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**Risk of abnormal serum potassium levels for cardiovascular events  
with specific attention to drugs affecting potassium excretion**

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This dissertation provides the first systematic review and meta-analysis of observational studies on the association of abnormal serum potassium levels ( $< 3.5$  or  $> 5.1$  mmol/L) and cardiovascular outcomes within specific populations. For this purpose, the medical databases *Medline* and *Web of Science* were systematically searched from inception until November 24, 2017. Data synthesis of 24 relevant studies was performed using random-effects model meta-analyses, which finally comprised the data of 310,825 participants.

In the older general population, low serum potassium was associated with a 1.6-fold increased risk of supraventricular arrhythmias (hazard ratio [95%-confidence interval]: 1.62 [1.02; 2.55]). Contrarily, high serum potassium was associated with increased cardiovascular mortality (1.38 [1.14; 1.66]). In patients with acute myocardial infarction, the risk of ventricular arrhythmias was increased for high serum potassium (2.33 [1.60; 3.38]). A U-shaped association was observed both with a composite cardiovascular outcome in hypertensive patients (2.6-fold increased risk with hypokalemia and 1.7-fold increased risk with hyperkalemia), and with cardiovascular mortality in dialysis patients (1.1-fold increased risk with hypokalemia and 1.4-fold increased risk with hyperkalemia) as well as in heart failure patients (not statistically significant). Further, only hyperkalemia was associated with an increased risk of a composite cardiovascular outcome in dialysis patients (1.12 [1.03; 1.23]) and also in chronic kidney disease patients (1.34 [1.06; 1.71]).

Due to both a lack of studies and a variety of investigated outcomes and populations, a maximum of six studies was pooled per meta-analysis. The studies included also partly differed with regard to statistical analyses, reporting of results, and cut-off values for serum potassium. However, by using explicit inclusion and exclusion criteria with respect to design, statistical methods and definition of serum potassium cut-off values, the studies pooled in meta-analyses were mostly comparable and similar to the cut-off values proposed by the American Heart Association (reference range: 3.5 to 5.1 mmol/L). Given the heterogeneous covariate adjustment among the studies included, I suggest a key set of covariates, which future studies on this topic could use, namely age,

sex, body mass index or other weight measure, smoking, diabetes, hypertension, history of cardiovascular disease, and kidney disease.

In conclusion, these results suggest that some populations, especially patients with hypertension or heart failure, might profit from more frequent potassium-monitoring and subsequent interventions, such as change or withdrawal of potassium-influencing drugs, in order to restore normal values and prevent cardiovascular outcomes.

Secondly, this dissertation presents the first investigation about the associations of use of diuretics overall, non-potassium-sparing diuretics in specific, and laxatives with cardiovascular mortality in participants with antihypertensive treatment. The drug classes were first analysed distinctly and then jointly to detect potential drug-drug interactions in two large-scale cohort studies. While the German ESTHER study served as a derivation cohort to generate hypotheses, the larger UK Biobank was used as a replication cohort to confirm the findings. Methodologically, Cox proportional hazard regression models were applied to estimate hazard ratios and 95%-confidence intervals in each study. Results from both studies were then combined in an individual patient-data meta-analysis using the random-effects model.

Analyses included 4,253 participants, aged 50 to 75 years, from the ESTHER study and 105,359 participants, aged 50 to 69 years, from the UK Biobank. During 14 and 7 years of follow-up, 476 and 1,616 cardiovascular mortality cases were observed in the ESTHER study and the UK Biobank, respectively. Compared to non-users, a 1.6-fold (1.57 [1.29; 1.90]), a 1.4-fold (1.39 [1.26; 1.53]), and no statistically significantly increased [1.13 [0.94; 1.36]) cardiovascular mortality rate was observed in users of diuretics overall, non-potassium-sparing diuretics in specific, and laxatives, respectively. Concurrent use of non-potassium-sparing diuretics and laxatives was associated with a 2-fold increased cardiovascular mortality (2.05 [1.55; 2.71]) when compared to users of neither diuretics nor laxatives. However, a test for interaction slightly missed statistical significance ( $p=0.075$ ).

The major limitations of these analyses include the prevalent user design with regard to laxatives users, no repeated drug assessments, and a limited extent to control for confounding, in particular for the severity of heart failure and coronary heart disease.

Nevertheless, an interaction of non-potassium-sparing diuretics and laxatives appears plausible. Therefore, physicians are highly recommended to clarify additional laxatives use and monitor serum potassium levels more closely (e.g. every 3 months) in concurrent users.