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Pooled Analysis of Multiple Crossover Trials To Optimize Individual Therapy Response to Renin–Angiotensin–Aldosterone System Intervention

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Abstract

Background and objectives In the treatment of CKD, individual patients show a wide variation in their response to many drugs, including renin–angiotensin–aldosterone system inhibitors (RAASi). To investigate whether therapy resistance to RAASi can be overcome by uptitrating the dose of drug, changing the mode of intervention (with drugs from similar or different classes), or lowering dietary sodium intake, we meta-analyzed individual responses to different modes of interventions.

Design, setting, participants, & measurements Randomized crossover trials were analyzed to assess correlation of individual responses to RAASi and nonsteroidal anti-inflammatory drugs (NSAIDs; $n=395$ patients). Included studies compared the antialbuminuric effect of uptitrating the dose of RAASi ($n=10$ studies) and NSAIDs ($n=1$), changing within the same class of RAASi (*e.g.*, angiotensin-converting enzyme inhibition to angiotensin receptor blockers; $n=5$) or NSAIDs ($n=1$), changing from RAASi to NSAIDs ($n=2$), and changing from high to low sodium intake ($n=5$). A two-stage meta-analysis was conducted: Deming regression was conducted in each study to assess correlations in response, and individual study results were then meta-analyzed.

Results The albuminuria response to one dose of RAASi or NSAIDs positively correlated with the response to a higher dose of the same drug ($r=0.72$; 95% confidence interval [95% CI], 0.66 to 0.78), changes within the same class of RAASi or NSAIDs ($r=0.54$; 95% CI, 0.35 to 0.68), changes between RAASi and NSAIDs ($r=0.44$; 95% CI, 0.16 to 0.66), and changes from high to moderately low salt intake ($r=0.36$; 95% CI, 0.22 to 0.48). Results were similar when the individual systolic BP and potassium responses were analyzed, and were consistent in patients with and without diabetes.

Conclusions Individuals who show a poor response to one dose or type of RAASi also show a poor response to higher doses, other types of RAASi or NSAIDs, or a reduction in dietary salt intake. Whether other drugs or drug combinations targeting pathways beyond the renin–angiotensin–aldosterone system and prostaglandins would improve the individual poor response requires further study.

chronic renal disease | renin angiotensin system | ACE inhibitors | renal dysfunction | Angiotensin Receptor Antagonists | albuminuria | Potassium | blood pressure | Sodium | Peptidyl-Dipeptidase A | Prostaglandins | Anti-Inflammatory Agents, Non-Steroidal | Cross-Over Studies | Angiotensin-Converting Enzyme Inhibitors | Diet, Sodium-Restricted | Renal Insufficiency, Chronic | Psychotherapy | Drug Combinations | Sodium, Dietary

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