis or death, reports a study in *JAMA Internal Medicine*.

The prospective cohort study included 28,497 hypertensive adults in Taiwan with predialysis stage 5 CKD. Eligible patients had serum creatinine greater than 6 mg/dL and hematocrit less than 28 percent, and they were being treated with erythropoiesis-stimulating agents. Of those, 14,117 patients were receiving an angiotensin-convert-

ing enzyme inhibitor or angiotensin receptor blocker (ACEI/ARB); the remaining 14,380 patients were not. The rates of long-term dialysis and all-cause mortality were compared by the use of Cox proportional hazards regression models.

At a median follow-up time of 7 months, 70.7 percent of patients had started long-term dialysis, and 20.0 percent had died before progressing to ESRD. Patients receiving ACEIs/ARBs had a small but significant reduction in the risk of long-term dialysis: hazard ratio 0.94. There was a similar reduction in a composite outcome of long-term

dialysis and death.

The renoprotective effect of ACEI/ARB use was apparent in most patient subgroups; benefits were also observed with ACEI or ARB treatment. The risk of hospital admission for hyperkalemia was higher among ACEI/ARB users. However, there was no increase in predialysis mortality caused by hyperkalemia.

There are few data on the benefits of ACEI/ARB therapy in patients with stage 5 CKD. In Taiwan, the prevalence and incidence of ESRD are very high, and dialysis is typically started late.

The new data suggest that ACEI/

ARB therapy has renal benefits for patients with advanced predialysis CKD. The risk of long-term dialysis or death is reduced by about 6 percent, with no increase in all-cause mortality. The researchers write, "We estimate that, every year, ACEI/ARB use could prevent 5.5 percent of the patients with advanced CKD from commencing long-term dialysis" [Hsu T-W, et al. Renoprotective effect of renin-angiotensin-aldosterone system blockade in patients with predialysis advanced chronic kidney disease, hypertension, and anemia. *JAMA Intern Med* 2013 Dec 16. doi: 10.1001/jamainternmed.2013.12700]. ●

Clarithromycin plus Calcium Channel Blockers Increase AKI Risk

An interaction between calcium channel blockers and clarithromycin is associated with an increased risk of acute kidney injury (AKI), according to a study in the *Journal of the American Medical Association*.

The population-based study included two groups of older adults in Ontario, mean age 76 years, who were newly prescribed a macrolide antibiotic during treatment with a calcium channel blocker—mainly amlodipine. Adverse out-

comes were compared for 94,083 patients receiving clarithromycin, an inhibitor of cytochrome P450 3A4 (CYP3A4), and 96,226 patients receiving azithromycin.

The primary outcome of hospitalization for AKI occurred in 0.44 percent of patients who were prescribed clarithromycin versus 0.22 percent of those taking azithromycin: odds ratio (OR) 1.98. The risk of AKI was highest for patients taking dihydropyridines, especially nifedipine: OR 5.33. Patients taking the com-

bination of clarithromycin and a calcium channel blocker were also at a higher risk of admission for hypotension, OR 1.60, and all-cause mortality, OR 1.75.

Calcium channel blockers are metabolized by CYP3A4, a process that raises the possibility of harmful blood drug concentrations in the presence of CYP3A4 inhibition. Clarithromycin is a CYP3A4 inhibitor, whereas azithromycin is not.

The new results strongly suggest that many older patients are coprescribed

clarithromycin with a calcium channel blocker, and this combination is associated with increased risk of AKI, hypotension, and death. The researchers write: "Our results suggest it is possible that hundreds of hospitalizations and deaths in our region may have been associated with this largely preventable drug-drug interaction" [Gandhi S, et al. Calcium-channel blocker-clarithromycin drug interactions and acute kidney injury. *2013; 310:2544-2553*]. ●

CORAL Study Finds No Benefit of Stenting in Renal Artery Stenosis

A worldwide, multicenter trial shows no reduction in clinical events with renal artery stenting for patients with atherosclerotic renal artery stenosis, reports the *New England Journal of Medicine*.

The "Cardiovascular Outcomes in Renal Atherosclerotic Lesions" (CORAL) study included 947 patients with atherosclerotic renal artery stenosis. Eligible patients were taking two or more antihypertensive drugs, had chronic kidney disease, or both. The open-label study randomly assigned patients to medical therapy alone or medical therapy plus renal artery stenting. The main outcome of interest was a composite of death resulting from cardiovascular or renal causes, myocardial infarction, stroke, hospitalization for congestive heart failure, progressive renal insufficiency, or renal replacement therapy.

At a median follow-up time of 43 months, the primary outcome rates were almost identical between groups: 35.1 percent with renal artery stenting and 35.8 percent with medical therapy alone. The individual

component outcomes and all-cause mortality were similar as well.

Stenting also showed no benefit in patients with global renal ischemia or in other high-risk subgroups. The lack of clinical benefit was observed despite a reduction in systolic blood pressure in the stenting group: 2.3 mm Hg lower than with medical therapy alone.

There is a long history of uncertainty over the role of stenting in treatment of renal artery stenosis related to atherosclerosis. The CORAL results show no improvement in outcomes with renal artery stenting, compared with medical therapy alone, for patients with renal artery stenosis and hypertension or chronic kidney disease. "From this result, it is clear that medical therapy without stenting is the preferred management strategy for the majority of people with atherosclerotic renal-artery stenosis," the researchers conclude [Cooper CJ, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med* 2013; 370:13-22]. ●

Statins and Diuretics May Increase Diabetes in High-Risk Patients

Patients with impaired glucose tolerance who take diuretics or statins may be at increased risk of new-onset diabetes, reports a study in the *British Medical Journal*.

The authors reanalyzed serial data on glucose levels from the "Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research" (NAVIGATOR) trial. The rates of new-onset diabetes were assessed for patients with no baseline history of treatment with β -blockers (5640 patients), diuretics (6346 patients), and statins (6146 patients). Another 6294 patients with no history of treatment with calcium channel blockers were studied as a "metabolically neutral" control group.

At a median follow-up time of 5 years, treatment with β -blockers was started in 16.2 percent of patients, diuretics in 20.7 percent, statins in 22.0 percent, and calcium channel blockers in 18.6 percent. After adjustment for baseline factors and time-varying confounders, both diuretics and statins were associated with an increased

risk of new-onset diabetes: hazard ratio 1.23 and 1.32, respectively.

The risk of diabetes was not increased for patients starting treatment with β -blockers or, as expected, calcium channel blockers.

Impaired glucose tolerance may be a risk factor for the development of diabetes during treatment with certain classes of medication. This reanalysis of randomized trial data shows a significant increase in the risk of new-onset diabetes with diuretics and statins.

Although there is no significant association with β -blockers, the authors term this effect "indeterminate." They conclude: "Our findings suggest that glycaemia should be better monitored when these drugs are initiated in high risk patients" [Shen L, et al. Role of diuretics, β blockers, and statins in increasing the risk of diabetes in patients with impaired glucose tolerance: Reanalysis of data from the NAVIGATOR study. *BMJ* 2013; 347:f6745]. ●

Something to Say?

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