

VITAMIN D RECEPTOR ACTIVATOR (VDRA) RESEARCH IN CKD: WHY OBSERVATIONAL STUDIES AND SURROGATE MARKER RANDOMIZED CONTROLLED TRIALS (RCTs) ARE IMPORTANT ADJUNCTS TO MORTALITY-RELATED RCTs.

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Paricalcitol is the most frequently prescribed VDRA in the US. Observational data suggest that paricalcitol may improve survival over calcitriol, in part, by mechanisms independent of calcium, phosphorus, and PTH; RCTs are underway to determine whether paricalcitol can prevent progression of left ventricular hypertrophy (LVH) in patients who have relatively low PTH levels (PRIMO, clinicaltrials.gov).

However, why not study the effect of paricalcitol on mortality? It is not widely known that a mortality-related 2,200 subject RCT with paricalcitol was initiated, but had to be halted due to the inability to enroll an adequate number of subjects. This RCT was designed to compare the effect of IV paricalcitol versus IV calcitriol on hard outcomes, and began enrolling in July 2003 from 55 active sites; by July 2006, only 242 subjects were randomized and only 21 sites remained. The study was terminated after separate reviews by the study's Independent Data Monitoring Committee and the American College of Epidemiology Ethics Committee concluded that it was unethical to continue since full enrollment would not be achieved primarily owing to the belief that paricalcitol was superior to calcitriol based on well-controlled observational data. Despite their limitation in establishing causality, rigorous observational data, which suggest strong treatment effects on mortality and consequently establish a standard of care, can result in an ethical conundrum, as in this case with the inability to enroll a mortality-related RCT. In the absence of mortality-related RCTs, surrogate marker RCTs, which can provide valuable information on disease-specific mechanisms if the surrogate is a well-accepted intermediate endpoint (e.g. LVH), and well-controlled cohort observational studies must remain as necessary and cost-effective alternatives.