

Chapter 5.2

Summary



CHAPTER 1: GENERAL INTRODUCTION AND THESIS OUTLINE

The societal burden of patients treated with renal replacement therapy (RRT) is extremely high and is expected to grow. As such, prevention of end-stage kidney disease and improved accessibility of renal transplantation, which is the preferred method of RRT, are highly required. Furthermore, continuous dialysis research is necessary as a substantial number of patients remain dependent on peritoneal dialysis or an extracorporeal RRT and mortality, morbidity and quality of life are severely impaired in this patient group, despite continuous research and increasing knowledge concerning the uremic state. The present thesis focuses on three aspects in patients treated with a chronic intermittent extracorporeal treatment, i.e. hemodialysis (HD) or hemodiafiltration (HDF): (1) identification of the preferred test to assess protein-energy wasting, (2) identification of cardiovascular risk factors and (3) determination of the role of the convection volume in patients treated with post-dilution online HDF and optimization of its magnitude.

CHAPTER 2: PROTEIN-ENERGY WASTING

Chapter 2.1

Protein-energy wasting (PEW) describes a state of decreased bodily protein and energy fuels. Various nutrition-related tests have been proposed to assess this syndrome. These nutritional indices indicate that PEW is highly prevalent in hemodialysis (HD) patients. Nonetheless, the concept PEW lacks a gold standard. An expert panel stated that PEW induces an impaired life expectancy and an increased morbidity. To add evidence in the quest to find the preferred nutrition-related test to assess PEW, we checked which nutrition-related test, out of a selected 8 (Malnutrition Inflammation Score (MIS), Subjective Global Assessment, Geriatric Nutritional Risk Index, composite score on Protein-Energy Nutritional Status, Body Mass Index, normalized Protein Nitrogen Appearance, serum creatinine and serum albumin (sAlb)), predicts mortality, the occurrence of cardiovascular events and the occurrence of infections best in 489 patients from the CONvective TRANsport STudy (CONTRAST). First, the discriminative value of all tests for each event was calculated with Harrell's C Statistic, after which the calibration was checked using the Hosmer-Lemeshow Goodness-of-Fit test. Thereafter, every test was divided into four groups. Within these groups, the hazard ratio (HR) of the best group versus the worst group, the HR of the worst group versus all groups and the HR per group was calculated using Cox proportional hazards models. It appeared that

the MIS and sAlb predict mortality and the occurrence of infections equally well. The MIS predicts the occurrence of cardiovascular events best.

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In this chapter, more evidence is added in the search for the preferred test to assess PEW. The abovementioned expert panel also stated that PEW is related to an impaired quality of life. As such, the 8 nutritional indices mentioned in chapter 2.1 were compared for their relation with quality of life in the same 489 patients from CONTRAST. Two cross-sectional analyses were performed, at baseline and 12 months thereafter, to identify the relation between every test and 13 domains of quality of life. To substantiate the results, a multivariable logistic regression analysis was also performed to calculate the odds to be in the upper (better) half of a domain of quality of life given that a patient is in the better half of a nutritional test. In all cases, the MIS clearly had the best relation with quality of life in terms of both quantity and magnitude of the association.

CHAPTER 3: VASCULAR DAMAGE

Chapter 3.1

The extremely high cardiovascular risk of patients treated with HD warrants identification of potential modifiable risk factors. As magnesium is possibly involved, we analyzed a subset of 365 patients from CONTRAST. Serum magnesium was measured at baseline and 6, 12, 24 and 36 months thereafter. Using Cox proportional hazards models, crude and adjusted hazard ratios (HRs) were calculated for every 0.1 mmol/L increase in serum magnesium for all-cause mortality, cardiovascular mortality and sudden death. A strong, independent association between serum magnesium and all end points was found (HRs 0.88 (95% CI 0.78-0.99) for all-cause mortality, 0.73 (95% CI 0.62-0.85) for cardiovascular mortality and 0.78 (95% CI 0.66-0.92) for sudden death in the fully adjusted model). A generalized linear mixed model with a random slope, a random intercept and a continuous autoregressive covariance matrix showed that serum magnesium decreases slightly but statistically significant over time (Δ -0.011 mmol/L/year, 95% CI -0.017 to -0.009).

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Another potentially modifiable cardiovascular risk factor in this patient group is sclerostin. Sclerostin is a 22kDa-sized glycoprotein that inhibits the Wnt pathway, which is involved in bone homeostasis and, possibly, extra-skeletal calcification.

In 396 patients from CONTRAST, serum sclerostin concentration was measured at the same time points as magnesium. Patients were categorized into quartiles according to their baseline serum sclerostin level. Using Cox proportional hazards models, hazard ratios were calculated for each quartile versus the lowest quartile, from which it appeared that patients in the highest serum sclerostin group had a significant better all-cause and cardiovascular survival in the adjusted models (HRs 0.49 (95% CI 0.31-0.78) and 0.23 (95% CI 0.09-0.59), respectively). The interaction term in a linear mixed model showed that the slope over time is different for patients treated with post-dilution online HDF or HD (p for interaction = 0.0004). In HD patients, serum sclerostin levels remained stable (Δ +2.89 pmol/L/year (95% CI -0.49 to +6.27)), whereas sclerostin decreased significantly in patients treated with HDF (Δ -4.45 pmol/L/year (95% CI -8.04 to -0.85)). Interestingly, an observational analysis revealed that the magnitude of change in patients treated with post-dilution online HDF depends on the magnitude of the convection volume.

Chapter 3.3

Left ventricular hypertrophy (LVH) is a known risk factor for adverse events in both the non-renal and the renal population. In this chapter, we investigated whether the type of LVH, i.e. eccentric or concentric hypertrophy, is associated with such adverse events. Out of the 328 patients from CONTRAST in whom a transthoracic echocardiography was performed at baseline, 233 had LVH. LVH itself was associated with a higher risk for all-cause mortality, cardiovascular mortality and sudden death. Within the LVH group, 146 had the eccentric and 87 the concentric type, which was determined according to the relative wall thickness (\leq or $>$ 0.42, respectively). Cox proportional hazards models, adjusted for a priori determined potential confounders using a propensity score, showed no difference for all-cause mortality or cardiovascular mortality between these two groups. The risk for sudden death, however, appeared to be significantly higher in those with eccentric LVH as compared to patients with concentric hypertrophy (adjusted HR 5.22, 95% CI 1.14-23.94).

CHAPTER 4: HEMODIAFILTRATION

Chapter 4.1

This chapter comprehends a review on post-dilution online HDF. Increasing evidence suggests a survival benefit for patients treated with high-volume HDF over subjects treated with conventional hemodialysis (HD). The available evidence on

the relation between HDF and survival relation is discussed, as well as some issues concerning safety and costs of this treatment modality.

Chapter 4.2

As mentioned above, available evidence shows an inverse relation between the magnitude of the convection volume and mortality in patients treated with post-dilution online HDF. The determinants of the convection volume have shown to be treatment-related rather than patient-related: treatment time, blood flow rate and filtration fraction. Treatment time itself, however, has also been associated with an improved survival. As such, the hypothesis was raised that the beneficial effect of high-volume HDF may be due to a higher treatment time in this patient group. In this chapter, we fitted various Cox proportional hazards models using data from CONTRAST to investigate whether the effect of high-volume HDF versus HD changed after statistical adjustment for mean treatment time during follow-up. As the HR for mortality did not markedly alter after adjustment for treatment time, we conclude that the inverse association between high-volume HDF and mortality is independent of treatment time.

Chapter 4.3

In this chapter, practical and technical problems and pitfalls in reaching high convection volume in patients treated with post-dilution online HDF are described. It addresses issues such as anticoagulation, needle size, filtration fraction and dialysers. Furthermore, five HDF systems are briefly described.

Chapter 4.4

Post hoc analyses of three large RCTs and several observational studies showed an inverse relation between the magnitude of the convection volume in HDF and mortality. Furthermore, as mentioned above, multiple studies showed that the magnitude of the convection volume is treatment-related rather than patient-related. In this chapter, a prospective multicenter study is described that was designed to investigate whether a high convection volume ($\geq 22\text{L}/\text{session}$) is feasible in the majority of patients ($>75\%$). A stepwise protocol to subsequently optimize the three aforementioned determinants of the convection volume was designed and applied in the study. During optimization and 4 and 8 weeks after the stepwise protocol, data on the dialysis treatment, including the convection volume, were collected. It appeared that approximately 80% of the included patients reached a volume $\geq 22\text{L}/\text{session}$, with a mean of approximately 26L. As treatment time remained unaltered during the study, these findings were due to an increase in blood flow

rate and filtration fraction. Importantly, these findings were not accompanied by unwanted high pressures.

CHAPTER 5: GENERAL DISCUSSION

In this chapter, the findings of this thesis are set into perspective. First, the MIS appears to be a promising candidate to assess PEW as this test associates with mortality, the occurrence of cardiovascular events, the occurrence of infections and QOL. However, as various other nutritional indices have not yet been investigated and multiple aspects of a preferred nutrition-related test have not been studied, various research questions remain. Second, we identified three potentially modifiable cardiovascular risk factors in end-stage kidney disease patients: magnesium, sclerostin and LVH, especially the eccentric type. Interventional research is warranted to investigate whether modification of these variables indeed results in improved clinical outcomes. Lastly, we showed that the association between high-volume HDF and improved survival is independent of treatment time. Furthermore, it is shown that high convection volumes are feasible in the majority of ESKD patients. Given the accumulating evidence of a survival benefit of treatment with HDF over treatment with HD, especially for subjects reaching high convection volumes on average, it is time to offer our patients primarily post-dilution online HDF rather than conventional HD.

