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Original Investigation

The Validity of Left Ventricular Mass as a Surrogate End Point for All-Cause and Cardiovascular Mortality Outcomes in People With CKD: A Systematic Review and Meta-analysis

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Background: Left ventricular mass (LVM) is a widely used surrogate end point in randomized trials involving people with chronic kidney disease (CKD) because treatment-induced LVM reductions are assumed to lower cardiovascular risk. The aim of this study was to assess the validity of LVM as a surrogate end point for all-cause and cardiovascular mortality in CKD.

Study Design: Systematic review and meta-analysis.

Setting & Population: Participants with any stages of CKD.

Selection Criteria for Studies: Randomized controlled trials with 3 or more months' follow-up that reported LVM data.

Intervention: Any pharmacologic or nonpharmacologic intervention.

Outcomes: The surrogate outcome of interest was LVM change from baseline to last measurement, and clinical outcomes of interest were all-cause and cardiovascular mortality. Standardized mean differences (SMDs) of LVM change and relative risk for mortality were estimated using pairwise random-effects meta-analysis. Correlations between surrogate and clinical outcomes were summarized across all interventions combined using bivariate random-effects Bayesian models, and 95% credible intervals were computed.

Results: 73 trials (6,732 participants) covering 25 intervention classes were included in the meta-analysis. Overall, risk of bias was uncertain or high. Only 3 interventions reduced LVM: erythropoiesis-stimulating agents (9 trials; SMD, −0.13; 95% CI, −0.23 to −0.03), renin-angiotensin-aldosterone system inhibitors (13 trials; SMD, −0.28; 95% CI, −0.45 to −0.12), and isosorbide mononitrate (2 trials; SMD, −0.43; 95% CI, −0.72 to −0.14). All interventions had uncertain effects on all-cause and cardiovascular mortality. There were weak and imprecise associations between the effects of interventions on LVM change and all-cause (32 trials; 5,044 participants; correlation coefficient, 0.28; 95% credible interval, −0.13 to 0.59) and cardiovascular mortality (13 trials; 2,327 participants; correlation coefficient, 0.30; 95% credible interval, −0.54 to 0.76).

Limitations: Limited long-term data, suboptimal quality of included studies.

Conclusions: There was no clear and consistent association between intervention-induced LVM change and mortality. Evidence for LVM as a valid surrogate end point in CKD is currently lacking.

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INDEX WORDS: Left ventricular mass (LVM); LVM regression; cardiovascular mortality; chronic kidney disease (CKD); left ventricular hypertrophy; surrogate endpoint; surrogate outcome; cardioprotection; erythropoiesis-stimulating agent (ESA); renin-angiotensin-aldosterone system (RAAS) inhibitor; nitrate; meta-analysis.

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Left ventricular mass (LVM) has been an attractive surrogate end point for cardiovascular outcomes in clinical trials.[1,2] It gained widespread acceptance among clinicians and researchers after secondary analyses of the HOPE (Heart Outcomes Prevention Evaluation) and LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) studies, both of which had a mean follow-up of more than 4 years. These studies showed that regression of LVM was associated with significant reductions in the risks for all-cause and cardiovascular mortality, myocardial infarction, stroke, atrial fibrillation, and heart failure in people with essential hypertension.[3-7] However, these and subsequent studies did not use randomized comparisons. Instead, comparisons of clinical outcomes were made between the group that achieved regression of left ventricular hypertrophy (LVH) during follow-up and the group that did not.[8]

LVH is extremely common in chronic kidney disease (CKD), affecting 30% to 45% of adults with non–dialysis-dependent CKD[9-12] and 40% to 75% of patients with end-stage kidney disease.[13-15] Its presence is associated with increased cardiovascular events and mortality in non−dialysis-dependent and dialysis-dependent CKD patient populations.[13,16-20]

LVM is widely reported as a surrogate end point in nephrology trials, either alone or as a component of a composite end point.[21-24] The use of LVM as a surrogate end point is based on the assumptions that LVH may be on the causal pathway between drug target and mortality and that treatment-induced reductions in LVM are cardioprotective and will ultimately lead to fewer cardiovascular events and deaths.[3-5] Other surrogate end points, such as proteinuria, estimated glomerular filtration rate, and blood pressure, are also frequently used to evaluate the effectiveness of interventions in the setting of CKD.[22,24-27] These outcomes are typically considered predictive of effects on patient-relevant outcomes, such as kidney failure and mortality, and presumed to lie along the causal pathway between the pharmacologic effects of these treatments and subsequent outcomes. Surrogate end points are widely used, particularly in trials of pharmaceutical agents, to increase trial efficiency (fewer participants and shorter follow-up).[28] Surrogates are ubiquitous in the field of CKD,[22,24] but it remains uncertain whether these end points, used in clinical trials and routine clinical care, can reliably predict clinically meaningful outcomes.[28,29]

The aim of this systematic review was to assess the validity of LVM as a surrogate end point in the setting of CKD by evaluating whether treatment-induced changes in LVM are associated with all-cause and cardiovascular mortality in people with CKD.

METHODS

The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[30]

Study Selection

Randomized trials that reported treatment effects on LVM in adults or children with any stages of CKD were considered eligible for inclusion. Randomized trials conducted in the general population were eligible for inclusion if a separate subgroup analysis of participants with CKD was reported. Because we aimed to evaluate the treatment-related correlation between effects on LVM and those on mortality, observational studies were excluded. Trials with follow-up duration less than 3 months were excluded because shorter follow-up may not be sufficient to detect treatment-related reductions in LVM or especially mortality.[31] Because kidney transplantation is associated with a reduction in LVM, trials involving kidney transplant recipients were also excluded.[32] If multiple secondary publications of the same data set were identified, the publication with the most complete data was used and additional data from secondary sources were extracted. Only data from the first phase of randomized crossover trials were eligible in order to reduce the risk of a carryover effect of interventions between treatment periods. Missing, incomplete, or unpublished data from the clinical trials were requested from the investigators.

Data Sources and Searches

Potentially relevant studies were identified using highly sensitive electronic searches of MEDLINE, Embase, and Cochrane databases without language restriction from inception to December 2015 (Table S1, available as online supplementary material). Initially, titles and abstracts identified in the literature search were screened independently by 2 investigators (S.V.B. and M.A.R.) for potentially eligible studies. All potentially eligible studies were then assessed in full text.

Data Extraction and Risk-of-Bias Assessment

Two investigators (S.V.B. and M.A.R.) independently extracted data and assessed risk of bias using the Cochrane tool.[33] The surrogate outcome of interest was defined a priori as change in LVM during treatment. Clinical outcomes of interest were effects on all-cause and cardiovascular mortality.

Data Synthesis and Analysis

For each study, the mean difference in treatment effect on LVM from baseline to last measurement between treatment groups was calculated together with the 95% confidence interval (CI). Mean differences in treatment effects across all studies were summarized as standardized mean differences (SMDs) and 95% CIs. Summary estimates were obtained by a random-effects meta-analysis model using the restricted maximum likelihood method[34] and the DerSimonian-Laird method if the restricted maximum likelihood model did not converge.[35] Treatment effects on LVM were summarized using the SMD due to substantial variation in the method by which LVM was measured (echocardiography or cardiac magnetic resonance imaging) and reported (regardless of whether indexed to body surface area). Summary treatment estimates for mortality outcomes were expressed as relative risks (RRs). Evidence of statistical heterogeneity was assessed using the Cochran Q statistic, and the extent of heterogeneity was evaluated using I^2.[36,37]

Correlation between intervention effects on surrogate and mortality end points was assessed by using data from all trials. The correlation was first visually assessed by generating scatterplots of