



INTRODUCTION

"Disease is very old and nothing about it has changed. It is we who change as we learn to recognize what was formerly imperceptible."

Jean-Martin Charcot

The heart–kidney interactions described in this thesis are based on our experience derived from clinical studies conducted among patients with heart failure (HF) and those with ischemic heart disease (IHD). The thesis describes heart–kidney interactions not only as the organs' interplay assessed at a single moment in time as is commonly done, but also their temporal relationships over time preceding adverse clinical events. This is important to note because these temporal patterns have so far received insufficient attention, mainly due to the methodological limitations of previous studies. However, these patterns are inherently linked to the progression of the conditions that affect both the heart and the kidneys such as HF and atherosclerosis.

HF and IHD are global health problems that pose a great burden on patients, healthcare systems, and society in general.^{1,2} Besides their high prevalence, HF and IHD are the leading causes of death worldwide, with HF being also the leading cause of re-hospitalization.¹⁻⁴ One of the common denominators in both conditions is kidney dysfunction, where approximately half of patients with HF and one fourth of those with IHD suffer from chronic kidney disease (CKD).^{5,6} Importantly, the kidney disease not only co-exists, but also interacts with cardiac diseases thereby further reducing patients' survival.^{1,5} Interestingly, CKD patients are six times more likely to die of cardiovascular diseases than to reach end-stage renal disease.⁷ Taken together, it is clear that heart–kidney interactions are bidirectional and that their identification, assessment and proper management still remain challenging.

"A scientist does not (only) aim at the immediate results. He does not expect that his advanced ideas will be readily taken up. His work is like that of a planter – for the future. His duty is to lay the foundation for those who are to come, and point the way."

Nikola Tesla

This book is divided into four main parts: "Methodological concepts", "The role of the kidneys in heart failure and beyond", "Implications of renal function for ischemic heart disease", and "Lessons learned from clinical practice". Each part contains chapters that explain specific aspects of heart–kidney interactions, but also build on the preceding chapter. In chapter 2, the concepts of the "temporal patterns" and the "personalized risk assessment" are described, which have not been extensively explored in medicine. These concepts were subsequently applied in clinical studies reported in chapters 4 to 9. Briefly, in these chapters we examined individual temporal trajectories of multiple blood and urine markers to derive estimates of patient-specific (i.e., personalized) prognosis. For this purpose, we assessed the marker's levels, but also the slope (i.e., rate of change) of the marker's trajectory, and the cumulative effect of all values that the marker has taken until the time of the assessment. These aspects are valuable as they provide us with a comprehensive picture of disease dynamics and the patient's prognosis.

"I did not care to get a diploma, but to get qualified as an independent scientist. That was my goal! I have realized that the true science makes only what is of general scientific significance."

Milutin Milankovic

This thesis was guided by four main objectives. The first objective was to perform a critical appraisal of dynamic prediction modeling (chapter 2) and interaction testing (chapter 3) in clinical studies.

The second objective was to investigate how trajectories of glomerular and tubular renal compartments relate to each other over time preceding adverse clinical events, and how their individual and joint assessments relate to the prognosis of patients with chronic HF (chapters 4 and 5). Thereafter, we determined the predictive utility of temporal patterns of new HF biomarkers that are expected to emerge in the near future (chapters 6 to 8).

The third objective was to determine the implications of renal function for IHD. Specific aims included assessment of the evolution of renal function from its ini-

tial change during acute coronary syndrome (ACS) until stabilization, and investigating the predictive value of serial renal assessments in these patients (chapter 9). Moreover, we examined the relation of a potent glomerular marker, cystatin C– and a tubular marker, NGAL– with coronary atherosclerosis assessed in-vivo by intravascular ultrasound (IVUS) virtual histology and with patients' adverse outcomes (chapter 10).

The fourth objective was to evaluate different perspectives of clinical practice in HF patients with special attention to the kidneys. Specific aims included evaluation of the temporal relationships between guideline-recommended HF medication adjustments and multiple cardio-renal biomarkers, patients' functional status, and clinical outcomes in patients with chronic HF (chapter 11). In patients with end-stage HF, we investigated the relation of right heart and pulmonary hemodynamic parameters measured before heart transplantation with severity of postoperative acute kidney injury (chapter 12). Finally, we assessed the relation of renal dysfunction and anemia with short- and long-term survival in patients with acute HF using our registry data from 1985 to 2008 (chapter 13).

To meet the objectives, this thesis has combined several disciplines including methodologies of dynamic prediction modeling and interaction testing, utilization of modern assays based on –omics technologies for assessment of new biomarkers, sophisticated cardiovascular imaging techniques, and unique repeated-measures study designs. In the longer term, the results carry potential to contribute to reducing mortality- and hospitalization-rates in patients with acquired heart disease, improving their quality of life, and reducing healthcare costs.

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