# Costs and outcomes in hemodialysis and hemodiafiltration

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# Costs and outcomes in hemodialysis and hemodiafiltration

Kosten en uitkomsten in hemodialyse en hemodiafiltratie
(met een samenvatting in het Nederlands)

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*Voor mijn ouders*

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**Renal replacement therapy**

Patients with end-stage renal disease have kidneys that no longer function adequately. Although cure is not an option, patients can be treated with various renal replacement therapies.

In 1943, the Dutchman Dr. Willem Kolff was the first to treat a patient with dialysis[1]. His invention could remove waste products from the body in patients with acute kidney failure. Through the years, this treatment called 'hemodialysis' has been refined to a stage in which patients with chronic kidney failure can be kept alive for years. Patients however face a strict regime of approximately 3 visits to the dialysis center per week. They sit in a chair for ± 4 hours while being attached to the dialysis machine with blood lines. By means of diffusion, an artificial kidney cleans their bodies of waste products and excess fluid and prevents the blood from becoming acid. In hemodiafiltration, a relatively new dialysis technique, the blood is not only cleaned with diffusion, but also with convection (a difference in pressure)[2]. Another type of dialysis is peritoneal dialysis. In peritoneal dialysis the blood is cleansed using the patients' abdomen (actually using a membrane in the abdomen, the peritoneum). Via a catheter, fluid enters the abdomen where it stays for ± 4 hours. By means of diffusion and convection, waste products and excess fluid accumulate in the added fluid after which it is drained. The patient does not have to undergo treatment at the dialysis center anymore, but there are downsides to this dialysis modality like the risk of peritonitis (an inflamed peritoneum)[3]. A recent study showed that in 1.5 years of follow-up this occurred in 42% of patients[4]. A third renal replacement option is a donor kidney. Ideally, all patients with end-stage renal disease receive this treatment. A donor kidney is far better equipped to replace the diseased kidney as compared to an artificial one, resulting in an improved survival and quality of life[5-7]. Five years after transplantation, the probability that the patient is still alive is 76%[5]. If on peritoneal or hemodialysis, this probability is 35% or 34% respectively. Not all patients are however healthy enough to undergo a kidney transplantation and even if they were, there are not enough donor kidneys.

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It has been estimated that in the Netherlands over a million people have some form of renal insufficiency (i.e. with a residual renal function below 90 ml/min/1.73m$^2$ and loss of proteins in the urine)[8]. In 2010, 14,690 of these patients were treated for end-stage renal disease; 5,155 were treated with hemodialysis, 1,137 with peritoneal dialysis and 8,398 had a functioning donor kidney[9].

**Quality of life**

Quality of life (QoL) has been defined as the presence of physical, mental and social-well being[10]. It is a subjective entity. Two patients with an identical illness might perceive their disease quite differently and therefore have a different QoL. Accordingly, if one is to measure a patient's QoL, one should ask the patient, not the treating physician. To indeed measure a patient's QoL, different techniques can be used. In dialysis care, patients are often asked to complete a questionnaire. Ideally, this questionnaire encapsulates the multiple domains that QoL comprises[11]. The most widely used questionnaire to assess generic QoL in dialysis patients is the Short Form 36 (SF-36)[12;13]. A demonstration version can be found at www.sf-36.org/demos/SF-36.html. As stated, the SF-36 is a generic questionnaire as opposed to a disease-specific questionnaire. The Kidney Disease Quality of Life – Short Form (KDQOL-SF) combines the SF-36 with a disease-specific part (Appendix II)[14;15]. After the patient has filled out its 82 questions, QoL can be comprised into 20 domains (with names like 'Physical functioning', 'Emotional well-being' and 'Burden of kidney disease'). These domains have a scale from 0 to 100 with higher scores indicating a preferable QoL.

**Hemodialysis and quality of life**

Not only survival is poor in patients on hemodialysis, QoL is hampered as well[16]. Their QoL is for instance lower than in patients with respiratory or coronary disease, arthritis or metastatic colorectal cancer[16]. Over the past decades, there have been multiple advances in dialysis care, for instance in the management of anemia, mineral metabolism, and dialysis dose[17-19].

Furthermore, targets have been set to indicate adequate dialysis care[20]. QoL is currently perceived as an important aspect of treatment[21]. Although it is expected that patients' QoL has improved accordingly, no evidence on this issue exists. It is unclear if the usual targets in dialysis care have any relation with QoL. Dialysis centers use these clinical performance targets in a uniform fashion. One may however question if that also results in a uniform level of patients' QOL between centers, especially since differences between centers have been described for mortality[22-25].

As clinical factors only explain QoL to a limited extent[26], there is a need for parameters that provide clinicians with guidance to improve the QoL of their patients. One promising parameter might be protein-energy nutritional status, a relatively new definition of body stores and protein and fat-masses[27]. Protein-energy nutritional status is however difficult to measure because multiple parameters need to be evaluated[27]. A simple composite score of protein-energy nutritional status could facilitate interpretation and form a parameter that may provide guidance towards an improved outcome.

**Outline of this thesis**

The main objective of this thesis is to evaluate the costs and outcome of hemodialysis and hemodiafiltration. The studies in this thesis will show the cost and effectiveness of both dialysis modalities, as well as various determinants of outcome in dialysis patients.

In the first part of this thesis, several determinants of QoL and survival in hemodialysis patients are evaluated. In **chapter 2**, changes in the QoL of hemodialysis patients over time are explored, which is set against the background of QoL changes in the general population. In **Chapter 3**, differences in the QoL of dialysis patients between centers and center characteristics associated with differences are evaluated. The question whether current clinical performance targets in dialysis care are related to QoL is adressed in **chapter 4**. **Chapter 5** reports on the relation between protein-energy nutritional status and kidney disease-specific quality of life. **Chapter 6** takes this one step further and evaluates a composite score of protein-energy nutritional status as a predictor of mortality in hemodialysis patients.

In the second part of this thesis, the costs and effectiveness of hemodiafiltration and hemodialysis are evaluated. **Chapter 7** describes the effect of hemodiafiltration versus hemodialysis on quality of life and **chapter 8** on mortality. **Chapter 9** combines these outcomes in a cost-utility analysis of hemodiafiltration versus hemodialysis.
The thesis is concluded with a summary and general discussion of the results in **chapter 10**.

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# 1

# Introduction II: The effect of hemodiafiltration on mortality, inflammation and quality of life

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## ABSTRACT

Online hemodiafiltration ([ol]-HDF) may improve clinical outcome in end-stage kidney disease. The supposed mechanism is the improved clearance of uremic toxins by the convective transport which is added to the standard diffusive transport. This review summarizes the effects of HDF on mortality, inflammation and health-related quality of life (HRQOL).

## INTRODUCTION

Online hemodiafiltration ([ol]-HDF) is an increasingly applied dialysis modality, especially in Europe[1]. This is most likely caused by the fact that sterile dialysis fluids can now be produced on-line. HDF has the advantage of combining clearance of small molecular weight substances by diffusion, with clearance of middle- and large molecular weight substances by convection[2]. HDF requires the use of synthetic high-flux membranes and ultrapure dialysate and sterile substitution fluids. Several studies suggest a potential benefit for patients treated with HDF[3-6]. It is hypothesized that increased clearance of a broader range of uremic substances leads to less inflammation, oxidative stress and endothelial dysfunction, which will result in less morbidity and mortality. We have previously reviewed several aspects of HDF[7-12].

This review provides an overview on studies on the effects of HDF on mortality, inflammatory state and health-related quality of life (HRQOL). The importance of several practical issues, such as water quality and different convection volumes will be discussed as well.

### Mortality

Several large observational studies suggest a survival benefit of HDF as compared to standard HD (summarized in Table 1). Locatelli et al. compared convective (HDF or hemofiltration[HF]) and diffusive dialysis modalities (hemodialysis, HD) using data from the Lombardy registry and found no significant survival benefit of HDF[13]. In contrast, in the observational Dialysis Outcomes and Practice Patterns Study (DOPPS) the adjusted mortality risk was 35% lower in high-efficiency HDF (i.e. HDF with a convection volume of ≥15 L per treatment session, in practice meaning ol-HDF) as compared to low-flux HD[3]. In addition, Jirka et al. published data of the European Clinical Database (EuCliD) network[4], showing that the use of ol-HDF was associated with a 35% lower adjusted mortality risk as compared to HD, so results very similar to DOPPS data. The RISchio CArdiovascolare nei pazienti afferenti all' Area Vasta In Dialisi (RISCAVID) study compared ol-HDF, HDF with sterile fluid in bags and low-flux HD[5]. After several adjustments, both HDF modalities had a 22%

lower all-cause mortality compared with HD, which was significant. However, the results were not adjusted for previous cardiovascular disease or residual renal function[14]. Recently, a retrospective analysis over an 18 year period of patients receiving predominantly ol-HDF (>50% of sessions) as compared to high-flux HD in the United Kingdom was published[6]. A total of almost 450.000 treatment sessions was analysed. After adjustments for confounders, a 55% lower hazard rate for mortality was found for HDF.

An important limitation of these studies is the lack of information on censored events. Most studies did not properly discuss the various reasons for loss to follow-up. Differences in drop-out rates and reasons for drop-out between groups may bias study outcome. The most important problem with the interpretation of these observational studies is confounding (by indication) due to the non-randomized design. There may be clinically important differences between patients treated with HD or HDF. Although adjustments were made for observed confounding in the applied regression models, this does not eliminate unobserved confounding due to (un)known risk factors. This limits the validity. Properly designed randomized clinical trials (RCTs) do not have these methodological limitations, because patient characteristics, as well as known and unknown confounders, will be equally distributed over study groups. Up till now, two small RCTs on the effect of HDF have been carried out with 44 patients (23 on HDF) and 208 patients (50 on HDF) both with a follow-up of 24 months[15;16]. These studies showed no survival benefit for patients treated by HDF as compared to HD, but were inadequately powered.

Finally, there may be important differences in convection volumes and water quality in the available studies. Convection volumes vary greatly between studies or are not mentioned. In Table 1, convection volumes and results of water quality monitoring are depicted. Results on water quality are difficult to compare, because cultures of the dialysis fluids were taken at different locations of the purification system. Nevertheless, there are differences in water quality within and between studies. We analyzed microbiological results of infusate in 8 centers during 12 months and showed that in over 99% of cases results met the reference quality levels with respect CFU count and endotoxin level[17].

**Table 1.** Effect of hemodiafiltration on mortality and inflammation.

| | Design & Intervention | N | Water quality | | Convection volume | Mortality | Inflammation | | Remarks | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | CFU | EU | | | CRP | IL-6 | Kt/V | β2m |
| Locatelli *et al.*[13] | Observational: HD ⇔ HDF / HF | 6444 HDF/HF 1082 | | | | ns. 10% ↓ | | | | |
| DOPPS[3] | Observational: LF-HD ⇔ HDF | 2165 HDF: 97 | | | 15 – 25 L | 35% ↓ | | | | |
| Jirka *et al.*[4] | Observational: LF-HD ⇔ olHDF | 2564 olHDF: 394 | | | [3] | 35% ↓ | | | | |
| RISCAVID[5] | Observational: LF-HD ⇔ olHDF ⇔ HDF sterile bags | 757 olHDF: 129 | sdf | up | 23 ± 3 L | 22% ↓ | = | ↓ | = | |
| Vilar *et al.*[6] | Observational: HF-HD ⇔ olHDF[1] | 858 olHDF:233 | up | up | 15 ± 4 L[4] | 55% ↓ | ↓ | ↓ | = | |
| Vaslaki *et al.*[32] | Cross-over: LF-HD ⇔ postdilution olHDF | 27 | up | | 5.6 ± 0.1 L/hour[2] | | = | = | | |
| Carracedo *et al.*[43] | Cross-over: HF-HD ⇔ olHDF | 31 | sdf | up | 20 L (16 – 24) | | | ns. ↓ | = | = |
| Panichi *et al.*[38] | Cross-over: HD ⇔ postdilution olHDF / HFR | 25 | | | 4.5 ± 0.3 L/hour[4] | | ↓ | ns. ↓ | | = |
| Vaslaki *et al.*[36] | Cross-over: LF-HD ⇔ postdilution olHDF | 70 | sdf | | 20 ± 3 L | | ↓ [5] | ↓ [5] | | = / ↓ |
| Schiffl *et al.*[37] | Cross-over: LF-HD ⇔ HF-HD/ postdilution olHDF | 76 | * ⇨ up | up | 4.5 L/hour | = [6] | ↓ [7] | | | ↓ |
| Filiopoulos *et al.*[35] | Observational: HD ⇔ postdilution HDF | 9 | * | | 10 L | | ↓ | ns. ↓ | = | |
| Kuo *et al.*[33] | Observational: HD ⇔ postdilution olHDF | 17 | sdf | sdf | 20 L | | = | = | | |
| Tiranatha-nagul *et al.*[34] | Observational: HF-HD ⇔ predilution olHDF | 22 | up | up | 9.6 L/hour[3] | | ns. ↓ | | = | ↓ |

Fields are left empty when parameter is not studied or mentioned. Depicted changes are patients treated HDF as compared to control group. Differences are statistically significant, unless otherwise specified (non significant=ns.). If not depicted, pre- or postdilution mode was not mentioned.
N: Number of patients, CRP: C-reactive protein, IL-6: Interleukin 6, β2m: β2-microglobulin, HD: hemodialysis (LF: low-flux, HF: high-flux), ol: on-line, HDF: hemodiafiltration; HF: hemofiltration, HFR: hemodiafiltration with regeneration of ultrafiltrate,
CFU: colony forming units per ml, EU: endotoxin units per ml, up: ultrapure (<0.1CFU/ml; <0.03EU/ml), sdf: standard dialysis fluid <100 CFU/ml; <0.25 EU/ml), * worse
Notes: [1] > 50% of the sessions HDF; [2] Flow rate substitution fluid; [3] Assumption of convective volume; [4] ultrafiltration volume or rate; [5] Only in the group that started on HD; [6] In HF-HD vs. olHDF; [7] In LF-HD vs HF-HD or HDF.

**Table 2.** Hemodialysis modality and health-related quality of life.

| Reference | Design | Intervention | Number of patients | Effect on HRQOL |
|---|---|---|---|---|
| HEMO[52] | RCT | High-flux ⇔ low-flux HD | 1846<br>921 on high-flux | No difference |
| Altieri *et al.*[53] | Cross-over | olHF ⇔ high-flux HD | 24 | No difference |
| Beerenhout *et al.*[54] | RCT | olHF ⇔ low-flux HD | 27<br>13 on HF | No difference (note: p=0.06 for better HRQOL in HF [14%]) |
| Moreno *et al.*[55] | Cross-sectional | HDF ⇔ HD ⇔ PD | 1013<br>71 on HDF | No difference |
| Ward *et al.*[56] | RCT | olHDF ⇔ high-flux HD | 44<br>24 on HDF | No difference |
| Lin *et al.*[57] | RCT | olHDF ⇔ high-flux HD | 111* | Better physical well-being in HDF (32%) |
| Schiffl *et al.*[37] | Cross-over | olHDF ⇔ high-flux HD | 76 | Better perception of physical symptoms in HDF (26%) |
| DOPPS[3] | Observational | HDF ⇔ High- ⇔ low-flux HD | 2165<br>253 on HDF | No difference |

HRQOL: health-related quality of life; RCT: randomized clinical trial; ol: on-line; HD: hemodialysis; HF: hemofiltration; HDF: hemodialfiltration
* Randomization into 4 groups: 3x/wk HD, 3x/wk HDF, and 2 intermediate versions with a 2x versus 1x/wk distribution of HD or HDF.

The need for RCT is further emphasized by the fact that sometimes cohort analyses show a considerable benefit, which is not confirmed by a RCT: an example is the use of statines in patients with end-stage kidney disease (ESKD)[18].

Several prospective randomized trials are now ongoing (Table 3). In three, mortality is the primary endpoint (CONTRAST, the Turkish HDF study and ESHOL)[19-21]. CONTRAST and the Turkish study have ended inclusion, results on primary endpoints are expected soon. Inclusion into the ESHOL study was ended September 2008, the study runs to September 2011. Two studies mainly focus on intradialytic morbidity (the French and Italian study)[22;23]. The Italian study shows that indeed the use of convective therapies is associated with less intradialytic morbidity (personal communication). An Australian study (FINESSE) is of particular interest, because the effect on neuropathy is

the primary endpoint[24]. Neuropathy affects the majority of end-stage renal disease patients, which results in function loss and discomfort.

In conclusion, most observational studies suggest a (substantial) survival benefit for patients receiving a therapy which also allows convective transport (Table 1). Prospective randomized trials will hopefully provide definite answers in the near future (Table 3).

**Table 3.** Hemodiafiltration and ongoing randomized clinical trials.

| Reference | Modality control group | Number of patients | Primary endpoint |
|---|---|---|---|
| CONTRAST[7;19] | Low-flux HD | 715 | Mortality |
| French study [22] | High-flux HD | Target ± 600 | Intradialytic morbidity |
| Italian study[23] | Low-flux HD and olHF | 146 | Hemodynamic stability |
| Turkish study[20] | High-flux HD | 782 | Cardiovascular morbidity and mortality |
| ESHOL[21] | HD (94% high-flux) | 939 | Mortality |
| FINESSE[24] | High-flux HD | Target ± 120 | Neuropathy |

HD: hemodialysis; ol: online; HF: hemofiltration.

### Inflammation

In patients with chronic kidney disease (CKD) a persistent low-grade inflammation is commonly observed[25]. Convective and diffusive therapies may differ in their effects on this inflammatory state. Therefore, it seems appropriate to focus on this issue. Especially in ESKD, the systemic concentrations of both pro-, but also anti-inflammatory cytokines are several folds higher due to decreased renal clearance and/or increased production. Several factors, both dialysis related (e.g. microbiological quality of the dialysate or membrane bio incompatibility) and non-dialysis related (e.g. retention of uremic toxins, infection, comorbidity), may contribute to a state of persistent inflammation[26]. Inflammation has been shown to play a major role in the pathogenesis of atherosclerosis[27] and to predict cardiovascular disease and mortality in ESKD[25;28]. HDF might exert a beneficial effect on outcome by removing and/or reducing the production of pro-inflammatory factors.

*CRP*

C-reactive protein (CRP, ±107kDa) is a reliable plasma marker of systemic inflammation and predicts cardiovascular risk and mortality in ESKD patients[28;29]. Whether CRP is only a marker of, or a causal factor in atherosclerosis remains a matter of debate[30]. Single CRP measurements can predict mortality in ESKD patients, however CRP levels fluctuate over time and are greatly influenced by transient infections and comorbidity. So, repeated measurements may give additional information about the actual inflammatory state as compared to a single measurement [31].

The association of CRP with treatment modality was investigated in two observational studies. In the RISCAVID study, no significant difference in hs-CRP levels (single measurement) was observed between HD, HDF (with sterile bags) and ol-HDF[5]. In the study by Vilar et al, CRP levels were lower in patients predominantly treated with HDF (median(IQR) 7.0(12.5) vs. 10.0(16.2) mg/L at twelve months)[6].

The influence of HDF on hs-CRP has been studied in small interventional studies, with number of patients ranging from 9 to 76. Whereas some studies found no (significant) reductions in CRP levels [32-34], possibly due to small sample size, others described a significant decrease [35-38] In one study, there was only a decrease in CRP levels after 9 months (mean ±SD 16.3±11.4 → 6.0±5.1mg/L) with a substitution volume of 10 liters[35]. The decreased CRP levels described by Vaslaki et al. might be influenced by different dialysis membranes or a different distribution of residual kidney function across groups[36]. In the study of Schiffl et al[37], CRP levels were significantly decreased when patients were shifted from LF-HD to HF-HD or ol-HDF (mean±SD 10.5(3)→ 5.0(3) mg/L), with no difference between the two latter groups. These results might be explained by differences in water quality. Finally, Panichi et al. showed a significant decrease in CRP after four months of therapy with ol-HDF(mean±SE 9.4±4.3→ 5.9±3.9 mg/L), with no difference between ol-HDF and HFR (HDF with regeneration of ultrafiltrate)[38]. It is interesting to note, that Panichi et al. showed that HDF with substitution volumes of <10 L resulted in an increase in CRP levels as compared to HD and HDF with substitution volumes > 20 L[39].

*IL6*

Interleukin 6 (IL-6) is a major pro-inflammatory cytokine. It plays a key role in the inflammatory response, regulating the hepatic synthesis of acute phase proteins. Furthermore, it may contribute to atherosclerosis. IL-6 mRNA is present in atherosclerotic arteries at a 10- to 40-fold higher level than in non-atherosclerotic vessels[40] and IL-6 gene polymorphisms have been described to influence cardiovascular disease risk in dialysis patients[41]. With regard to prognosis, IL-6 has been shown to be one of the strongest predictors of inflammation, cardiovascular disease and mortality in ESKD[28;42]. It is attractive to hypothesize that IL-6, with a molecular weight of approximately 25 kDa, can be lowered by HDF. However, there is very limited evidence available.

In an observational setting, the RISCAVID study found lower IL-6 levels in HDF as compared HD[5]. Interventional studies however showed no significant differences[32;33;35;38]. In a very elegant cross-over study by Carracedo et al. showed that the percentage of pro-inflammatory CD14+CD16+ monocytes lowered during ol-HDF[43]. Also a trend towards lower IL-6 levels in ol-HDF was described (mean (min-max) 18.9(10.6-17.8)→ 13.2(5-19) pg/mL).

So, some (but not all) studies suggest that there might be a difference between diffusive and convective therapies in their effect on inflammatory state. As mentioned earlier, water quality may act as an effect modifier, when less pure water is used in LF-HD as compared to HDF. In the available studies, it is not always clear if water of the same quality was applied. In addition, cultures of dialysis fluids were taken at different locations. So, differences in inflammatory state may be a result of differences in water quality and/or monitoring procedures.

**Health-related quality of life**

Patients on HD not only face the physical, mental and social burden of their disease, but also the limitations caused by the time-consuming nature of the therapy. As a result, it has been shown that the HRQOL of HD patients is even less than that of patients with cancer[44]. Although an important outcome, HRQOL is difficult to measure and interpret[45;46]. It is not a single entity like mortality,

nor is it assessable by measuring for instance biomarkers. Measuring HRQOL means assessing multiple domains of physical, psychological and social status taken from the patients' perspective[45;47].

With the now available standardised and validated questionnaires[48;49], HRQOL is increasingly investigated in dialysis care[50]. In an understanding that survival is not all that counts, cost-utility studies on new interventions combine mortality and HRQOL as their effect measure[51]. As HRQOL is a key outcome in HD patients, we evaluated the literature not only with regard to mortality and inflammation, but also on perceived health status (Table 2). Do high-flux or convective therapies lead to a better HRQOL? The HEMO study found no differences in HRQOL between patients treated with low- or high-flux HD[52]. However, an increased dialysis dose (eKt/V 1.05 vs. 1.45) was associated with minor improvements in HRQOL, i.e. better physical health and less bodily pain. Two small studies compared the effects of HD with on-line HF on HRQOL[53;54]. Although no significant differences were found, both studies describe a trend towards an improved HRQOL in patients on HF, especially in patients' assessed physical symptoms. With regard to HDF, the results are inconclusive: three studies found no differences between HD or HDF[3;55;56], but two other describe a significant improvement in physical well-being[37;57]. Further studies are warranted to provide definite results. It is important to note that, if HDF does not lead to an improved survival, the dialysis modality may still be the treatment of choice, if it is associated with a better HRQOL. Three of the ongoing trials depicted in Table 3 will evaluate HDF with regard to HRQOL: CONTRAST, the Turkish HDF study and FINESSE[19;20;24].

Finally, the additional costs of HDF should be taken into account. Medical resources are limited and current dialysis modalities are already among the most expensive therapies[58]. In CONTRAST, a formal cost-utility analysis will be performed to compare the additional costs with a possible difference in quality-adjusted life-years (QALYs). QALYs combine survival with HRQOL in one effect measure. At present, there is no scientific literature on HDF costs or QALYs available.

**Treatment optimisation parameters**

in every day clinical practice, there is a clear need for clinical and/or laboratory parameters to guide or to "dose" the HDF treatment. This parameter should be sensitive, valid, and be related to meaningful clinical outcome variables. Given the considerations outlined above on the results of inflammatory markers, it is questionable if these can be used to guide therapy. The levels of these substances are determined by many factors other than the treatment.

β2-Microglobulin (β2m, 11,8 kDa), could also be used as a variable to guide treatment, as it is one of the middle sized molecules. However, the plasma levels of ß2m are determined substantially by factors other than the extracorporeal clearance, i.e. residual kidney function and inflammatory state. Further, there is a relative resistance of β2m transfer between body compartments[59], so plasma levels decrease more rapidly than interstitial levels during HDF. This phenomenon limits enhanced β2m clearance by increasing convection volumes. We recently showed that change in β2m after six months of therapy was not related to applied convection volumes[60]. Therefore, assessment of β2m levels does not seem appropriate.

It seems reasonable to assume that there is a dose-effect relationship, when applying HDF, i.e. that a certain minimum amount of convection volume needs to be applied in order to obtain the beneficial effect. The results of the DOPPS suggest that this volume should be ≥ 15 $L^3$. This is the only set of data relating treatment related factors with meaningful clinical endpoints. Further studies on this subject are clearly needed.

## CONCLUSION

Results of observational studies suggest an improved survival of patients on HDF as compared to HD. Furthermore, some (but not all) studies suggest that there might be a difference between diffusive and convective therapies in their effect on inflammatory state. At present, the effect of HDF on HRQOL is unclear, and there is no scientific literature on HDF costs or QALYs.

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RCTs are needed in nephrology[61]. Well designed randomized clinical trials are now underway to (hopefully) provide an answer, whether HDF is associated with any survival benefit (Table 3). In addition, meta-analysis of the individual trials may also help to define an evidence-based approach towards HDF. Apart from survival, differences in other clinical endpoints, including non-fatal cardiovascular morbidity and HRQOL, are important as well and are studied in (some of) these trials. Differences between HDF and standard HD in these endpoints seem reason enough to choose for ol-HDF as a standard treatment, especially now it has been shown that ol-HDF can be applied safely. Finally, the ongoing trials may help to define variables such as biomarkers or levels of convection volumes, which can be used to guide and optimize the therapy.

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# Changes in quality of life over time – Dutch hemodialysis patients and general population compared

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On behalf of the CONTRAST investigators

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## ABSTRACT

**Background.** Improving the health-related quality of life (HRQOL) for hemodialysis patients is a considerable challenge. The aim of the present study was to compare changes in HRQOL in hemodialysis patients with those observed in the general population over a ten year period, and explore factors that might explain possible differences.

**Methods.** We compared 126 hemodialysis patients assessed in 1995 in the Netherlands Cooperative Study on the Adequacy of Dialysis-1 (NECOSAD-I) with 515 patients enrolled in 2006 in the ongoing Convective Transport Study (CONTRAST). Changes in HRQOL in these cohorts were compared with two representative samples from the general Dutch population, assessed in 1992 (N=1,063) and 2001 (N=10,600). HRQOL was measured with the SF-36 questionnaire. Differences in HRQOL were analyzed with ANCOVA to adjust for demographic variables. To assess possible differences we used multivariable regression analysis.

**Results.** HRQOL in hemodialysis patients in 2006 (CONTRAST, mean age 63 ± 14 years (SD), 62% male) was significantly better than in 1995 (NECOSAD-I, 59 ± 16 years, 53% male) in 4 domains of the SF-36: bodily pain (+5 points, P=0.009), vitality (+7, P<0.001), role-emotional (+14, P<0.001), and mental health (+8, P<0.001), after adjusting for demographic variables. This increment could partly be explained by improved hemoglobin and phosphate levels. Compared to the general population, HRQOL improvement was most outspoken in 2 domains: bodily pain (+6, P=0.01) and role-emotional (+8, P=0.007).

**Conclusions.** This study showed an improvement of HRQOL in hemodialysis patients over an 11 year period of time, independent of global changes in the general population.

## INTRODUCTION

Health-related quality of life (HRQOL) is a multidimensional concept that reflects a patient's perceived well-being and functioning in physical, psychological, and social domains of health. Hemodialysis patients have an unfavourable HRQOL as compared to the general population[1;2]. The goal for the clinician is to provide optimal patient care in order to maximize both duration and quality of life. Clinical care has improved over the past decades, for instance with regard to the management of anemia, mineral metabolism, and dialysis dose[3-5]. This resulted in an improved survival[3-5], but did HRQOL increase as well? Are we on the right track, especially when put against the background of HRQOL observed in the general population? Cohort studies that followed HRQOL over a maximum period of two years showed different results: an increase[6;7], no changes[2], or decrease[8] in HRQOL. Cohort studies in hemodialysis patients are however faced with therapy switches, center changes, and a high attrition rate. This complicates a prolonged follow-up and may affect the results, especially because HRQOL is related to mortality[9]. Only one study analyzed the change in HRQOL of hemodialysis patients over time with a repeated cross-sectional design[10]. It compared patients in the United States with one year of follow-up between 1997 and 2006 and showed a negligible increase in HRQOL. Unclear however is how these observations correspond to the development of HRQOL in the general population. Furthermore, as the quality of life of the dialysis population differs between continents[11], the results of the study in the United States may not be transferred to Europe. To answer these questions we first compared two dialysis cohorts: the Netherlands Cooperative Study on the Adequacy of Dialysis-1 (NECOSAD-I), initiated in 1994, and the ongoing Convective Transport Study (CONTRAST), initiated in 2004[8;12]. Both are multi-center studies that included hemodialysis patients in the Netherlands. We then took the development of HRQOL in the general population into account by comparing the results with two large samples of the general Dutch population[13;14].

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Our aim was to compare changes in HRQOL in hemodialysis patients with those observed in the general population over a ten year period, and explore factors that might explain possible differences.

## METHODS

### Patients and study design

This study compares two cohorts in a cross-sectional design: NECOSAD-I and CONTRAST. From NECOSAD-I, we analyzed 126 hemodialysis patients enrolled consecutively between October 1993 to April 1995 from 14 dialysis centers in the Netherlands[8]. Eligible were patients aged ≥ 18 years who started with chronic dialysis, had not received renal replacement therapy in the past and had survived the first 3 months on dialysis. We analyzed the cohort after one year of follow-up to compensate for the inclusion of incident patients. The cohort contained 147 hemodialysis patients at baseline. After one year, 13 patients had died, 5 had been transplanted, 2 had moved to another hospital, and 1 had refused further participation.

From CONTRAST, we analyzed baseline data of the first consecutive 515 hemodialysis patients enrolled from June 2004 to January 2009 from 26 dialysis centers in The Netherlands. CONTRAST is an ongoing randomized controlled trial (ISRCTN38365125) comparing low-flux hemodialysis and online hemodiafiltration with regard to all-cause mortality and cardiovascular events, as described elsewhere[12]. Patients were eligible if treated with hemodialysis 2 or 3 times a week, for at least 2 months, with a minimum dialysis urea Kt/V ≥ 1.2, and who were able to understand the study procedures. Exclusion criteria were age < 18 years, treatment by hemodiafiltration or high flux hemodialysis in the 6 months preceding randomization, severe incompliance defined as non-adherence to the dialysis prescription, a life expectancy < 3 months due to non kidney disease, and participation in another clinical intervention trial evaluating cardiovascular outcomes.

Both studies were conducted in accordance with the Declaration of Helsinki and approved by the medical ethics review boards of all participating dialysis

centers. Written informed consent was obtained from all patients prior to enrolment.

The differences between the dialysis cohorts were compared with two samples from the general Dutch population, assessed in 1992 and 2001[13;14]. The first sample comprised a random sample (N=1,063) of inhabitants aged ≥ 18 years from the population register of the Dutch city of Emmen[13]. The second sample (N=10,600) was randomly drawn from all registered people aged ≥ 18 years from 104 representative Dutch general practices, that participated in the Second Dutch National Study of General Practice[14].

**Data collection**

For both hemodialysis cohorts, standardized forms were used to collect demographic, clinical and laboratory data at baseline. Demographic data included age, gender, educational level and employment status. Clinical characteristics studied in both cohorts were data on medical history, including the cause of kidney failure, diabetic state, vascular access, hemodialysis adequacy (Kt/V urea), time on renal replacement therapy in years, dialysis frequency, treatment time in hours, blood pressure measured before dialysis, body mass index measured after dialysis (BMI), residual renal function expressed as an estimated glomerular filtration rate (eGFR), and smoking habit (yes/no). The second generation Daugirdas formula was used to calculate single pool Kt/V for urea[15]. The eGFR was calculated as the mean of creatinine and urea clearance, corrected for body surface area[16]. The normalized protein nitrogen appearance (nPNA), also known as protein catabolic rate (nPCR), was calculated from two blood urea nitrogen measurements and adjusted for residual kidney urea clearance as described by Depner[17].

*Health-related quality of life*

HRQOL was measured using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), version 1[18]. This is the most widely used instrument to assess generic HRQOL in hemodialysis patients[19]. The SF-36 is a subjective self-assessment questionnaire, which reflects generic HRQOL in 8 domains of

functioning and well-being (Table 1). For each domain a score is calculated from 0 to 100, with a higher score indicating a more favorable HRQOL. The reliability, validity, and sensitivity of the SF-36 have been shown in hemodialysis patients[20]. The Dutch version has been validated by Aaronson et al[21]. A demonstration of the SF-36 can be found at http://www.sf-36.org/demos/SF-36.html.

**Data analysis**

Patient characteristics were reported as means with standard deviations, medians with interquartile ranges, or proportions when appropriate. Differences between the dialysis cohorts were analyzed using the independent t-test or Mann-Whitney test for continuous variables, and Fisher's exact test for nominal parameters. Differences in HRQOL were assessed with ANCOVA, which allowed for adjustments for age and gender between all groups. A difference in HRQOL of 5 points or more has been proposed as relevant[18]. The distribution of the residuals was assessed with Q-Q and box plots. Multivariable regression models were applied to explain the differences in HRQOL between NECOSAD-I and CONTRAST. Social-economic and clinical patient characteristics were treated as potential explanatory factors. Normal distributed HRQOL domains were analyzed using linear regression, and non-parametric domains with logistic regression. To facilitate logistic regression the non-parametrically distributed domains were dichotomized using the median as cut-off value. Table 1 describes the dichotomized disease-specific HRQOL domains to facilitate interpretation. Finally, to exclude that possible effects between NECOSAD-I and CONTRAST could be explained by differences in dialysis vintage, a sensitivity analysis was performed in which only CONTRAST patients with a dialysis vintage of 0.5 to 1.5 years were compared with NECOSAD-I. Results were considered statistically significant when $P < 0.05$ (two-tailed comparison). We used single regression analysis to account for missing values[22]. All analyses were conducted using SPSS (version 15.0.1; SPSS Inc. Headquarters, Chicago, Illinois, USA).

**Table 1.** The Short Form-36 (SF-36).

| Domains | Meaning | | Questions |
|---|---|---|---|
| | Low | High | |
| Physical Functioning (PF) | Severe limitations in physical activity, including bathing and dressing | Performs vigorous activity without limitations | 10 |
| Role-Physical (RP) | Limited ability to work because of physical health | Physical health does not limit work or other activity | 4 |
| Bodily Pain (BP) | Severe limiting pain | No pain or limitations due to pain | 2 |
| General Health (GH) | Perceives health as poor | Perceives health as excellent | 5 |
| Vitality (VT) | Feels tired and worn out all the time | Feels full of pep and energy all the time | 4 |
| Social Functioning (SF) | Physical and emotional symptoms severely limit normal social activities | No physical or emotional limits to normal social activities | 2 |
| Role-Emotional (RE) | Emotions limit daily function and work | Emotions do not interfere with daily function or work | 3 |
| Mental Health (MH) | Feels nervous and depressed all the time | Feels peaceful, happy, and calm all the time | 5 |

Adapted from Ware et al[18].



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## RESULTS

### Patient characteristics

The characteristics of the 126 patients from NECOSAD-I (mean age 59 ± 16 years (SD), 53% male) and 515 patients from CONTRAST (mean age 63 ± 14 years, 62% male) are summarized in Table 2. The assessment in CONTRAST was approximately 11 years later than in NECOSAD-I. Demographic and social-economic parameters between the cohorts were similar, except for a small but significant difference in age (59 vs 63). Multiple treatment-related variables were significantly different between NECOSAD-I and CONTRAST patients (e.g. hemoglobin 6.5 vs 7.4 mmol/L, weekly Kt/V 3.6 vs 4.0).

### Changes in health-related quality of life

When adjusted for age and gender, HRQOL in hemodialysis patients was significantly better in 2006 as compared to 1995 in four domains: bodily pain (+5 points, P=0.009), vitality (+7, P<0.001), role-emotional (+14, P<0.001), and mental health (+8, P<0.001) (Table 3), although a positive trend was seen for all domains. In the sensitivity analysis including only CONTRAST patients with a dialysis vintage of 0.5 to 1.5 years (N=168), all differences remained significant. The changes were slightly more pronounced with regard to bodily pain (+6, P=0.04), but reduced in vitality (+5, P=0.03), role-emotional (+8, P=0.02), and mental health (+7, P<0.001).

### Factors that explain the changes in health-related quality of life

The difference in vitality between NECOSAD-I and CONTRAST could partly be explained by the higher hemoglobin levels in the CONTRAST study. When adjusted for hemoglobin, the difference in vitality was reduced by 46%. The better Kt/V had a limited effect of 6% on this domain, which diminished if differences in eGFR were taken into account. The difference in both bodily pain and role-emotional could to a limited extent be explained by the lower phosphate levels in CONTRAST (10% and 9% respectively). The higher in hemoglobin levels played a minor role in the increase of mental health (11%). No other variables showed a noteworthy effect (i.e. ≥ 5%).

**Table 2.** Patient characteristics.

| | NECOSAD-I (N=126) | CONTRAST (N=515) |
|---|---|---|
| **Time period of assessment** | 1995 (1995-1996) | 2006 (2005-2007) |
| **Demographic** | | |
| Age (years) | 59 ± 16 | 63 ± 14* |
| Gender (% male) | 53 | 62 |
| **Socio-economic status** | | |
| Employed (%) | 12 | 12 |
| High educational status# (%) | 7 | 13 |
| **Clinical parameters** | | |
| Cause of renal failure (%) | | |
| Glomerulonephritis | 10 | 13 |
| Nephritis | 9 | 9 |
| Cystic kidney disease | 14 | 8* |
| Other congenital | 2 | 1 |
| Renal vascular | 25 | 30 |
| Diabetes mellitus | 12 | 14 |
| Other multisystem | 6 | 5 |
| Other / unknown | 22 | 20 |
| Dialysis vintage (years) | 1.0 (1.0 – 1.0) | 2.0 (1.0 – 3.8)* |
| Dialysis frequency (%) | | |
| 2x per week | 34 | 6* |
| 3x per week | 63 | 94* |
| Treatment time (hours per week) | 11 (9 – 12) | 12 (11 – 12)* |
| spKt/V urea per week | 3.6 ± 1.1 | 4.0 ± 0.7* |
| eGFR (mL/min/1.73m$^2$) | 2.4 (0.7 – 5.6) | 0.0 (0.0 – 2.8)* |
| nPNA (g/kg/d) | 1.3 (1.1 – 1.6) | 1.1 (0.9 – 1.2)* |
| Body mass index (kg/m$^2$), post-dialysis | 25 ± 5 | 25 ± 4 |
| Systolic blood pressure (mmHg), pre-dialysis | 151 ± 20 | 149 ± 22 |
| Diastolic blood pressure (mmHg), pre-dialysis | 82 ± 10 | 77 ± 12* |
| Current smoker (%) | 27 | 21 |
| Diabetes (%) | 14 | 20 |
| Hemoglobin (mmol/L) | 6.5 ± 0.8 | 7.4 ± 0.7* |
| Albumin (g/L) | 39 ± 6 | 37 ± 5* |
| Creatinine (µmol/L), pre-dialysis | 920 ± 245 | 826 ± 236* |
| Calcium (mmol/L) | 2.5 ± 0.2 | 2.3 ± 0.2* |
| Phosphate (mmol/L) | 2.0 ± 0.6 | 1.7 ± 0.5* |

Mean ± SD or median (interquartile range)
* P < 0.05, two-tailed comparison.
# high educational status: college or university level.
nPNA: normalized protein nitrogen appearance; eGFR: estimated glomerular filtration rate.
To convert hemoglobin in mmol/L to g/dL divide by 0.62; albumin in g/L to g/dL, divide by 10; creatinine in µmol/L to mg/dL divide by 88.4.

**Table 3.** Health-related quality of life of the NECOSAD-I and CONTRAST cohort.

| | NECOSAD-I (N=126) | CONTRAST (N=515) |
|---|---|---|
| **SF-36 scales** | | |
| Physical functioning | 51 ± 29 | 52 ± 28 |
| Role-physical | 34 ± 41 | 44 ± 43 |
| Bodily pain | 67 ± 28 | 72 ± 27* |
| General health | 43 ± 21 | 44 ± 21 |
| Vitality | 50 ± 21 | 56 ± 21* |
| Social functioning | 65 ± 28 | 68 ± 28 |
| Role-emotional | 54 ± 45 | 70 ± 43* |
| Mental health | 66 ± 21 | 74 ± 19* |

Mean ± SD
The domains range from 0 to 100, with higher scores indicating a preferable health state.
* P < 0.05 when adjusted for age and gender.

**Changes in health-related quality of life as compared to the general population**

Table 4 depicts the HRQOL of the general Dutch population in 1992 and 2001. When adjusted for age and gender, there was a significant difference between the two cohorts in physical functioning (+6 points, P<0.001), vitality (+2, P<0.001), role-emotional (+6, P<0.001), and mental health (+3, P<0.001).

Figure 1 shows the changes of HRQOL in the dialysis population as compared to the changes in the general population. This suggests that the increase of HRQOL in the dialysis population was more pronounced in five out of eight scales, especially with regard to bodily pain (+6, P=0.01) and role-emotional (+8, P=0.007).

**Table 4.** Health-related quality of life in the general Dutch population in 1992 and 2001.

| | 1992 (N=1,063) | 2001 (N=10,600) |
|---|---|---|
| Age (years) | 45 ± 17 | 46 ± 19 |
| Gender (% male) | 35 | 45* |
| **SF-36 scales** | | |
| Physical functioning | 81 ± 24 | 87 ± 21* |
| Role-physical | 79 ± 36 | 80 ± 35 |
| Bodily pain | 79 ± 26 | 79 ± 24 |
| General health | 73 ± 23 | 71 ± 20 |
| Vitality | 67 ± 20 | 70 ± 19* |
| Social functioning | 86 ± 22 | 86 ± 21 |
| Role-emotional | 84 ± 32 | 90 ± 26* |
| Mental health | 77 ± 19 | 80 ± 16* |

Mean ± SD
The domains range from 0 to 100, with higher scores indicating a preferable health state.
* P < 0.05; differences in HRQOL were adjusted for age and gender.

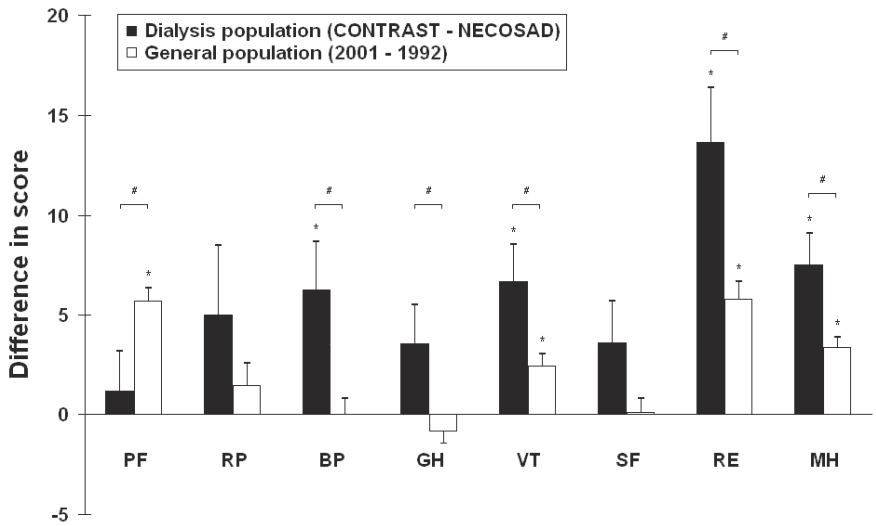


**Figure 1.** Changes in health-related quality of life in the dialysis and general population. Depicted are the differences with standard error within and between the dialysis population (CONTRAST [2006] minus NECOSAD-I [1995]) and the general population (2001 minus 1992), after adjustments for age and gender.
* P < 0.05 NECOSAD-I versus CONTRAST or 1992 versus 2001.
# P < 0.05 between changes in the dialysis versus the general population.
PF: physical functioning; RP: role-physical; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role-emotional; MH: mental health.

## DISCUSSION

This study showed a clinically relevant and statistically significant improvement in the HRQOL of the Dutch hemodialysis population between 1995 and 2006 in four domains. These four domains were: bodily pain, vitality, limitations due to emotional health problems, and the emotional well-being. To a limited extent this could be explained by improved phosphate and hemoglobin levels. When compared with the general population, these differences were still significant, but only clinical relevant for bodily pain and role-emotional.

We are to the best of our knowledge the first to analyse the changes in HRQOL in hemodialysis patients over time while taking the development of HRQOL in the general population into account. We furthermore present data of a West European cohort, as until now only one study in the United States compared HRQOL trends in dialysis patients over a prolonged period of time[10]. As we corrected for relevant demographic and clinical differences between NECOSAD-I and CONTRAST, we interpret quality of life differences between cohorts as quality of life changes over time. We believe this study design is preferable to a follow-up analysis as the latter would be affected by center changes, therapy switches and a high attrition rate.

In the US study, an improved bodily pain, role-emotional and mental health was described between 1997 and 2006[10]. These results are in accordance with our study, although the changes in that study were less profound, and not significant for vitality (+1). The improvement of hemoglobin and phosphate levels in the US study was similar to our findings, and therefore does not explain the less profound differences in HRQOL in this study as compared to our analysis. Other factors that have been related to the four HRQOL domains that showed improvement over time are education, employment, income, and comorbidity (especially psychiatric disease)[23]. Differences in these factors might have played a role, although in our analysis the first two did not change between patients in 1995 and 2006. In accordance with a recent meta-analysis[24], we found no clinically relevant effect of hemoglobin on vitality and mental health. We found a negligible effect of dialysis dose on vitality, which

is in accordance with the HEMO study[25]. Maybe counterintuitively, treatment time was not related to differences in HRQOL. Finally, the improvement of bodily pain and role-emotional HRQOL could to a small extent be explained by a decrease in phosphate levels. Although interesting, this relation was again limited. A link with bone pain has been described[26], but a small study found no relation between phosphate levels and HRQOL in general[27]. Merkus et al. already showed that clinical variables only explain HRQOL to a limited extent in dialysis patients[28].

With regard to the clinical variables, it is of note that patients in both 1995 and 2006 equally suffered from systolic hypertension. Diastolic blood pressure was lower in 2006, but overall this finding questions the improvement of anti-hypertensive therapy over time.

How clinical relevant are the changes in HRQOL? As a difference of 5 points or more has been proposed as relevant[18], the significant improvement of bodily pain, vitality, role-emotional and mental health only has clinical relevance if the concurrent development in HRQOL in the general population is not taken into account. If we do compare, a picture arises in which there is still a relevant change in two domains: bodily pain and role-emotional.

Physical functioning seems to stay behind over time and, when compared to other HRQOL domains, physical HRQOL is already predominantly affected in hemodialysis patients. The results therefore indicate that, to further improve the HRQOL of hemodialysis patients, we should focus on improving their physical status. While a kidney transplantation would be the ideal approach[1;29], the reality of clinical practice forces us to explore different options. Randomized clinical trials have identified different strategies to improve the physical status of hemodialysis patients, including exercise[30-32], hormonal therapy[31;33], and carnitine treatment[34]. Our results will strengthen the awareness that interventions to improve the physical HRQOL of dialysis patients should be implemented in daily clinical care.

This study has several limitations. First, the times of assessment of the dialysis cohorts and the general population do not precisely coincide. We however compare trends with regard to the changes in HRQOL. Second, the selection

criteria between both dialysis cohorts are not identical. A Kt/V of 1.2 or higher per treatment was an inclusion criterion in CONTRAST. Kt/V only had a minor influence on the difference in vitality, which suggests that the effect of this criterion is likely to be negligible. Furthermore, our results may be influenced by unmeasured confounding such as differences in predialysis therapy or fistula failures. Although no social-economic or clinical variable could abolish the significant differences in HRQOL between both dialysis cohorts, it is still possible that unmeasured confounding may have occurred.

This study showed an improvement of HRQOL in Dutch hemodialysis patients between 1995 and 2006. When compared with the development in the general population, the changes between the dialysis cohorts were less pronounced but still relevant for bodily pain and role-emotional. These results are encouraging, but as the HRQOL of hemodialysis patients remains far worse than in the general population, a continuous effort is needed to improve their perceived health status.

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# Differences in quality of life of hemodialysis patients between dialysis centers

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## ABSTRACT

**Background.** Hemodialysis patients undergo frequent and long visits to the clinic to receive adequate dialysis treatment, medical guidance and support. This may affect health-related quality of life (HRQOL). Although HRQOL is a very important management aspect in hemodialysis patients, there is a paucity of information on the differences in HRQOL between centers. We set out to assess the differences in HRQOL of hemodialysis patients between dialysis centers and explore which modifiable center characteristics could explain possible differences.

**Methods.** This cross-sectional study evaluated 570 hemodialysis patients from 24 Dutch dialysis centers. HRQOL was measured with the Kidney Disease Quality Of Life-Short Form (KDQOL-SF).

**Results.** After adjustment for differences in case-mix, three HRQOL domains differed between dialysis centers: the physical composite score (PCS, P=0.01), quality of social interaction (P=0.04) and dialysis staff encouragement (P=0.001). These center differences had a range of 11 to 21 points on a scale of 0 to 100, depending on the domain. Two center characteristics showed a clinical relevant relation with patients' HRQOL: dieticians' fulltime-equivalent and the type of dialysis center.

**Conclusion**. This study showed that clinical relevant differences exist between dialysis centers in multiple HRQOL domains. This is especially remarkable as hemodialysis is a highly standardized therapy.

## INTRODUCTION

Health-related quality of life (HRQOL) can be defined as the perceived health status in physical, social and mental domains[1]. Attention to and focus on HRQOL is illustrated by the growing number of studies on HRQOL[2]. Different clinical variables that contribute to HRQOL have been evaluated[3], but a paucity of information remains on the potential important role of the clinic itself.

The HRQOL of hemodialysis patients is hard-pressed. They not only face the chronic health problems of renal failure, but also the intrusiveness of a time-consuming therapy. As a result, the HRQOL of hemodialysis patients is lower than in patients with congestive heart failure, chronic lung disease or cancer[4]. For in-center hemodialysis patients, frequent and long visits to the clinic are required in order to receive adequate dialysis treatment, medical guidance and support. Does this entwinement lead to differences between dialysis centers in patients' HRQOL? And if so, can modifiable center characteristics be identified that are related with HRQOL? Relevant differences between dialysis centers have been shown for mortality[5-9] and intermediate outcomes such as dialysis adequacy[10], hematocrit[11] and vascular access[12]. It was our aim to assess differences in HRQOL between dialysis centers using the Kidney Disease Quality of Life - Short Form (KDQOL-SF), which combines the well-known, generic Short Form 36 (SF-36) with a kidney disease-specific assessment of HRQOL[13]. Our second aim was to explore center characteristics that were related to HRQOL.

## METHODS

### Patients and study design

This cross-sectional study used baseline data of the ongoing Convective Transport Study (CONTRAST)[14]. The analyses are based on 570 participating hemodialysis patients from 24 dialysis centers in The Netherlands. Centers were only included in this analysis if at least 10 patients participated in CONTRAST. CONTRAST is a randomized controlled trial (ISRCTN38365125) comparing the effects of low-flux hemodialysis with online hemodiafiltration

on all-cause mortality and cardiovascular events, as described elsewhere[14]. In short, patients were eligible if treated with hemodialysis 2 or 3 times a week, for at least 2 months, with a minimum dialysis urea Kt/V ≥ 1.2, and able to understand the study procedures. Exclusion criteria were age < 18 years, treatment by hemodiafiltration or high-flux hemodialysis in the 6 months preceding randomization, severe incompliance defined as non-adherence to the dialysis prescription, a life expectancy < 3 months due to causes other than kidney disease, and participation in another clinical trial. The study was conducted in accordance with the Declaration of Helsinki and approved by the medical ethics review boards of all participating hospitals. Written informed consent was obtained from all patients prior to enrolment.

**Data collection**

At baseline, standardized forms were used to collect demographical, clinical and laboratory data. Demographical data included age, gender, race, and educational level. Clinical characteristics included cause of kidney failure, diabetic state and previous cardiovascular disease, vascular access, hemodialysis dose (single pool Kt/V urea), time on renal replacement therapy in years, treatment time in hours, blood pressure, body mass index (BMI), dialysis frequency, residual kidney function, and smoking habit (yes/no). Laboratory values were measured using standard techniques. The second generation Daugirdas formula was used to calculate single pool Kt/V for urea[15]. Residual kidney function was expressed as estimated glomerular filtration rate (eGFR), calculated as the mean of creatinine and urea clearance and adjusted for body surface area[16]. Center characteristics included the number of dialysis patients per center, nurse and dialysis session; the proportion of available patients enrolled in CONTRAST; frequency of patient – physician (assistant) contacts; the fulltime-equivalent (FTE) of nephrologists, nurses, social workers and dieticians; availability of exercise during dialysis (yes/no); dialysis modalities offered (peritoneal, home and nocturnal dialysis); university hospital (yes/no) and regional satellite unit (yes/no).

*Kidney Disease Quality of Life – Short Form (KDQOL-SF)*

HRQOL was assessed with the validated KDQOL-SF version 1.3 (http://gim.med.ucla.edu/kdqol/downloads/-download.html)[13;17]. It covers different domains to face the multidimensional nature of HRQOL. The KDQOL-SF can be split in a generic part and a disease-specific part. First, the generic part is formed by the SF-36 version 1. The domains of the SF-36 can be summarized in two summary scores, one for physical functioning (Physical Component Summary – PCS) and one for mental functioning (Mental Component Summary – MCS). These summaries are constructed so that a score of 50 represents the mean of the general United States population with a standard deviation of 10[18]. Second, the disease-specific part of the KDQOL-SF consists of 44 kidney-disease targeted questions. The responses to these items are condensed in 12 domains (Appendix II). These domains have a score from 0 to 100, with higher scores indicating the absence of problems. A difference of 5 points has been proposed to be clinical relevant with regard to individual domains, and a difference of 3 points with regard to the composite scores[18;19].

**Data analysis**

Patient characteristics were reported as means with standard deviation (SD), medians with interquartile ranges, or proportions when appropriate. First, differences in HRQOL between dialysis centers were assessed, while adjusting for case-mix covariates and the variation in the proportion of enrolled patients. Case-mix covariates were age, gender, race, educational status, history of cardiovascular disease, diabetes, eGFR and time on renal replacement therapy in years. Second, additional adjustments were made for process variables. Process variables are characteristics that may be influenced by patient factors as well as dialysis staff modifications, e.g. Kt/V, type of vascular access, hemoglobin, albumin and phosphate levels[20]. The relation between center characteristics and HRQOL was evaluated independent of case-mix covariates. Multilevel linear models or logistic regression was applied, depending on the distribution of the residuals: parametric or non-parametric. To facilitate logistic regression, non-parametrically distributed domains were dichotomized using

the median as cut-off value. We used single regression analysis to account for missing values[21]. The median extent of missings was 5% in the HRQOL domains analyzed, 2% of case-mix covariates, 0% of center variables and 0% of process variables. Results were considered statistically significant if $P < 0.05$ (two-tailed comparison). All analyses were conducted using SPSS 18 (SPSS Inc. Headquarters, Chicago, Illinois, USA).

## RESULTS

### Patient characteristics

The characteristics of the 570 hemodialysis patients are summarized in Table 1. The mean age was 64 ± 14 (SD) years, 62% of the patients were male, and 93% dialyzed 3 times per week.

### Dialysis center characteristics

Table 2 depicts the center characteristics (N=24 centers). The median number of dialysis patients that was treated in a participating center was 109 (interquartile range 85 – 155) of which 81 (64 – 125) were on HD or HDF. Twenty-seven percent (17-35) of these patients were enrolled for the current study. Based on the median fte per patient, there were 2.6 (2.1 – 3.2) nephrologists per 100 dialysis patients. Fourteen centers (58%) offered home dialysis and 4 (17%) were part of a university hospital.

### Quality of life differences between dialysis centers

Three HRQOL domains differed between the dialysis centers when the variation in case-mix covariates and proportion of enrolled patients was taken into account (Table 3, Figure 1): the PCS (P=0.01), quality of social interaction (P=0.04) and dialysis staff encouragement (P=0.001). These results did not change if the differences in HRQOL between centers were furthermore adjusted for process variables. The differences in HRQOL had a maximum range of 11 to 21 points.

**Table 1.** Patient characteristics (N=570)

| | |
|---|---|
| **Demographic** | |
| Age (years) | 64 ± 14 |
| Gender (% male) | 62 |
| Caucasian (%) | 86 |
| High educational status[a] (%) | 24 |
| **Clinical parameters** | |
| Dialysis vintage (years) | 1.9 (1.0 – 4.2) |
| Dialysis frequency (%) | |
| 2x per week | 6 |
| 3x per week | 93 |
| 4x per week | 1 |
| Session duration (hours) | 4.0 (3.5 – 4.0) |
| spKt/V urea | 1.4 ± 0.2 |
| eGFR (mL/min/1.73m$^2$)[b] | 2.8 (1.2 – 5.2) |
| Vascular access (% fistula) | 84 |
| Body mass index (kg/m$^2$), after dialysis | 25 ± 4 |
| Systolic blood pressure (mmHg), before dialysis | 142 ± 20 |
| Diastolic blood pressure (mmHg), before dialysis | 73 ± 11 |
| Current smoker (%) | 21 |
| Diabetes mellitus(%) | 20 |
| History of cardiovascular disease (%) | 42 |
| Hemoglobin (mmol/L) | 7.3 ± 0.8 |
| Albumin (g/L) | 36 ± 5 |
| Calcium (mmol/L) | 2.3 ± 0.2 |
| Phosphate (mmol/L) | 1.6 ± 0.5 |

Mean ± SD or median (interquartile range).
[a]high educational status: college or university level.
[b]In 278 patients with diuresis ≥100 mL/24hr (52%).
eGFR: estimated glomerular filtration rate.
To convert hemoglobin in mmol/L to g/dL divide by 0.62; albumin in g/L to g/dL, divide by 10; calcium in mmol/L to mg/dL, divide by 0.25; phosphate in mmol/L to mg/dL, divide by 0.323.

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**Table 2.** Center characteristics (N=24 centers).

| | |
|---|---|
| **Number of patients treated** | |
| Total | 109 (85 – 155) |
| On HD or HDF | 81 (64 – 125) |
| Per dialysis shift | 20 (15 – 25) |
| Per nurse | |
| 2 – 2.5 | 5 (21%) |
| 3 – 3.5 | 17 (71%) |
| 4 – 4.5 | 2 (8%) |
| **Setting** | |
| General hospital | 18 (75%) |
| University hospital | 4 (17%) |
| Regional satellite unit | 2 (8%) |
| **Offered dialysis modalities** | |
| Peritoneal dialysis | 23 (96%) |
| Home dialysis | 14 (58%) |
| Nocturnal dialysis | 13 (54%) |
| **FTE dialysis staff per 100 patients** | |
| Nephrologist | 2.6 (2.1 – 3.2) |
| Nurse | 30 (26 – 34) |
| Social worker | 1.6 (1.3 – 1.8) |
| Dietician | 0.9 (0.6 – 1.2) |
| **Patient - physician (assistant) contacts per month** | |
| 2x | 3 (13%) |
| 4x | 18 (75%) |
| >4x | 3 (13%) |
| **Availability of physical exercise during dialysis** | 20 (83%) |

Center medians (interquartile ranges) or percentages.
HD: hemodialysis, HDF: hemodiafiltration, FTE: fulltime-equivalent.

**Table 3.** Differences in quality of life between dialysis centers (N=24 centers).

| | Score | P-value | | |
|---|---|---|---|---|
| | | Crude | Adjusted | |
| | | | case-mix | case-mix + process variables |
| **Generic domains (SF-36)** | | | | |
| Physical component summary (PCS) | 40 ± 4 | **0.002** | **0.01** | **0.01** |
| Mental component summary (MCS) | 51 ± 3 | **0.01** | 0.20 | 0.27 |
| **Kidney disease-specific domains** | | | | |
| Symptom / problem list | 80 ± 4 | 0.06 | 0.68 | 0.94 |
| Effects of kidney disease on daily life | 73 ± 5 | 0.35 | 0.59 | 0.48 |
| Burden of kidney disease | 47 ± 8 | **0.01** | 0.46 | 0.54 |
| Work status | 0 (0 – 0) | 0.71 | 0.67 | 0.58 |
| Cognitive function | 80 ± 6 | **0.01** | 0.11 | 0.19 |
| Quality of social interaction | 83 ± 5 | **0.04** | **0.04** | **0.02** |
| Sleep | 62 ± 7 | **0.08** | 0.20 | 0.42 |
| Social support | 78 ± 7 | 0.44 | 0.33 | 0.18 |
| Dialysis staff encouragement | 78 ± 7 | **<0.001** | **0.001** | **0.001** |
| Overall health | 60 ± 4 | **0.04** | 0.98 | 0.76 |
| Patient satisfaction | 70 ± 5 | 0.99 | 0.99 | 0.99 |

Center mean ± SD or median (interquartile range). The P-values depict the difference in quality of life between dialysis centers as assessed with mixed effect modelling, both crude and adjusted. Case-mix covariates were: age, gender, race, educational status, history of cardiovascular disease, diabetes, eGFR and time on renal replacement therapy in years. Process variables were: Kt/V, type of vascular access, hemoglobin, albumin and phosphate level. Adjusted comparisons were also corrected for the proportion of enrolled patients.
Bold P-values are significant ($P < 0.05$).
The domains have a range from 0 to 100, with higher scores indicating a preferable health status or relative absence of problems.

### Center characteristics and quality of life

Two center characteristics showed a clinical relevant relation with patients' HRQOL (table 4): dieticians' FTE and the type of center. Dieticians' FTE per patient was positively related to perceived dialysis staff encouragement. Multiple HRQOL domains were better in satellite units and worse in university hospitals.

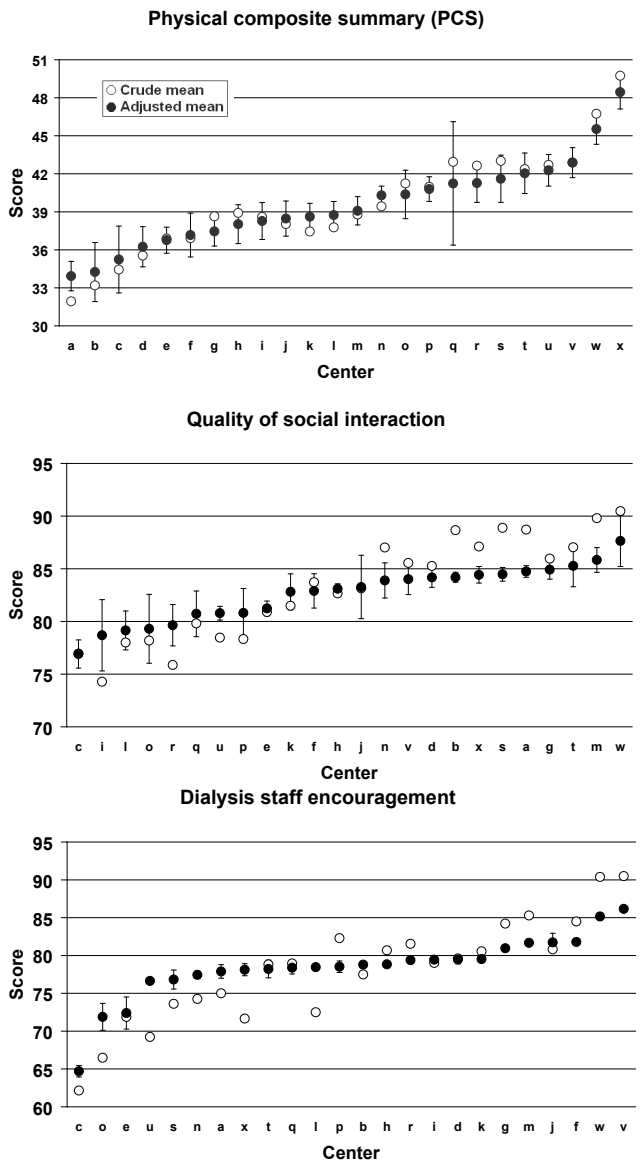


**Figure 1.** Mean quality of life scores per dialysis center.
Depicted are the mean quality of life scores per clinical center, both crude (white circles) and adjusted for case-mix covariates (black circles) with standard deviations. Case-mix covariates were: age, gender, race, educational status, history of cardiovascular disease, diabetes, eGFR and time on renal replacement therapy in years. The domains have a range from 0 to 100, with higher scores indicating a preferable health status or a relative absence of problems. A difference of 5 points has been proposed to be clinical relevant with regard to individual domains, and a difference of 3 points with regard to the composite scores[18,19]. Please note that both the scales on the y-axis and the ranking on the x-axis are different for each graph.

**Table 4.** Center variables and quality of life: the clinical relevant relations.

| | β | 95% CI | P-value |
|---|---|---|---|
| **FTE dietician per 100 patients** | | | |
| Dialysis staff encouragement | 7.1 | 0.8 to 13.5 | 0.03 |
| **University hospital** | | | |
| Mental component summary (MCS) | -3.7 | -7.1 to -0.3 | 0.03 |
| Effects of kidney disease on daily life | -7.0 | -11.4 to -2.6 | 0.002 |
| Burden of kidney disease | -11.5 | -18.9 to -4.1 | 0.004 |
| Cognitive function | -8.0 | -13.7 to -2.2 | 0.01 |
| Quality of social interaction | -5.7 | -10.6 to -0.8 | 0.02 |
| Social support | -8.0 | -14.0 to -2.0 | 0.01 |
| Overall health | -5.1 | -9.5 to -0.7 | 0.03 |
| **Satellite unit** | | | |
| Physical component summary (PCS) | 8.4 | 2.3 to 14.6 | 0.01 |
| Symptom / problem list | 8.9 | 1.9 to 15.8 | 0.01 |
| Effects of kidney disease on daily life | 9.3 | 1.0 to 17.7 | 0.03 |
| Burden of kidney disease | 15.1 | 1.6 to 28.6 | 0.03 |
| Sleep | 11.1 | 1.6 to 20.7 | 0.02 |

Depicted are the clinical relevant relations between center variables (determinant) and quality of life domains (outcome), i.e. $\beta \geq 3$ for composite summaries and $\geq 5$ for individual domains. All comparisons were analyzed with multilevel linear models and adjusted for case-mix covariates. The $\beta$ shows the amount of change in quality of life if the FTE of dieticians increases with 1 per 100 patients or if patients in a university or satellite dialysis center are compared with a non-university or non-satellite center.
CI: confidence interval, FTE: fulltime-equivalent.

## DISCUSSION

This study showed clinical relevant differences in the HRQOL of hemodialysis patients between dialysis centers in three domains: the PCS, quality of social interaction, and dialysis staff encouragement. Two center characteristics showed a clinical relevant relation with patients' HRQOL: dieticians' FTE and the type of dialysis center. Perceived dialysis staff encouragement was higher if more dieticians were available per patient. HRQOL was worse in patients that dialyzed in a university hospital and better in regional satellite units.

In the nineties, an Israeli study evaluated the differences in generic HRQOL of dialysis patients between seven centers in Tel Aviv with the Spitzer's QL-index[20]. In accordance with our results, they found that the variance in HRQOL was not entirely explained by known case-mix covariates. We now expand these

results with more recent data from a larger number of dialysis centers using the KDQOL-SF, a kidney disease-specific HRQOL questionnaire that includes the SF-36.

While there is a lack of information on the differences in HRQOL between dialysis centers, multiple studies have been conducted on center variability in mortality [5-8]. Center characteristics that were related to improved survival were: pre-dialysis care [6], center access to transplantation[5], non-profit vs. for-profit[5;7] and length of ownership[9]. It would be of interest to explore these factors in relation to HRQOL. In the Netherlands all centers are non-profit organizations and all have access to renal transplantation. Differences in pre dialysis care have been described[22], which may lead to differences in case-mix between centers. We did however adjust for case-mix, so it is unlikely that pre-dialysis care explain our findings.

The FTE of dieticians per patient was positively related to perceived dialysis staff encouragement. This might reflect patients' appreciation of dietary advice[23], the relatively large variation in dieticians' FTE per patient, or the positive relation between nutritional status and HRQOL[24]. No relevant associations were found between the FTE of other dialysis staff professionals and HRQOL. Plantinga et al[25] showed that less frequent patient-physician contact in the United States was associated with lower patient satisfaction and with a higher non-adherence to dialysis treatment, but not with generic HRQOL, hospitalization and mortality. We found no relation between the frequency of patient-physician contact and HRQOL, which included patient satisfaction. The discrepancy with regard to the latter result may be caused by a somewhat larger variation in the frequency of patient-physician contact in US dialysis centers as compared to The Netherlands (>4x patient-physician contacts per month: 11% in US centers versus 13% in Dutch; >1x/month: 71 vs. 88%; ≤1x/month: 19 vs. 0%)[25]. It should be noted that only the frequency and not the length or quality of the contact was studied. This might explain the absence of a relation with HRQOL. Furthermore, the physician is engaged in more activities than face-to-face contact to promote the care of the individual patient[25].

HRQOL was lower in patients that received dialysis in a university hospitals and higher in regional satellite units. This may indicate patient selection. For instance, patients with a higher disease burden might be urged to dialyze in a university hospital, and healthier patients may be more likely to visit a satellite facility. However, irrespective of patient characteristics, type of center may still affect HRQOL. The improved HRQOL in regional satellite units has been attributed to improved geographic access and reduced patients' travel time[26;27]. In a study that compared in-hospital dialysis with regional satellite units (N=12 centers)[26], patient satisfaction was higher in satellite units. We did not find a difference in patient satisfaction between in-hospital versus satellite dialysis, but only 2 out of 24 dialysis centers were satellite units in our analysis. A more recent analysis (N=9 centers) suggested that patients in satellite units experienced less stress[27].

Adjustment for process variables did not change the differences in HRQOL between centers. Whereas a relation between serum albumin and HRQOL has been described, variable results were found for Kt/V, hemoglobin, phosphorus, and the type of vascular access[4;20;24;27-34]. If anything, these results attenuate the role of medical interventions on HRQOL as perceived by dialysis patients.

A difference of 5 points has been proposed to be clinical relevant with regard to individual HRQOL domains, and a difference of 3 points with regard to the composite scores[18;19]. Figure 1 thus indicates that the differences in HRQOL between the centers not only have statistical, but also clinical relevance. The largest variation was found in the perceived dialysis staff encouragement. To evaluate this domain, the patient has to value two statements on a scale of 1 (definitely true) to 5 (definitely false), namely "The dialysis staff encourages me to be as independent as possible" and "The dialysis staff supports me in coping with my kidney disease". As health promotion is the desired objective of dialysis treatment[35], it is striking that in some centers patients experience far less encouragement and support than in others. Dialysis staff encouragement has been associated with better compliance, e.g. improved adherence to dialysis treatment and improved fluid control[25;36].

The variation in perceived dialysis staff encouragement was not explained by center characteristics like differences in the frequency of patient – physician (assistant) contacts, the amount of patients per nurse, or the FTE of nephrologists, nurses and social workers. Future studies should evaluate other aspects of care to enhance center performance on encouragement. The variation in dialysis staff encouragement furthermore underlines the need for a regular evaluation of patient-centred care. When it is made clear that patients' perceptions on encouragement are relatively low, the dialysis staff may be motivated to make an additional effort.

This study has several limitations. First, the cross-sectional design excludes assessment of the temporal relation, and second, potential significant relations due to multiplicity should be taken into account. As this is an exploratory analysis, we refrained from an adjustment for multiple comparisons and instead facilitated the interpretation of differences found by providing quantitative measures and focussing on clinical relevance. Finally, although we have adjusted for a large amount of case-mix covariates and center characteristics, bias due to unmeasured center- and patient-level parameters may still be present. An example of this latter limitation might be the unknown rate of patient agreement to participate.

In conclusion, this study showed that between dialysis centers, relevant differences exist in HRQOL. The differences in HRQOL include both generic and disease-specific domains like perceived dialysis staff encouragement. The latter is a modifiable factor that affects compliance, which underlines that patient encouragement should be a continuous effort of the dialysis staff. Furthermore, although the number of satellites and university hospitals was relatively low, our results show a better HRQOL in the first and a worse HRQOL in the latter. Whether these findings are due to patient selection is not readily apparent from our data and should be a topic for further research.

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# 4

# Clinical performance targets and quality of life in hemodialysis patients

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Blood Purif 2011, in press

## ABSTRACT

**Background**. Patients value health-related quality of life (HRQOL) over survival. It was our aim to study the relation between attainment of widely accepted performance targets and HRQOL in hemodialysis patients.

**Methods.** This study included baseline data from 715 hemodialysis patients from 29 dialysis centers. Six clinical performance targets, as recommended by the Kidney Disease Outcomes Quality Initiative (KDOQI), were evaluated: spKt/V (≥1.2), hemoglobin (11-13 g/dL), vascular access (fistula), phosphorus (2.3-4.5 mg/dL), parathyroid hormone (150-300 pg/mL), and blood pressure (predialysis <140/90 mmHg and postdialysis <130/80).

**Results.** After correction for case-mix and multiple comparisons, no association was found between the six KDOQI clinical performance targets and fourteen HRQOL domains, or between the number of performance targets reached and HRQOL.

**Conclusion.** Attainment with widely accepted clinical performance targets was not related to the HRQOL of hemodialysis patients. Hence, in clinical guidelines HRQOL should be adopted as an explicit treatment goal for these individuals.

## INTRODUCTION

Health-related quality of life (HRQOL) can be defined as the subjective well-being and functioning of patients in mental, physical and social domains of life[1]. Patients with kidney failure have a HRQOL that is inferior to patients with cancer or heart or lung failure[2]. Therefore, HRQOL is an important management aspect in dialysis care, especially as patients value HRQOL over survival[3]. Clinical performance targets are however not based on HRQOL. The "National Kidney Foundation Kidney Disease Outcomes Quality Initiative" (KDOQI) provides guidelines on clinical performance targets that have been adopted worldwide[4]. The associations between these targets and survival have been well studied[5-7]. However, there is a paucity of information on their relation with HRQOL, although it is one of the objectives of the KDOQI guidelines to improve the HRQOL of dialysis patients[4]. Therefore, it was our aim to study the relation between attainment of clinical performance targets and HRQOL in hemodialysis patients.

## MATERIALS AND METHODS

### Patients and study design

This cross-sectional study included baseline data from 715 hemodialysis patients, who enrolled in the Convective Transport Study (CONTRAST) from dialysis centers in The Netherlands (n=26), Canada (n=2) and Norway (n=1)[8]. CONTRAST is a randomized controlled trial (ISRCTN38365125) comparing the effects of low-flux hemodialysis with online hemodiafiltration on all-cause mortality and cardiovascular events, as described elsewhere[8]. In short, patients were eligible if treated with hemodialysis 2 or 3 times a week, for at least 2 months, with a minimum dialysis urea Kt/V ≥ 1.2, and able to understand the study procedures. Exclusion criteria were age < 18 years, treatment by hemodiafiltration or high-flux hemodialysis in the 6 months preceding randomization, severe incompliance defined as non-adherence to the dialysis prescription, a life expectancy < 3 months due to causes other than kidney

disease, and participation in another clinical trial. The study was conducted in accordance with the Declaration of Helsinki and approved by the medical ethics review boards of all participating hospitals. Written informed consent was obtained from all patients prior to enrolment.

**Data collection**

Standardized forms were used to collect demographical, clinical and laboratory data. Demographical data included age, gender, race, and educational level. Clinical characteristics included cause of kidney failure, diabetic state and previous cardiovascular disease, vascular access, hemodialysis dose (single pool Kt/V urea), time on renal replacement therapy in years, treatment time in hours, blood pressure, body mass index (BMI), dialysis frequency, residual renal function, and smoking habit (yes/no). Laboratory values were measured using standard techniques. The second generation Daugirdas formula was used to calculate single pool Kt/V for urea[9]. Residual renal function was expressed as estimated glomerular filtration rate (eGFR), calculated as the mean of creatinine and urea clearance in a twenty-four hour urine collection and adjusted for body surface area[10].

*Clinical performance targets*

Six clinical performance targets, as recommended by the Kidney Disease Outcomes Quality Initiative (KDOQI), were evaluated[11-15]: spKt/V (≥1.2), hemoglobin (11 to 13 g/dL), vascular access (arteriovenous [AV] fistula), phosphorus (2.3 to 4.5 mg/dL), parathyroid hormone (PTH; 150-300 pg/mL), and blood pressure (predialysis <140/90 mm Hg and postdialysis <130/80 mm Hg). The pre- and postdialysis blood pressure targets were combined to take into account the respective over- and underestimation of interdialytic ambulatory blood pressure[16].

*Kidney Disease Quality of Life – Short Form (KDQOL-SF)*

HRQOL was assessed with the validated KDQOL-SF version 1.3 (http://gim.med.ucla.edu/kdqol/downloads/-download.html)[17;18]. It covers different

domains to face the multidimensional nature of HRQOL. The KDQOL-SF can be split in a generic part and a disease-specific part. First, the generic part is formed by the SF-36 version 1[19]. The eight domains of the SF-36 can be summarized in two summary scores, one for physical functioning (Physical Component Summary – PCS) and one for mental functioning (Mental Component Summary – MCS). These summaries are constructed so that a score of 50 represents the mean of the general United States population with a standard deviation of 10[20]. Second, the disease-specific part of the KDQOL-SF consists of 44 kidney-disease targeted questions. The responses to these items are condensed in 12 domains: 'Symptom / problem list' which evaluates the bother by dialysis-related symptoms; 'Effect of kidney disease on daily life' which evaluates the bother by for instance restrictions and dependency on doctors, 'Burden of kidney disease' which evaluates the bother by the time consumed on dialysis and its intrusiveness; Work status; Cognitive function; Quality of social interaction; Sexual function; Sleep; Social support; Dialysis staff encouragement; Overall health and Patient satisfaction. Disease-specific domains may be more responsive and clinically sensible as compared to generic HRQOL domains[21]. All domains have a score from 0 to 100, with higher scores indicating the absence of problems. A difference of 5 points has been proposed to be clinically relevant with regard to individual domains, and a difference of 3 points regarding the composite scores[19;20].

**Data analysis**

Patient characteristics were reported as means with standard deviation (SD), medians with interquartile ranges, or proportions when appropriate. Differences in HRQOL were assessed with ANCOVA or logistic regression, dependent on the distribution of the HRQOL domains (parametric or non-parametric respectively). To facilitate logistic regression, non-parametric HRQOL domains were dichotomized using the median as cut-off value. All comparisons were adjusted for case-mix variables: age, gender, race, educational status, dialysis vintage, eGFR, diabetes and previous cardiovascular disease. Bonferroni correction was applied for multiple comparisons. As six performance targets

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were compared with fourteen HRQOL domains, results were prone to include type I errors. To reduce the likelihood of type II errors while implementing Bonferroni, the Benjamini and Hochberg False Discovery Rate (FDR) was also used to correct for multiple comparisons. In comparison with Bonferonni, the FDR tolerates more false positives[22]. By means of a sensitivity analysis, the relation between the variables that contributed to the performance targets and HRQOL was assessed by regression analyses in which the variables were not dichotomized. A second sensitivity analysis was performed in which we analyzed non-parametric outcomes with the Mann-Whitney test and Kruskal-Wallis test. This allowed for a comparison of rank instead of a dichotomous outcome, but not for adjustments for case-mix. Results were considered statistically significant if $P < 0.05$ (two-tailed comparison). We used single regression analysis to account for missing values, which means that a regression model predicts missing values based on available information [23]. All analyses were conducted using SPSS 18 (SPSS Inc. Headquarters, Chicago, Illinois, USA).

## RESULTS

### Patient characteristics

The mean age of our population (N=715) was 64 ± 14 years (± SD) and 62% was male (Table 1). The median time on renal replacement therapy was 2 years (interquartile range: 1 – 4 years).

Table 1 shows the values of the different clinical performance parameters. Eighty-six percent had a Kt/V of 1.2 or higher, 79% had an AV fistula, 57% a hemoglobin level of 11-13 g/dL, 39% had a phosphorus level 2.3-4.5 mg/dL, 31% had a PTH 150-300 pg/mL, and 25% had both a predialysis blood pressure <140/90 and a postdialysis blood pressure <130/80 mm Hg. On average patients reached 3 ± 1 of these six targets.

HRQOL scores are depicted in table 2. The average PCS was 39 ± 11 and the average MCS was 50 ± 12.

**Table 1.** Patient characteristics at baseline (N=715).

| | |
|---|---|
| **Demographic** | |
| Age (years) | 64 ± 14 |
| Gender (% male) | 62 |
| Caucasian (%) | 84 |
| High educational status[a] (%) | 21 |
| **Clinical performance targets** | |
| spKt/V urea | 1.4 ± 0.2 |
| Hemoglobin (g/dL) | 12 ± 1 |
| Vascular access (%) | |
| Arteriovenous fistula | 79 |
| Graft | 14 |
| Central venous catheter | 7 |
| Phosphorus (mg/dL) | 5.1 ± 1.5 |
| Diastolic blood pressure (mmHg), before dialysis | 73 ± 11 |
| Systolic blood pressure (mmHg), before dialysis | 141 ± 19 |
| Parathyroid hormone (pg/mL) | 195 (100 – 335) |
| **Other clinical parameters** | |
| Cause of kidney failure (%) | |
| Vascular | 28 |
| Diabetes mellitus | 19 |
| Nephritis | 22 |
| Cystic kidney disease | 7 |
| Other / unknown | 24 |
| Time on renal replacement therapy (years) | 2.0 (1.0 – 4.0) |
| Dialysis frequency (% 3x per week) | 94 |
| Session time (hours) | 4.0 (3.5 – 4.0) |
| eGFR (ml/min/1.73m$^2$)[b] | 3.2 (1.3 – 5.5) |
| BMI (kg/m$^2$) | 25 ± 5 |
| Current smoker (%) | 20 |
| Diabetes (%) | 24 |
| History of cardiovascular disease (%) | 44 |
| Albumin (g/dL) | 3.7 ± 0.5 |
| Calcium (mg/dL) | 9.3 ± 0.7 |

Mean ± SD or median (interquartile range)
[a] High educational status: college or university level.
[b] In 377 patients with diuresis ≥100 mL/24 hr (53%).
eGFR: estimated residual glomerular filtration rate.
To convert hemoglobin in mmol/L to g/dL multiply by 0.62; phosphorus in mg/dL to mmol/L multiply by 0.323; parathyroid hormone in pmol/L to pg/mL multiply by 0.1053.

**Table 2.** Health-related quality of life at baseline (N=715).

| **Generic domains (SF-36)** | |
|---|---|
| Physical Composite Score (PCS) | 39 ± 11 |
| Mental Composite Score (MCS) | 50 ± 12 |
| **Kidney disease-specific domains** | |
| Symptom / problem list | 79 ± 14 |
| Effects of kidney disease on daily life | 71 ± 19 |
| Burden of kidney disease | 45 ± 25 |
| Work status | 0 (0 – 50) |
| Cognitive function | 79 ± 19 |
| Quality of social interaction | 82 ± 17 |
| Sleep | 61 ± 20 |
| Social support | 83 (67 – 100) |
| Dialysis staff encouragement | 75 (63 – 100) |
| Overall health | 58 ± 17 |
| Patient satisfaction | 70 ± 23 |

Mean ± SD or median (interquartile range) dependent on the distribution (parametric or non-parametric respectively).

### Clinical performance targets and HRQOL

Twice did a HRQOL domain significantly differ if a recommended performance target was reached (yes versus no).These differences however lost significance after Bonferroni correction for multiple comparisons. After adjustment for case-mix, the disease-specific HRQOL domain 'Effects of kidney disease on daily life' was 4.0 ± 1.5 (± SE) points higher in patients with a phosphorus level of 2.3-4.5 mg/dL (adjusted HRQOL score 73.6 versus 69.6, original P-value = 0.008, Bonferroni corrected P-value = 0.6, FDR corrected P-value = 0.6). The PCS was 2.3 ± 0.9 points lower in patients with a blood pressure as recommended (37.1 versus 39.5, adjusted for case-mix, original P-value = 0.006, Bonferroni corrected P-value = 0.5, FDR corrected P-value = 0.5).

### Number of performance targets reached and HRQOL

Physical functioning was found to be different according to the cumulative number of performance targets reached (Figure 1). This difference did however not persist after correction for multiple comparisons (original P-value = 0.04, Bonferroni corrected P-value = 0.5, FDR corrected P-value = 0.5). There was no

association between the cumulative compliance with performance targets and other HRQOL domains.

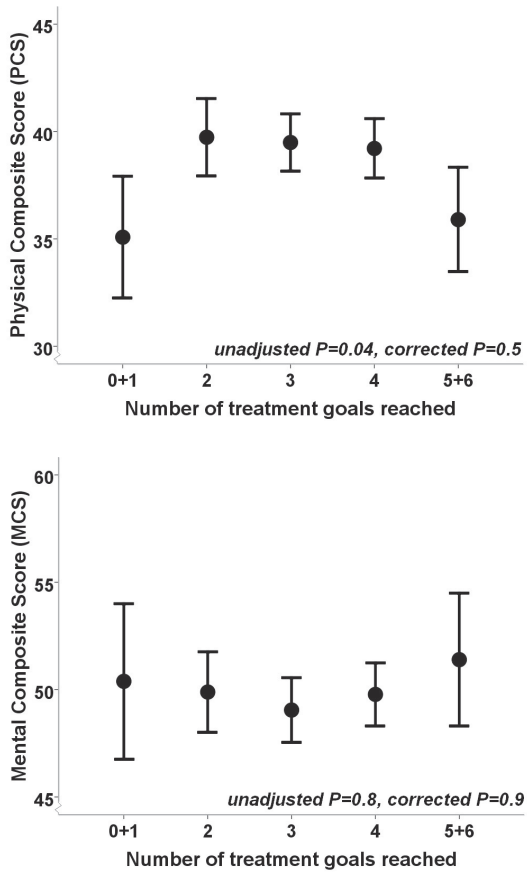


**Figure 1.** Number of clinical performance targets reached and generic health-related quality of life.
Depicted are health-related quality of life means with 95% confidence intervals. The comparisons were adjusted for differences in case-mix covariates (age, gender, race, educational status, dialysis vintage, residual renal function, diabetes and previous cardiovascular disease). The groups with 0 and 1 treatment goal reached were combined as well as the group with 5 and 6 treatment goals, as the groups with 0 and 6 goals only included 5 and 10 patients respectively (number of patients in the group with 0 and 1 treatment goal reached = 39, N 2 = 143, N 3 = 255, N 4 = 213, N 5+6 = 65). Note that the scales on the y-axis differ for both graphs. Corrected P means P-value corrected for multiple comparisons.

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**Sensitivity analysis**

The sensitivity analysis in which the variables that contributed to the performance targets were analyzed as continuous measures, resulted in one significant relation with HRQOL after correction for multiple comparisons: blood pressure (as a combined measure of pre- and postdialysis diastolic and systolic pressure) was inversely related to the HRQOL domain 'patient satisfaction' ($\beta$ -0.3, i.e. a 10 point increase in mean blood pressure was related to a 3 point lower patient satisfaction; P-value < 0.001, adjusted P-value = 0.001). This could be contributed to the relation with systolic blood pressure: the adjusted P-values before and after dialysis were respectively 0.004 and 0.01 for systolic blood pressure and 0.06 and 0.9 for diastolic blood pressure. However, there was no difference in 'patient satisfaction' if the blood pressure target was reached or not (69 versus 71, unadjusted P-value = 0.25).

The second sensitivity analysis in which we analyzed non-parametric outcomes with the Mann-Whitney test and Kruskal-Wallis test, did not result in significant differences in the three non-parametric HRQOL domains Work status, Social Support or Dialysis staff encouragement if clinical performance targets were met or not.

## DISCUSSION

This study showed that there was no relation between attainment with six widely accepted clinical performance targets and the HRQOL of hemodialysis patients, or between the number of clinical performance targets reached and HRQOL. Even without corrections for multiple comparisons, there was no clinical relevant difference in HRQOL if a target was reached (i.e. $\Delta \geq 5$ points). Leinau et al[24] (N=109) evaluated the association between hemodialysis guidelines and five non-specific end-stage renal disease conditions: impaired physical performance, depression, pain, fatigue and cognitive impairment. In agreement with our results, they only found a limited correlation between compliance with the KDOQI guidelines and these conditions (Kendall's tau b correlation between PTH <150 or >300 pg/dl with cognition, r=0.19, P=0.02;

not adjusted for case-mix covariates or multiple comparisons). On the other hand, Lacson et al[25] (N=33,879) evaluated quality-of-care indicators of Fresenius Medical Care, North America, and found clinical relevant differences in generic HRQOL domains. These indicators differ from the six performance targets as explored in our study. The only target to correspond with our analysis was Kt/V ≥1.2. Different cut-off values were analyzed for hemoglobin (11-12 g/dL), phosphorus (3.5-5.5 mg/L) and vascular access (no catheter) and, in contrast to our study, albumin (≥4.0 mg/dL) was analyzed. They found a higher generic HRQOL in patients with a Kt/V ≥ 1.2 [25], which is contrary to our results. This discrepancy might be due to a different distribution in Kt/V, but this distribution is not described by Lacson et al. Furthermore, both the distribution of Kt/V in our study, as well as its relation with HRQOL, is in accordance with results from the DOPPS[26] (N=9,256). To clarify the different results, we performed a sensitivity analysis to study if compliance with the indicators as applied by Fresenius Medical Care, North America, were indeed associated with a favourable HRQOL as compared to the evaluated KDOQI targets. Although the Fresenius' guidelines were indeed associated with a preferable HRQOL, especially in the generic domains, again no association remained significant after correction for multiple comparisons. In a study of incident hemodialysis patients, Wasse et al[27] (N=1,536) found a favourable health status in patients with an AV fistula as compared to patients with a central venous catheter. We compared patients that had an AV fistula with patients who used a different type of vascular access and found no differences in HRQOL. Besides the different reference category, this discrepancy might be explained by the different population (i.e. incident versus prevalent patients). As Wasse et al[27] themselves suggest, hemodialysis patients may grow accustomed to their type of vascular access. In other words, differences in HRQOL between vascular access types might diminish over time due to coping. Furthermore, a fistula at the start of dialysis may be linked with adequate pre-dialysis care, which in itself might positively affect the HRQOL of incident hemodialysis patients.

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Whereas patients value quality of life over survival, in patient care clinicians usually go for the latter[3]. This may influence the development of guidelines, for instance if a higher target is beneficial for quality of life, but not for survival. It has been suggested that this is the case for hemoglobin, but it was shown in a meta-analysis that targeting hemoglobin levels in excess of 12.0 g/dL does not lead to clinically meaningful improvements in HRQOL[28].

Even though clinical performance targets in nephrology are generally based on level B/C evidence, we had expected that attainment with widely accepted determinants of dialysis adequacy had shown a positive relation with an important outcome in dialysis care like patients' HRQOL. Whereas patients value quality of life over survival, in patient care clinicians usually go for the latter[3]. This may have influenced the development of guidelines, for instance if a higher target is beneficial for quality of life, but not for survival. It has been suggested that this is the case for hemoglobin, but it was shown in a meta-analysis that targeting hemoglobin levels in excess of 12.0 g/dL does not lead to clinically meaningful improvements in HRQOL[28]. Another explanation why we found no relation between performance targets and HRQOL, might be that these clinical targets only have a minor contribution to the multidimensional nature of HRQOL. Indeed, it has been described that clinical factors only explain patients' HRQOL to a limited extent[29]. It seems logic to address the multidimensional challenges of QoL in a multidisciplinary way. Whereas clinicians are guided by clinical parameters, social workers may act on social domains and psychologists or psychiatrists on mental domains. A multidisciplinary group can provide a care strategy that is both broad and patient-specific, as such a team will not only focus on a clinical approach, but may also implement psychosocial or psychoeducational strategies. Ideally, such care strategies include the patients' environment. Social support has been shown to be a relevant determinant of outcome[30,31].

One should note that our study population differs from the general dialysis population in the United States, with for instance a higher percentage of Caucasians and a lower prevalence of diabetes. Our patients also had a lower percentage of catheters, but other performance targets were comparable.

Of interest was the finding that systolic blood pressure before and after dialysis was related to 'patient satisfaction'. Based on the cross-sectional design of our study, it is however not possible to discern cause and effect. Another limitation of our study was that Kt/V was an inclusion criterion (e.g. Kt/V ≥ 1.2). However, as previously described, the variation in Kt/V in our population is comparable to a large international sample (CONTRAST: 1.38 ± 0.2; DOPPS: 1.32 ± 0.3)[26]. Finally, although all comparisons were adjusted for case-mix covariates, a possible effect of unmeasured confounding can not be ruled out. Attainment with widely accepted clinical performance targets was not related to the HRQOL of hemodialysis patients. An effort should be made to identify clinical performance targets that do have a relation with HRQOL. In this light, we previously showed the relevance of the recommended targets on protein-energy nutritional status[32]. Ideally however, HRQOL should be implemented as a clinical performance target in itself. Whereas current performance targets inform the physician on the preferences of clinical care, repeated measurement of HRQOL will provide information about the outcomes of medical care that patients seem to value most.

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# 5

# Protein-energy nutritional status and kidney disease-specific quality of life in hemodialysis patients

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## ABSTRACT

**Objective.** Health-related quality of life (HRQOL) is an important outcome in dialysis care. Protein-energy nutritional status has been related to generic HRQOL domains, but it is not yet clear how it relates to HRQOL domains that are unique to hemodialysis patients. Therefore, our aim was to study the relation between protein-energy nutritional status and kidney disease-specific HRQOL domains in hemodialysis patients.

**Design.** cross-sectional

**Setting.** multi-center

**Patients or other participants.** the first 590 hemodialysis patients enrolled in the CONTRAST study.

**Determinants.** We measured protein-energy nutritional status by the Subjective Global Assessment (SGA), albumin, normalized nitrogen appearance, creatinine, body mass index, and cholesterol.

**Main outcome measure.** HRQOL was assessed using the Kidney Disease Quality Of Life – Short Form.

**Results.** Eighty-three percent of the cohort was well-nourished according to the SGA. Multiple nutritional parameters were positively related to the physical summary of generic HRQOL, and kidney disease-specific HRQOL scales: the effects of the kidney disease on daily life, the burden of the kidney disease, and overall health.

**Conclusions.** This study shows that, even in predominantly well-nourished hemodialysis patients, protein-energy nutritional status is significantly related to kidney disease-specific HRQOL.

## INTRODUCTION

Patient care in hemodialysis is more than facing the challenges of morbidity and mortality. This awareness is expressed in the guidelines of the Kidney Disease Outcomes Quality Initiative (KDOQI)[1], and underlined by an increasing number of publications on health-related quality of life (HRQOL)[2]. HRQOL is a broad concept that includes physical, psychological, and social domains of health. It is based on one's subjective sense of well-being, since no two individuals hold the same preferences or values[2]. "Health-related" indicates a focus on those aspects of quality of life that are most affected by health or illness. Besides a key outcome in itself, HRQOL is a predictor of treatment compliance, morbidity and mortality in patients with end-stage renal disease[3-7]. It has been well established that patients on hemodialysis have an impaired HRQOL as compared to the general population[8;9]. Since cure of kidney failure is not an option, the goal for dialysis patients is the delivery of the best possible care aimed at improving HRQOL. Protein-energy nutritional status has been shown to be related to general HRQOL domains in hemodialysis patients[2;7;10]. However, the relation with HRQOL domains specifically relevant and unique to these patients is less clear. This knowledge is important since a disease-specific measure may be more responsive and clinically sensible compared to a generic assessment of HRQOL[11].

Protein-energy nutritional status is the term defined to reflect the body stores of protein and fat-masses[12]. International guidelines recommend measuring multiple markers to assess protein-energy nutritional status[13;14], since no single marker that is feasible in daily clinical practice provides a conclusive indication. An expert panel of the International Society of Renal Nutrition and Metabolism (ISRNM) has recommended to estimate protein-energy nutritional status by four categories: serum chemistry, total body mass, muscle mass and dietary intake[12].

The aim of this study was therefore to analyze the relationship between protein-energy nutritional status and HRQOL domains that are specifically important for hemodialysis patients, using the four categories as recommended by the ISRNM.

## METHODS

### Patients and study design

This cross-sectional study used baseline data of the ongoing Convective Transport Study (CONTRAST). This analysis is based on the first consecutive 590 hemodialysis patients enrolled in CONTRAST by January 2009 from dialysis centers in The Netherlands (n=26), Norway (n=1), and Canada (n=1). CONTRAST is a randomized controlled trial (ISRCTN38365125) comparing the effects of low-flux hemodialysis and online hemodiafiltration on all-cause mortality and cardiovascular events, as described elsewhere [15]. Inclusion criteria are patients treated with hemodialysis 2 or 3 times a week, for at least 2 months, with a minimum dialysis urea Kt/V ≥ 1.2, and who are able to understand the study procedures. Exclusion criteria are age < 18 years, treatment by hemodiafiltration or high-flux hemodialysis in the 6 months preceding randomization, severe incompliance defined as non-adherence to the dialysis prescription, a life expectancy < 3 months due to causes other than kidney disease, and participation in another clinical intervention trial evaluating cardiovascular outcome. The study is conducted in accordance with the Declaration of Helsinki and was approved by the medical ethics review boards of all participating hospitals. Written informed consent was obtained from all patients prior to randomization.

### Measurements

At baseline, standardized forms were used to collect demographical, clinical and laboratory data. Demographical data included age, gender, race, educational level and employment status. Clinical characteristics studied were data on medical history, including the cause of kidney failure, the diabetic state and previous cardiovascular disease, vascular access, hemodialysis dose (single pool Kt/V urea), time on kidney replacement therapy in years, treatment time in hours, statin use, blood pressure, residual kidney function (rGFR), alcohol use (yes/no), and smoking habit (yes/no). Laboratory values were measured in the different participating hospitals using standard techniques. The normalized

protein nitrogen appearance (nPNA), also known as protein catabolic rate (nPCR), estimates the urea nitrogen appearance, which correlates with protein intake. The nPNA was calculated from two blood urea nitrogen measurements and adjusted for residual kidney urea clearance as described by Depner[15]. Further information on the measured characteristics can be found elsewhere[16].

*Protein-energy nutritional status*

The ISRNM recommends to measure protein-energy nutritional status by analyzing 4 categories: serum chemistry, total body mass, muscle mass and dietary intake. We assessed serum chemistry with serum albumin and serum cholesterol, body mass with post-dialysis body mass index (BMI), muscle mass with pre-dialysis serum creatinine and dietary intake with the nPNA. In addition we used the 7-point subjective global assessment (SGA) as advised by the KDOQI guidelines[13]. The SGA is a simple technique that measures nutritional status by combining a medical history with a physical examination[17;18]. The medical history of the SGA examines weight change, dietary intake and gastrointestinal symptoms. The physical examination explores subcutaneous fat and muscle mass.

Both protein-energy nutritional status and HRQOL are described with multiple parameters, and with a large number of relationships under study interpretations may become more difficult. We therefore constructed a composite score of protein-energy nutritional status (cPENS) that might facilitate the interpretation of the results. The cPENS is a summary score of the different nutritional parameters, each of which describes a different aspect of protein-energy nutritional status. The ISRNM describes cut-off values to diagnose protein-energy wasting: serum albumin <3.8 g/dl, cholesterol <100 mg/dl and BMI <23 kg/m$^2$ [12]. International guidelines furthermore indicate cut-off values for nPNA (≤1g/kg/d), serum creatinine (<10 mg/dL), and the SGA (<6)[13;14]. Based on these target values, we created the cPENS. All values above the cut-off contributed to this scale with a score of 1, whereas a value below the cut-off did not contribute any points. BMI was divided into tertiles since it showed a non-linear reverse U-shaped relationship with HRQOL (≤23, >23

to <25, and ≥25 kg/m$^2$). The upper cut-off level is based on the overweight classification for BMI of the World Health Organization[19]. The middle tertile of BMI contributed 1 point, the lower and upper tertiles no points. The combination of these parameters resulted in a 7-point scale, in which a score of 0 means that all nutritional parameters were below their target values and a score of 6 that all recommended levels were met. We did not apply a weighted scoring because of insufficient data on the relations between the nutritional parameters and a reference standard.

*Kidney Disease Quality of Life – Short Form (KDQOL-SF)*

HRQOL was assessed with the validated KDQOL-SF version 1.3 (http://gim.med.ucla.edu/kdqol/downloads/-download.html)[20;21]. It covers different domains to face the multidimensional nature of HRQOL. The KDQOL-SF can be split up in a generic part and a disease-specific part. First, the generic part is formed by the SF-36 (Short Form with 36 questions) version 1. The domains of the SF-36 can be summarized in two summary scores, one for physical functioning (Physical Component Summary – PCS) and one for mental functioning (Mental Component Summary – MCS). These summaries are constructed so that a score of 50 represents the mean of the general United States population with a standard deviation of 10[21]. Second, the disease-specific part of the KDQOL-SF consists of 44 kidney-disease targeted questions. The responses to these items are condensed in 12 domains (Appendix II). These domains have a score from 0 to 100, with higher scores indicating the absence of problems.

**Data analysis**

Patient characteristics were reported as means with standard deviations for continuous variables or proportions for dichotomous and categorical variables. Missing values were imputed with single regression analysis[22]. By means of sensitivity analysis the original dataset with missing values was also analyzed. Non-linear relationships between protein-energy nutritional parameters and HRQOL domains were examined with scatterplots. Confounders were identified with hierarchical modelling. In this procedure every potential confounder was

ranked according to its effect on the crude odds ratio. Based on rank, the confounders were cumulatively added to the univariable model, and when the odds ratio stabilized, the included confounders were chosen. In our hierarchical model the cPENS was chosen as the determinant and the dichotomized overall health domain as the outcome, as they both form a general contemplation. All patient characteristics were treated as potential confounders, except for serum urea since it is mathematically related with nPNA. Normal distributed HRQOL domains were analyzed using univariable and multivariable linear regression. Non-parametric domains were analyzed with Spearman's correlation and multivariable logistic regression. To facilitate logistic regression the non-parametrically distributed domains were dichotomized using the median as cut-off value. Appendix II describes the dichotomized kidney disease-specific HRQOL domains to facilitate interpretation. The results were considered statistically significant when $P < 0.05$ (two-tailed comparison). All analyses were conducted using SPSS (version 15.0.1; SPSS Inc. Headquarters, Chicago, Illinois, USA).

## RESULTS

### Patient characteristics

The characteristics of the 590 patients on low-flux hemodialysis are summarized in Table 1. The mean age was 64 ± 14 years and 62% of patients were male. Eighty-three percent had a SGA ≥ 6 (i.e. well-nourished), 79% had a BMI ≥ 23 to 25 kg/m$^2$, 62% had a nPNA > 1.0 g/kg/d, 43% had a serum albumin of ≥ 3.8 g/dL or higher, 90% had a serum cholesterol of ≥ 100 mg/dL, and 38% had a serum creatinine of ≥ 10 mg/dL. This resulted in a mean cPENS of 3.0 ± 1.3. BMI showed reverse 'U-shaped' relationships with multiple HRQOL domains as mentioned earlier. All other parameters of protein-energy nutritional status had linear relationships with HRQOL.

**Table 1.** Patient characteristics

| | | N |
|---|---|---|
| **Demographic** | | |
| Age (years) | 64 ± 14 | 589 |
| Male (%) | 62 | 589 |
| Caucasian (%) | 85 | 588 |
| **Socio-economic status** | | |
| Employed (%) | 11 | 539 |
| High educational status* (%) | 12 | 527 |
| **Parameters of protein-energy nutritional status** | | |
| SGA classification (%) | | 583 |
| Well-nourished | 83 | |
| Mild to moderate malnutrition | 17 | |
| Severe malnutrition | 0 | |
| Albumin (g/dL) | 3.7 ± 0.5 | 580 |
| nPNA (g/kg/d) | 1.1 ± 0.3 | 582 |
| Body mass index (kg/m$^2$), post-dialysis | 25 ± 5 | 586 |
| Creatinine (mg/dL), pre-dialysis | 9.2 ± 2.7 | 482 |
| Cholesterol (mg/dL) | 142 ± 38 | 564 |
| cPENS | 3.3 ± 1.2 | |
| **Other clinical parameters** | | |
| Dialysis vintage (years) | 2.0 (1.0 – 4.0) | 590 |
| Dialysis frequency (% 3x per week) | 93 | 589 |
| Session time (hours) | 3.8 ± 0.4 | 569 |
| spKt/V urea | 1.4 ± 0.2 | 584 |
| rGFR (mL/min/1.73m$^2$) | 0.3 (0.0 - 3.2) | 567 |
| Vascular access (% fistula) | 79 | 587 |
| Systolic blood pressure (mmHg), pre-dialysis | 142 ± 19 | 589 |
| Diastolic blood pressure (mmHg), pre-dialysis | 74 ± 11 | 589 |
| Diabetes (%) | 23 | 565 |
| History of cardiovascular disease (%) | 44 | 589 |
| Statin use (%) | 50 | 589 |
| Alcohol use (%) | 35 | 563 |
| Current smoker (%) | 20 | 566 |
| Hemoglobin (g/dL) | 11.9 ± 1.2 | 589 |
| Bicarbonate (mEq/L) | 22 ± 3 | 572 |
| Phosphate (mg/dL) | 5.1 ± 1.5 | 588 |
| PTH (pg/ml) | 193 (95 – 332) | 565 |
| ß2 microglobulin (g/L) | 32 ± 13 | 535 |

Mean ± SD or median (interquartile range)
* high educational status: education beyond the secondary level.
SGA: subjective global assessment; nPNA: normalized protein nitrogen appearance; cPENS: composite score of protein-energy nutritional status; rGFR: residual glomerular filtration rate; PTH: parathyroid hormone.
To convert albumin in g/dL to g/L, multiply with 10; creatinine in mg/dL to µmol/L multiply with 88.4; cholesterol in mg/dL to mmol/L multiply with 0.0259.

Table 2 shows the kidney disease-specific HRQOL scores. The most severely impaired kidney disease-specific HRQOL domains were: burden of kidney disease, work status, sexual function, sleep, and overall health. The sexual function domain contained 90% missings. The average amount of missing values in the other HRQOL domains was 7%.

**Table 2.** Kidney disease-specific quality of life at baseline.

| KDQOL-SF | Mean ± SD | Median (IR) | N |
|---|---|---|---|
| **Kidney disease-specific domains** | | | |
| Symptom / problem list | 79 ± 14 | 81 (71 – 90) | 563 |
| Effects of kidney disease on daily life | 72 ± 19 | 75 (63 – 88) | 563 |
| Burden of kidney disease | 46 ± 26 | 44 (25 – 63) | 559 |
| Work status | 18 ± 28 | 0 (0 – 50) | 556 |
| Cognitive function | 79 ± 19 | 80 (67 – 93) | 555 |
| Quality of social interaction | 82 ± 17 | 87 (73 – 100) | 555 |
| Sexual function | 52 ± 36 | 50 (25 – 91) | 58 |
| Sleep | 61 ± 20 | 63 (48 – 78) | 561 |
| Social support | 78 ± 26 | 83 (67 – 100) | 553 |
| Dialysis staff encouragement | 79 ± 21 | 75 (63 – 70) | 555 |
| Overall health | 58 ± 18 | 60 (50 – 70) | 547 |
| Patient satisfaction | 69 ± 24 | 67 (50 – 83) | 554 |

SD: standard deviation. IR: interquartile range.
These domains have a score from 0 to 100, with higher scores indicating the absence of problems.

### Identified confounders

Without adjustment for confounding the odds ratio of the cPENS versus dichotomized Overall Health was 1.381 (95% CI 1.203 to 1.584). This ratio reached 1.392; 95% CI 1.164 to 1.666) when the relation was adjusted for all measured potential confounders. The relative effect of added confounders diminished after adjusting for 9 variables: age, employment status, clinical center, a history of diabetes and cerebrovascular disease, alcohol use, and phosphate, β2-microglobulin and parathyroid hormone levels (odds ratio: 1.397 (95% CI 1.180 to 1.653). All models were adjusted for these confounders, except the kidney disease-specific HRQOL domain work status. Employment status was not considered to be an eligible confounder for this domain because of overlap, and therefore left out of its analysis.

**Table 3.** Regression models of the physical and mental quality of life summaries by protein-energy nutritional parameters.

| | Physical summary (PCS) | | | | Mental summary (MCS) | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariable model | | Multivariable model | | Univariable model | | Multivariable model | |
| | B | 95% CI | B | 95% CI | B | 95% CI | B | 95% CI |
| SGA | 2.26* | 1.36 to 3.16 | 1.61* | 0.64 to 2.59 | 1.88* | 0.92 to 2.84 | 1.81* | 0.77 to 2.86 |
| Albumin (per g/dL) | 4.57* | 2.67 to 6.48 | 4.42* | 1.84 to 6.99 | 0.17 | -1.88 to 2.21 | 1.22 | -1.58 to 4.02 |
| nPNA (per g/kg/d) | 3.62* | 0.22 to 7.03 | 3.27 | -0.25 to 6.80 | 0.11 | -3.50 to 3.71 | -0.01 | -3.82 to 3.81 |
| BMI (vs. < 23 per kg/m$^2$) | | | | | | | | |
| ≥ 23 to 25 kg/m$^2$ | 1.22 | -1.20 to 3.64 | 0.87 | -1.57 to 3.32 | 2.92* | 0.36 to 5.47 | 1.86 | -0.77 to 4.49 |
| ≥ 25 kg/m$^2$ | -0.92 | -2.92 to 1.07 | -0.74 | -2.96 to 1.07 | 0.51 | -1.59 to 2.61 | -0.01 | -2.18 to 2.16 |
| Cholesterol (per mg/dL) | 0.02 | -0.00 to 0.04 | 0.00 | -0.02 to 0.03 | -0.00 | -0.03 to 0.02 | -0.01 | -0.03 to 0.02 |
| Creatinine (per mg/dL) | 0.67* | 0.35 to 0.99 | 0.57* | 0.18 to 0.96 | -0.02 | -0.37 to 0.32 | 0.12 | -0.30 to 0.55 |
| cPENS | 2.00* | 1.30 to 2.71 | 1.47* | 0.67 to 2.27 | 0.56 | -0.21 to 1.33 | 0.62 | -0.25 to 1.49 |

* P < 0.05, two-tailed comparison.

The B is the unstandardized regression coefficient that reflects the change in the HRQOL score related with one unit increase of the protein-energy nutritional parameter. In the multivariable models the relations were adjusted for confounders identified by hierarchical modeling.

SGA: Subjective global assessment; nPNA: normalized protein nitrogen appearance; cPENS: composite score of protein-energy nutritional status.

**Protein-energy nutritional status and general quality of life**

The generic HRQOL summaries, PCS and MCS, were normally distributed. They were therefore analyzed using univariable and multivariable linear regression. Three of the six nutritional parameters were related to the PCS in multivariable analyses (Table 3). Only the SGA was related to the MCS. The cPENS was associated with the PCS, but not the MCS. The size of this relationship indicated that between achieving no nutritional target values and achieving all 6 recommended levels, the PCS differed 9 points.

**Protein-energy nutritional status and kidney disease-specific quality of life**

The kidney disease-specific HRQOL domains were non-parametrically distributed and therefore analyzed using Spearman's correlation and multivariable logistic regression. Table 4 shows the Spearman's correlation coefficients between the different nutritional markers and the kidney disease-specific HRQOL domains. In the multivariable analyses (Table 5), multiple nutritional markers were positively associated with three kidney-disease specific HRQOL domains: the effects of the kidney-disease on daily life, the burden of the kidney disease, and overall health. The cPENS parameter underlined these results. Scatterplots of these associations are depicted in Figure 1. A sensitivity analyses without imputation of missing values showed comparable results.

**Table 4.** Spearman's correlation coefficients between the protein-energy nutritional parameters and kidney disease-specific quality of life domains.

| | Symptoms/ Problems | Effect on daily life | Burden of disease | Work status | Cognitive Function | Social Interaction | Sexual Function | Sleep | Social Support | Dialysis Staff | Overall Health | Patient Satisfaction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SGA** | **0.19** | **0.19** | **0.15** | **0.11** | 0.07 | **0.10** | 0.10 | **0.11** | 0.08 | **0.10** | **0.21** | 0.06 |
| **Albumin** | **0.10** | **0.10** | 0.04 | 0.07 | **0.09** | 0.06 | -0.09 | **0.11** | -0.05 | 0.03 | **0.15** | 0.00 |
| **nPNA** | -0.01 | 0.02 | **0.10** | 0.06 | 0.03 | -0.03 | -0.07 | 0.02 | -0.05 | -0.01 | **0.12** | 0.07 |
| **BMI** (vs. < 23) | | | | | | | | | | | | |
| ≥ 23 to 25 kg/m$^2$ | 0.06 | 0.06 | **0.14** | 0.05 | 0.04 | 0.01 | 0.07 | 0.05 | 0.05 | 0.04 | **0.09** | 0.06 |
| ≥ 25 kg/m$^2$ | -0.08 | -0.05 | -0.06 | 0.01 | -0.03 | 0.04 | -0.12 | -0.01 | 0.04 | 0.03 | -0.01 | -0.01 |
| **Cholesterol** | 0.05 | 0.06 | **0.12** | 0.01 | 0.08 | **0.09** | 0.07 | 0.03 | -0.02 | 0.00 | 0.05 | **0.09** |
| **Creatinine** | 0.05 | -0.03 | 0.02 | 0.02 | **-0.08** | **-0.14** | 0.07 | -0.01 | -0.02 | -0.03 | 0.04 | **-0.09** |
| **cPENS** | **0.13** | **0.10** | **0.14** | 0.07 | 0.05 | 0.01 | 0.04 | **0.10** | -0.01 | 0.02 | **0.18** | 0.03 |

Bold correlations are significant ($P < 0.05$, two-tailed comparison).
Effect on daily life: Effect of kidney disease on daily life; Burden of disease: Burden of kidney disease; Social interaction: Quality of social interaction; Dialysis staff: Dialysis staff encouragement; SGA: Subjective global assessment; nPNA: normalized protein nitrogen appearance; cPENS: composite score of protein-energy nutritional status.

**Table 5.** Adjusted relationships between protein-energy nutritional parameters and the 12 domains of kidney disease-specific HRQOL.

| | Symptoms/ Problems | Effect on daily life | Burden of disease | Work status | Cognitive Function | Social Interaction | Sexual Function | Sleep | Social Support | Dialysis Staff | Overall Health | Patient Satisfaction |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SGA** | **1.46** | **1.26** | **1.41** | 1.16 | 1.06 | 1.16 | 1.62 | 1.21 | 1.09 | 1.21 | **1.44** | 1.08 |
| **Albumin** (per g/dL) | 0.93 | **1.96** | **1.75** | 1.26 | 1.21 | **2.13** | 0.84 | **1.81** | **0.50** | 1.13 | **2.50** | 1.04 |
| **nPNA** (per g/kg/d) | 0.79 | 1.72 | 1.74 | 1.69 | 1.19 | 0.83 | 29.7 | 1.10 | 0.87 | 0.73 | **2.61** | **2.32** |
| **BMI** (vs. < 23) | | | | | | | | | | | | |
| ≥ 23 to 25 kg/m$^2$ | 0.99 | 1.01 | 1.58 | **1.69** | 0.86 | 0.93 | 1.57 | 1.21 | 1.30 | 1.46 | 1.58 | 1.06 |
| ≥ 25 kg/m$^2$ | 0.75 | 0.74 | 0.95 | 1.23 | 0.74 | 1.04 | 7.19 | 1.33 | 1.32 | 1.01 | 1.04 | 1.02 |
| **Cholesterol** (per mg/dL) | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.02 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **Creatinine** (per mg/dL) | 1.06 | 1.03 | 1.04 | 0.99 | 0.97 | 0.94 | 0.93 | 1.04 | 1.04 | 1.07 | **1.10** | 1.00 |
| **cPENS** | 1.10 | **1.20** | **1.35** | 1.07 | 1.04 | 1.03 | 1.93 | 1.14 | 0.98 | 1.09 | **1.42** | 1.07 |

Presented are odds ratios adjusted for confounders identified by hierarchical modeling. Bold ratios are significant ($P < 0.05$, two-tailed comparison). The odds ratios describe the ratio between the odds of having a higher protein-energy nutritional status among those of being above the median versus the odds of having a higher nutritional status among those below the median. In general, these odds ratios will be interpreted as relative risk estimates, while keeping in mind that the higher the quality of life score, the better.
Effect on daily life: Effect of kidney disease on daily life; Social interaction: Quality of social interaction; Dialysis staff: Dialysis staff encouragement; SGA: Subjective global assessment; nPNA: normalized protein nitrogen appearance; cPENS: composite score of protein-energy nutritional status.



R3 R3 R3 R3 R3 R2 R2 R2 R2 R2 R2 R2 R2 R2 R2 R2 R1 R1 R1 R1 R1 R1 R1 R1 R1 R9 R8 R7 R6 R5 R4 R3 R2 R1

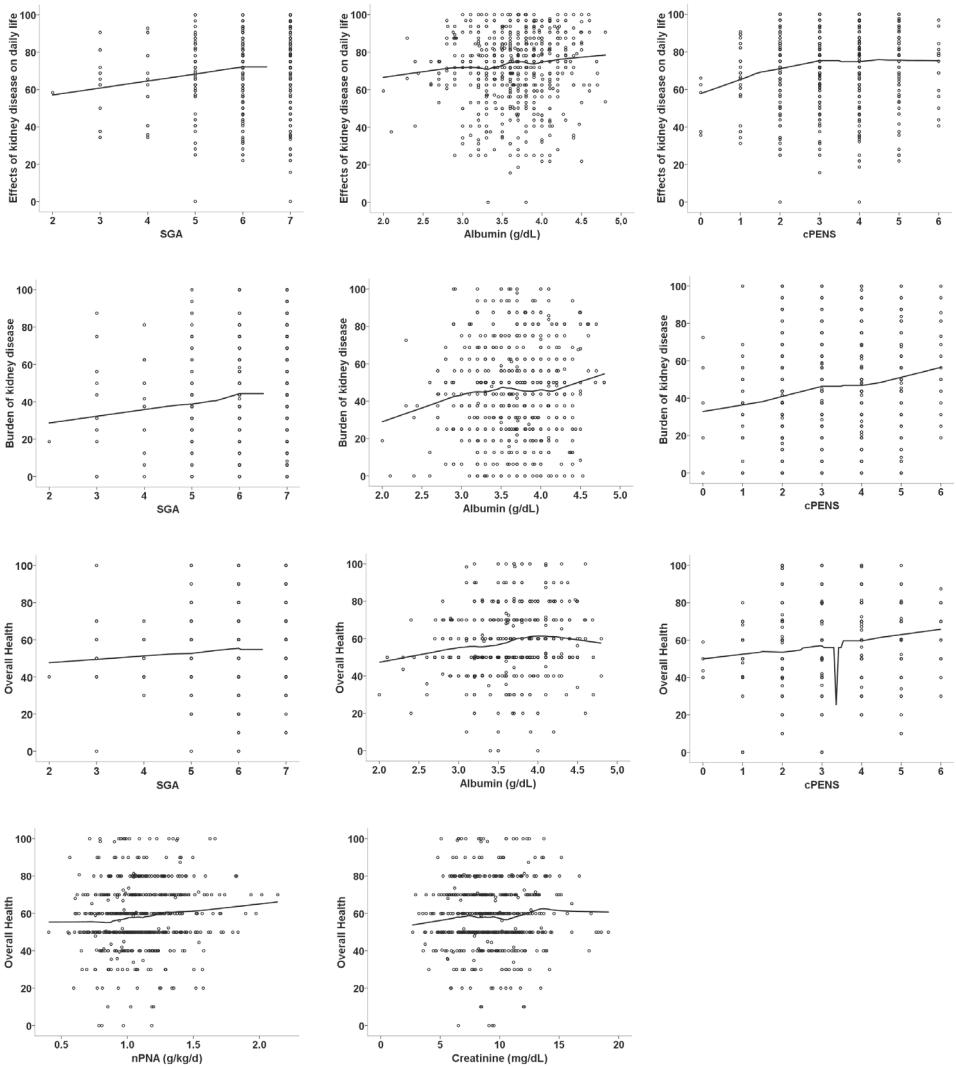


**Figure 1.** Scatterplots of protein-energy nutritional status versus quality of life.
Depicted are scatterplots of the relations between nutritional parameters and kidney disease-specific HRQOL that were significant after adjustment for confounders, for those domains that had multiple associations with protein-energy nutritional status.
The line represents a locally weighted scatterplot smoothing (loess) curve.
SGA: subjective global assessment; cPENS: composite score of protein-energy nutritional status; nPNA: normalized protein nitrogen appearance.
The quality of life domains have a score from 0 to 100, with higher scores indicating the absence of problems.
A more detailed figure can be found at http://contrast-ned.nl/onderzoekers/Contrast-ned:Protein-energy_status_and_HRQOL_in_HD_patients.pdf

## DISCUSSION

This study showed that, even in relatively well-nourished hemodialysis patients, protein-energy nutritional status is significantly related with kidney disease-specific HRQOL.

Multiple nutritional markers were positively related to the effects of the kidney disease on daily life, the burden of kidney disease, and the more general HRQOL domain overall health. These include 2 of the 5 kidney disease-specific domains that were more severely impaired. The generic summary scores indicated that physical functioning was severely impaired, while mental functioning was comparable to the general population. Multiple nutritional markers were associated with the PCS, but only the SGA was related to the MCS. The cPENS showed comparable results. The data suggest that the most severely impaired kidney disease-specific HRQOL domains in hemodialysis patients might be ameliorated by treating protein-energy wasting, even in mild to moderately malnourished patients.

This study is to the best of our knowledge the first to describe the relationship of protein-energy nutritional status with kidney disease-specific HRQOL domains in hemodialysis patients, using multiple nutritional markers. The Dialysis Outcomes and Practice Patterns Study (DOPPS) showed that dichotomized serum albumin and BMI were not significantly related with kidney disease-specific HRQOL[23]. However, to provide a conclusive indication of protein-energy nutritional status, multiple categories should be evaluated[12], as was done in the current study.

The nutritional status of the dialysis patients in CONTRAST turned out to be fairly adequate, which is comparable to the Hemodialysis Study (HEMO) and DOPPS[6;10] (Table 6). It may be reasoned that in dialysis patients with a worse protein-energy nutritional status, the associations found with HRQOL would be even more pronounced. However, it has been observed that demographic and clinical variables can only explain HRQOL to a limited extent[24].

When we compare our results on generic HRQOL with other studies, they support our findings that although the PCS was severely impaired, the MCS was comparable to the general population (Table 6). Protein-energy nutritional

status has been related with generic HRQOL[7;10]. The relation we found between nutritional status and the PCS seems more positive, but the relation with the MCS was rather similar[7;10].

**Table 6.** Generic quality of life at baseline compared with other large cohorts.

| | CONTRAST (N=590) | HEMO (N=1,545) | DOPPS (N=17,236) |
|---|---|---|---|
| **SF-36 summary scores** | | | |
| Physical Summary (PCS) | 37 ± 11 | 36 ± 10 | 35 ± 11 |
| Mental Summary (MCS) | 50 ± 12 | 50 ± 11 | 45 ± 12 |
| **Parameters of protein-energy nutritional status** | | | |
| SGA classification (%well-nourished) | 83 | | |
| Albumin (g/dL) | 3.7 ± 0.5 | 3.6 ± 0.4 | 3.6 ± 0.6 |
| nPNA (g/kg/d) | 1.1 ± 0.3 | 1.0 ± 0.2 | 1.0 ± 0.3 |
| Body mass index (kg/m2) | 25 ± 5 | | 24 ± 5 |
| Creatinine (mg/dL) | 9.2 ± 2.7 | 10.4 ± 3.0 | 9.1 ± 3.4 |
| Cholesterol (mg/dL) | 142 ± 38 | | |

Mean ± SD
A summary score of 50 ± 10 represents the mean of the general United States population.
HEMO: Hemodialysis Study. DOPPS: Dialysis Outcomes and Practice Patterns Study.
Data from Allen et al[10] and Mapes et al[6].

While the KDQOL-SF gives an overview of the different kidney-disease specific HRQOL domains, some studies focused on a single domain. For instance, Merkus et al.[24] studied the relation between different variables and symptom burden, using a self-developed questionnaire. They found no relation of serum albumin or nPNA with kidney disease-specific symptoms, which is in comparison with our results. Our findings are furthermore substantiated by studies that focused on work status[25], which did not show a relation with some nutritional parameters. Our data indicate a possible relation between protein-energy nutritional status and sleep in hemodialysis patients. These results are however in contrast with another large study that found no relation[26]. This discrepancy might be due to the inclusion of incident instead of prevalent patients or the use of a different questionnaire.
A limitation of this study is the cross-sectional nature of the analysis which does not exclude a bilateral cause-effect relation between protein-energy wasting

and deteriorated HRQOL. Longitudinal analyses have however indicated a positive effect of nutritional status on generic HRQOL[27]. A second limitation is the possibility of bias due to unmeasured confounding. This effect is likely to be minimal based on the hierarchical modelling procedure. Inflammatory status was not assessed, but a systematic review indicated that inflammatory markers are poor HRQOL correlates[28].

There is a lack of randomized controlled trials on how to improve protein-energy nutritional status in hemodialysis patients, and even more so regarding the effects of protein-energy nutritional status on outcome[13]. Positive effects have been shown using nutritional supplementation[27], growth hormone[29], L-Carnitine[30], exercise training and nandrolone decanoate[31;32].

Although the cPENS did not yield relations with HRQOL of a magnitude greater than found for, for example, the SGA, the construct might be easier interpreted than the use of multiple different parameters in studies looking into protein-energy nutritional status. This finding supports the notion that the composite might be studied further in terms of validity, prediction of events and ability for change over time in response to interventions.

In conclusion, our study showed that even in predominantly well-nourished hemodialysis patients, protein-energy nutritional status was significantly related with multiple kidney disease-specific HRQOL domains. These results suggest that a moderate improvement of protein-energy nutritional status might have an impact on the more severely impaired kidney disease-specific HRQOL domains. This underscores the need for large-scale randomized clinical trials[33], which investigate whether improvement of nutritional status improves HRQOL.

R1 R2 R3 R4 R5 R6 R7 R8 R9 R1 R1 R1 R1 R1 R1 R1 R1 R1 R1 R2 R2 R2 R2 R2 R2 R2 R2 R2 R2 R3 R3 R3 R3 R3

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# 6

# A composite score on protein-energy nutritional status predicts mortality in hemodialysis patients no better than its individual components

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## ABSTRACT

**Background.** Protein-energy wasting is tightly associated with mortality in hemodialysis patients. An expert panel of the International Society of Renal Nutrition and Metabolism (ISRNM) has published a consensus on the parameters that define protein-energy nutritional status, and posed the question which scoring system most effectively predicts outcome. The aim of our study was therefore to develop a composite score of protein-energy nutritional status (cPENS) and to assess its prediction of all-cause mortality.

**Methods.** We used data of 560 hemodialysis patients participating in the CONvective TRAnsport STudy (CONTRAST). All participants were followed for occurrence of death. International recommended nutritional targets were used as components of the cPENS, including the Subjective Global Assessment (target score ≥6), albumin (≥4.0 g/dL), normalized protein nitrogen appearance (≥0.8g/kg/d), cholesterol (≥100 mg/dL), creatinine (≥10 mg/dL), and BMI (>23 kg/m$^2$). A Cox regression model was used to analyze the relation between different cPENS variants and mortality.

**Results.** The median follow-up time was 1.4 years (max 4.2). One hundred and five patients (19%) died. A cPENS variant based on albumin, BMI, creatinine and the nPNA yielded the strongest relation with mortality (hazard ratio 0.63, 95% CI 0.54 to 0.74, P<0.001), after adjustments for confounders. Some of the individual parameters of the cPENS, notably albumin and creatinine, were related to mortality with similar strength and magnitude.

**Conclusions.** In conclusion, albumin reflects mortality risk similar to multiple nutritional parameters combined. This questions the clinical value of the proposed diagnostic criteria for protein-energy wasting.

## INTRODUCTION

Mortality remains exceptionally high in hemodialysis patients and is closely related to malnutrition[1-3]. Protein-energy wasting is a more distinct description of malnutrition and has been defined by an expert panel of the International Society of Renal Nutrition and Metabolism (ISRNM) as a state of decreased body stores of protein and fat masses[4]. Although it is estimated that 10 to 70% of hemodialysis patients suffer from protein-energy wasting[5-7], it is hard to assess its presence and degree. As no single clinically applicable parameter provides a conclusive indication of protein-energy nutritional status, international guidelines recommend the use of multiple nutritional markers[8;9]. This introduces the need for a composite score that facilitates assessment. The ISRNM recently published a consensus statement defining which elements describe protein-energy nutritional status[4]. It describes four categories: serum chemistry, body mass, muscle mass and dietary intake, and poses the question what scoring system predicts outcome most effectively[4]. Current composite scores do not integrate all mentioned categories[10] or include inflammatory markers to describe the malnutrition-inflammation syndrome[11-13]. The ISRNM however states that inflammatory markers should not be used to determine protein-energy nutritional status, as these parameters do not define protein-energy nutritional status[4]. A recent publication described joint associations of nutritional parameters with mortality risk[3] and it has been shown that a combination of nutritional parameters provides an improved specificity for adverse prognosis[14]. As a composite score of protein-energy nutritional status may be a meaningful guidance to improve outcome, the aim of our study was to develop such a score and assess its prediction of all-cause mortality in a cohort of chronic hemodialysis patients.

R1 R2 R3 R4 R5 R6 R7 R8 R9 R1 R1 R1 R1 R1 R1 R1 R1 R1 R1 R2 R2 R2 R2 R2 R2 R2 R2 R2 R2 R2 R3 R3 R3 R3 R3

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## METHODS

### Patients and study design

This prospective study is based on the first 560 hemodialysis patients in the CONvective TRansport STudy (CONTRAST), who had completed at least 3 months of follow-up by January 2009 or had died during follow-up. They were enrolled from dialysis centers in The Netherlands (n=26), Norway (n=1), and Canada (n=1). CONTRAST is an ongoing randomized controlled trial (ISRCTN38365125 [controlled-trials.com]) comparing low-flux hemodialysis and online hemodiafiltration with regard to all-cause mortality and cardiovascular events, as described elsewhere[15]. Inclusion criteria were treatment with hemodialysis 2 or 3 times per week, for at least 2 months, a minimum dialysis urea Kt/V ≥ 1.2, and the ability to understand the study procedures. Exclusion criteria were age < 18 years, treatment by hemodiafiltration or high flux hemodialysis in the 6 months preceding randomization, severe incompliance defined as non-adherence to the dialysis prescription, a life expectancy < 3 months due to morbidity other than kidney disease, and participation in another clinical intervention trial evaluating cardiovascular outcome. The study was conducted in accordance with the Declaration of Helsinki and was approved by the medical ethics review boards of all participating hospitals. Written informed consent was obtained from all patients prior to randomization.

CONTRAST is still ongoing. The investigators who performed the statistical analyses were blinded to the allocation of treatment (hemodialysis or online hemodiafiltration) as they had access to a dataset without that information. As time-dependent measurements could have been affected by allocated treatment, only baseline levels of protein-energy nutritional status were analyzed. To act as a confounder, treatment should be related to both exposure and outcome[16]. Since CONTRAST is a randomized clinical trial, protein-energy nutritional status is randomly distributed between both treatment groups. Thus, at baseline, nutritional status is not related to treatment and confounding by treatment is excluded. In addition, due to the ongoing adjudication process of fatal and non-fatal events in CONTRAST, the present analysis was restricted to all-cause mortality without providing cause-specific information.

**Data collection**

At baseline, standardized forms were used to collect demographical, clinical and laboratory data. Clinical characteristics studied were data on medical history, including the cause of kidney failure, the diabetic state and previous cardiovascular disease, vascular access, hemodialysis adequacy (Kt/V urea), time on kidney replacement therapy in years (dialysis vintage), treatment time in hours, blood pressure, residual kidney function (rGFR), statin use (yes/no), alcohol use (yes/no), and smoking habit (yes/no). The systolic and diastolic blood pressures reported are values prior to dialysis (mmHg). Blood samples were drawn prior to dialysis for routine laboratory assessments. Samples for the determination of urea and creatinine were also drawn after the dialysis session. The samples were analyzed in the local hospitals using standard techniques. Interdialytic urinary samples were collected in patients with a urinary production of 100 mL per day or more. In these patients, residual renal function was expressed as glomerular filtration rate (GFR), calculated as the mean of creatinine and urea clearance and adjusted for body surface area (mL/min/1.73m$^2$)[9]. The second generation Daugirdas formula was used to calculate single pool Kt/V for urea[17]. The normalized protein nitrogen appearance (nPNA), also known as protein catabolic rate (nPCR), estimates the urea nitrogen appearance, which correlates with protein intake. The nPNA was calculated from two blood urea nitrogen measurements and adjusted for residual kidney urea clearance as described by Depner[18]. More detailed information on the study measurements can be found elsewhere[15]. Fatal events were reported immediately by the participating centers. Survival time was defined as the number of days between randomization and the date of death or the end of follow-up for this sub-study. There was no loss to follow-up as dropouts (e.g. because of transfer to a nonparticipating dialysis center or switch to a renal replacement therapy other than hemodialysis or online hemodiafiltration) were still followed for mortality.

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*Composite score of protein-energy nutritional status (cPENS)*

Based on the recommendations of the International Society of Renal Nutrition and Metabolism (ISRNM)[4] we assessed protein-energy nutritional status with serum albumin and serum cholesterol as parameters of serum chemistry, body mass index calculated with dry weight (BMI) to assess body mass, pre-dialysis serum creatinine to assess muscle mass and the nPNA to assess dietary intake. In addition, we used the 7-point subjective global assessment (SGA) to measure nutritional status by combining a medical history with a physical examination[19]. The medical history of the SGA examines weight change, dietary intake and gastrointestinal symptoms. The physical examination explores subcutaneous fat and muscle mass. To diagnose protein-energy wasting, the ISRNM describes cut-off values for serum albumin (<3.8 g/dl), cholesterol (<100 mg/dl) and BMI (<23 kg/m$^2$)[4]. International guidelines furthermore indicate cut-off values for nPNA (≤1g/kg/d), serum creatinine (<10 mg/dL), and the SGA (<6)[8;9]. Based on these target values, a composite score of protein-energy nutritional status (cPENS) was created. Several variations of the cPENS were evaluated to identify the one with the strongest relationship with mortality, for instance by applying a weighted scoring or by leaving out nutritional parameters redundant for the determination of protein-energy nutritional status. The weighted scoring increased the influence of nutritional parameters with a relative stronger relation to mortality. The parameters were multiplied with a factor that represented their relative strength as a predictor of mortality, as compared to the nutritional parameter that showed the weakest hazard ratio. If cholesterol ≥100 mg/dL for instance had the weakest hazard ratio, and the hazard ratio for albumin ≥3.8 g/dL was three times as strong, cholesterol would get a weight of 1 and albumin of 3. By means of sensitivity analysis we also analyzed cPENS variants with a double cut-off value for BMI (>23 to ≤26 kg/m$^2$) or cholesterol (≥150 to ≤200 mg/dL). BMI showed a non-linear U-shaped relationship with outcome, and a non-linear relationship of cholesterol with mortality has been described [9]. We also explored variants that integrated continuous instead of dichotomous components while using standardized values of the nutritional parameters.

### Data analysis

Patient characteristics were reported as means with standard deviations, medians with interquartile ranges, or as proportions, when appropriate. Non-linear relationships between protein-energy nutritional parameters and mortality were examined using scatterplots with local regression ("smoothers"). Confounders were selected when they caused ≥ 5% change compared to the crude relation. Specific confounders were identified for each relation. All patient characteristics were treated as potential confounders, except serum urea which is mathematically related with nPNA. We used Cox regression analysis to estimate hazard ratios with 95% confidence intervals (CI) for all-cause mortality. To compare the hazard ratios, the different nutritional parameters and composite score variants were standardized (value minus mean, divided by the standard deviation). When the CIs between the estimated relations of these variants with all-cause mortality did not overlap, the difference was considered to be significant. Correlations between parameters of protein-energy nutritional status were analyzed with Spearman's correlation coefficient. Results were considered statistically significant when $P < 0.05$ (two-tailed comparison). Missing values were imputed with single regression analysis[20]. All analyses were conducted using SPSS (version 15.0.1; SPSS Inc. Headquarters, Chicago, Illinois, USA).

## RESULTS

### Patient characteristics

The characteristics of the 560 patients are summarized in Table 1. The mean age was 64 ± 14 years and 62% of patients were male. Eighty-three percent had a SGA ≥6, i.e. well-nourished, 88% had a nPNA ≥0.8g/kg/d, 90% had a serum cholesterol of ≥100 mg/dL, 38% had a serum creatinine of ≥10 mg/dL, 65% had a BMI ≥23 kg/m$^2$, and 42% had a serum albumin of 3.8 g/dL or higher. The maximum follow-up time was 4.2 years (median 1.4 years, interquartile range 0.8–2.4). One hundred and five patients (19%) died from any cause during follow-up. There was no loss to follow-up.

**Table 1.** Patient characteristics (N=560).

| | |
|---|---|
| **Demographic** | |
| Age (years) | 64 ± 14 |
| Male (%) | 62 |
| Caucasian (%) | 85 |
| **Socio-economic status** | |
| Employed (%) | 11 |
| High educational status* (%) | 22 |
| **Parameters of protein-energy nutritional status** | |
| SGA | 6.3 ± 1.0 |
| SGA classification (%) | |
| Well-nourished | 83 |
| Mild to moderate malnutrition | 17 |
| Severe malnutrition | 0 |
| Albumin (g/dL) | 3.7 ± 0.5 |
| nPNA (g/kg/d) | 1.1 ± 0.3 |
| Body mass index after dialysis (kg/m$^2$) | 25 ± 5 |
| Creatinine (mg/dL), pre-dialysis | 9.2 ± 2.7 |
| Cholesterol (mg/dL) | 142 ± 38 |
| cPENS | 3.8 ± 1.8 |
| **Other clinical parameters** | |
| Dialysis vintage (years) | 2.0 (1.0 – 4.0) |
| Dialysis frequency (% 3x per week) | 93 |
| rGFR (mL/min/1.73m$^2$) | 0.4 (0.0 – 3.4) |
| Vascular access (% fistula) | 78 |
| Systolic blood pressure (mmHg), pre-dialysis | 149 ± 21 |
| Diastolic blood pressure (mmHg), pre-dialysis | 77 ± 12 |
| Diabetes (%) | 23 |
| History of cardiovascular disease (%) | 45 |
| Statin use (%) | 50 |
| Current smoker (%) | 20 |
| Hemoglobin (g/dL) | 12 ± 1 |
| Bicarbonate (mEq/L) | 22 ± 3 |
| **Follow-up** | |
| Death from any cause | 105 (19%) |
| Follow-up time (years) | 1.4 (0.8 – 2.4) |

Mean ± SD or median (interquartile range)
* high educational status: education beyond the secondary level.
SGA: subjective global assessment; nPNA: normalized protein nitrogen appearance; cPENS: composite score of protein-energy nutritional status; rGFR: residual glomerular filtration rate.
To convert albumin in g/dL to g/L, multiply with 10; creatinine in mg/dL to μmol/L multiply with 88.4; cholesterol in mg/dL to mmol/L multiply with 0.0259; hemoglobin in g/dL to mmol/L multiply with 0.62.

### The cPENS in relation to mortality

Table 2 depicts the various variants of the cPENS, indicating that the score with the strongest hazard ratio combined albumin, BMI, creatinine and the nPNA on a weighted scale (variant 5). The addition of serum cholesterol or the SGA to the composite did not significantly improve its relation to mortality. The weighted score depicts protein-energy nutritional status on a scale from 0 to 7 (Table 3). A score of 0 implies that no target values are met, and a score of 7 that all 4 target values are met. The crude hazard ratio on this scale was 0.69 (95% CI 0.62 to 0.78, P<0.001), and when adjusted for identified confounders (age, gender and clinical center) 0.63 (95% CI 0.54 to 0.74, P<0.001). The influence of age on the crude hazard ratio was 5% (hazard ratio per year: 1.05; 1.03 to 1.07, P<0.001), of gender 5% (HR male versus female: 1.12; 0.73 to 1.70, P=0.6) and clinical center 7% (HR not depicted as there were multiple centers).

**Table 2.** Comparison of different composite scores of protein-energy nutritional status in relation to mortality.

| Variant | Composition* | Hazard ratio (95% CI) per standard deviation |
|---|---|---|
| 1 | Albumin, BMI, creatinine and nPNA | 0.51 (0.40 – 0.65) |
| 2 | Variant 1 including cholesterol | 0.45 (0.35 – 0.58) |
| 3 | Variant 1 including SGA | 0.52 (0.42 – 0.65) |
| 4 | Variant 1 including cholesterol and SGA | 0.50 (0.40 – 0.63) |
| **5** | **Variant 1 with weighted scoring#** | **0.44 (0.32 – 0.58)** |
| 6 | Variant 5 including cholesterol | 0.44 (0.34 – 0.57) |
| 7 | Variant 5 including SGA | 0.46 (0.36 – 0.58) |
| 8 | Variant 5 including cholesterol and SGA | 0.45 (0.35 – 0.57) |

* Albumin (≥3.8 g/dL), BMI after dialysis (≥23 kg/m$^2$), pre-dialysis creatinine (≥10 mg/dL), nPNA (normalized protein nitrogen appearance, ≥0.8g/kg/d), cholesterol (≥100 mg/dL), SGA (Subjective Global Assessment, target score ≥6).

# The influence of individual components is based on the relative strength of their relation with mortality, taking the weakest association as a reference value (see methods section).

All hazard ratios were adjusted for confounders that caused ≥ 5% change, as identified for every individual relation. Variant 5 was adjusted for age, gender and clinical center.

**Table 3.** Composition of the cPENS.

| Nutritional target value | Score |
|---|---|
| BMI (≥ 23 kg/m²) | 1 |
| nPNA (≥ 0.8 g/kg/d) | 1.5 |
| Creatinine (≥ 10 mg/dL) | 2 |
| Albumin (≥ 3.8 g/dL) | 2.5 |
| cPENS | 0 – 7 |

The score (influence) of the individual components is based on the relative strength of their relation with mortality, taking the weakest association as a reference value (see methods section).
BMI: body mass index measured after dialysis; nPNA: normalized protein nitrogen appearance; Creatinine: pre-dialysis creatinine; cPENS: composite score of protein-energy nutritional status.

Sensitivity analyses showed that the strength of the relation between the cPENS and mortality did not significantly increase with a double cut-off value for BMI (>23 to ≤26 kg/m²) or cholesterol (≥150 to ≤200 mg/dL), or continuous instead of dichotomous components (data not shown).
Figure 1 depicts adjusted Cox survival curves per cPENS quartile. The number of patients and hazard ratios per quartile are shown in Table 4.

**Table 4.** cPENS scores versus mortality.

| cPENS | | | Hazard ratio (95% confidence intervals) | |
|---|---|---|---|---|
| Quartile | Score | N | Crude | Adjusted* |
| 1 | 0 – 2 | 106 | 1 | 1 |
| 2 | 2.5 – 4 | 214 | 0.60 (0.39 – 0.93) | 0.48 (0.29 – 0.80) |
| 3 | 4.5– 5 | 150 | 0.26 (0.14 – 0.48) | 0.17 (0.08 – 0.34) |
| 4 | 5.5 – 7 | 90 | 0.19 (0.08 – 0.44) | 0.22 (0.08 – 0.61) |

* Analysis was adjusted for confounders that caused ≥ 5% change (in this model: age, gender and clinical center).

### The cPENS versus individual nutritional parameters

As a predictor of mortality, the cPENS did not perform better than some of its individual components (Table 5). When the different parameters were standardized, the strength and magnitude of the hazard ratio of the cPENS were comparable to that of serum albumin and creatinine. The cPENS showed a strong correlation with most nutritional parameters (Table 6). Mutual correlations of the individual parameters were small to mediocre.

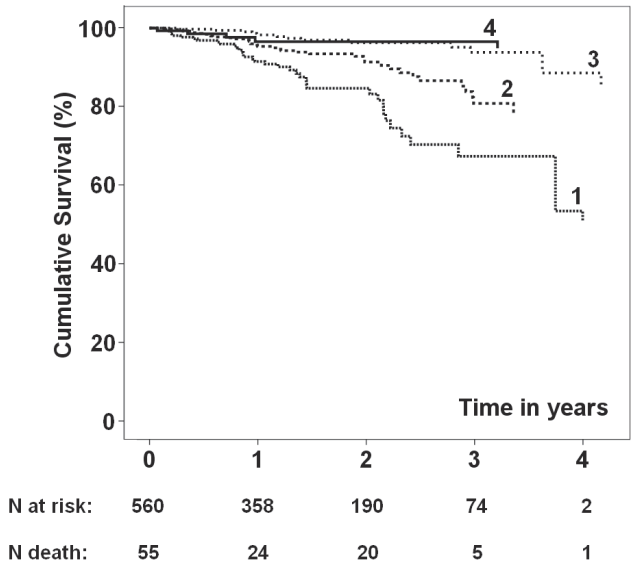


**Figure 1.** Adjusted survival per cPENS quartile.
Depicted are Cox regression survival curves per cPENS quartile while adjusting for confounders that caused ≥ 5% change (in this model: age, gender and clinical center).

**Table 5.** Protein-energy nutritional status as a predictor of mortality.

| | Hazard ratio (95% CI) | |
|---|---|---|
| Nutritional parameter | Per unit | Per standard deviation |
| SGA (1-7) | 0.61 (0.50 – 0.75) | 0.63 (0.52 – 0.76) |
| Albumin (g/dL) | 0.15 (0.08 – 0.27) | 0.42 (0.31 – 0.55) |
| Cholesterol (mg/dL) | 1.00 (1.00 – 1.01) | 1.01 (0.83 – 1.23) |
| BMI (kg/m$^2$) | 1.00 (0.96 – 1.04) | 1.00 (0.82 – 1.22) |
| Creatinine (mg/dL) | 0.72 (0.64 – 0.82) | 0.41 (0.30 – 0.58) |
| nPNA (g/kg/d) | 0.25 (0.10 – 0.64) | 0.70 (0.55 – 0.89) |
| cPENS (0 – 7) | 0.63 (0.54 – 0.74) | 0.44 (0.32 – 0.58) |

All hazard ratios were adjusted for confounders that caused ≥ 5% change, which were identified for every individual relation.
SGA: Subjective global assessment; BMI: post-dialysis body mass index; Creatinine: pre-dialysis creatinine; nPNA: normalized protein nitrogen appearance; cPENS: composite score of protein-energy nutritional status.

**Table 6.** Correlations between parameters of protein-energy nutritional status.

| | SGA | Albumin | Cholesterol | BMI | Creatinine | nPNA |
|---|---|---|---|---|---|---|
| Albumin | **0.19** | | | | | |
| Cholesterol | 0.01 | **0.19** | | | | |
| BMI | **0.29** | 0.02 | 0.03 | | | |
| Creatinine | **0.19** | **0.10** | -0.02 | 0.22 | | |
| nPNA | **0.08** | **0.18** | 0.06 | 0.02 | 0.05 | |
| cPENS | **0.29** | **0.68** | **0.11** | **0.25** | **0.49** | **0.26** |

Depicted are Spearman's correlation coefficients.
Bold correlations are significant ($P < 0.05$).
SGA: Subjective global assessment; BMI: post-dialysis body mass index; Creatinine: pre-dialysis creatinine; nPNA: normalized protein nitrogen appearance; cPENS: composite score of protein-energy nutritional status.

## DISCUSSION

Based on the recommendation of the ISRNM we have created a composite score to assess protein-energy nutritional status. The cPENS includes 4 more readily available nutritional parameters: serum albumin, BMI, creatinine and the nPNA. The cPENS had a strong association with mortality, but as a predictor of outcome it did not surpass serum albumin or creatinine.

We are to the best of our knowledge the first to evaluate a composite score based on the international consensus on the elements that define protein-energy nutritional status[4]. Our results add evidence to answer the question what scoring system of protein-energy wasting predicts outcome most effectively, as posed by the ISRNM. It furthermore puts the clinical value of the proposed diagnostic criteria for protein-energy wasting to question.

Eighty-three percent of our cohort was well-nourished according to the SGA, and on average 4 of the 6 measured nutritional target levels were reached. Nutritional parameter levels were roughly in line with other large cohorts[2;3;21]. Serum cholesterol was lower in our patients as compared to the Hemodialysis study (HEMO: 173 ± 41; CONTRAST: 142 ± 38 mg/dL)[2]. This may be due to a possible higher use of lipid-lowering medication in our population. The predictive values of the different nutritional parameters were roughly comparable to other studies including HEMO[2;21;22], but somewhat different as

compared to DOPPS[3]. These differences are hard to explain as they do not point in one direction: the hazard ratio of BMI was somewhat lower in our population as compared to DOPPS, whereas the ratio of nPNA was comparable and the ratios of creatinine and albumin somewhat stronger. The identified non-linear U-shaped relation of BMI to mortality has been described before in hemodialysis patients[23].

The different cPENS variants showed comparable hazard ratios for mortality. SGA was significantly related to mortality in a multivariable Cox regression model, but it showed no added value to the cPENS as a predictor. Although the SGA is acknowledged as a potential marker of protein-energy nutritional status by the expert panel of the ISRNM, there is no consensus on the mutual relationship[4]. The expert panel of the ISRNM describes different variables that can be used to measure the 4 categories of protein-energy nutritional status. We used the most simple and readily available nutritional parameters. Future analyses should explore the possible added value of less common variables, like serum pre-albumin, mid-arm muscle circumference or dietary diaries, as well as the use of repeated measurements. It should be mentioned however that the addition of such not-routinely measured variables would limit the applicability of the composite score in clinical practice.

A limitation of this study is that, as CONTRAST is still ongoing, we could only analyze baseline levels of protein-energy nutritional status whereas repeated measures are recommended. As explained in the methods section, time-dependent measurements could have been affected by allocated treatment. By using only baseline data, confounding by treatment was not possible in the current analysis. Second, it might be that the difference in strength of the association between the cPENS and the individual parameters is due to a more restricted variability in the composite score as compared to the individual parameters. Our results may for instance be affected by the relatively preferable protein-energy nutritional status of our population with less variance around the cut-off value of SGA as compared to serum creatinine and albumin. The nutritional parameters are however roughly in line with other large cohorts as mentioned earlier[2;3;21]. A final limitation is the possibility of bias due to

unmeasured confounding. Adjustment for measured confounders like age and gender did however not result in distinct changes.

At present it is difficult to measure protein-energy nutritional status in daily practice. A composite score of protein-energy nutritional status may facilitate this assessment. Our results contribute evidence to the development of such a score, but it should be noted that composition and weighting should be evaluated in different populations.

Interactions between nutritional parameters have been described[3], but whereas the correlations between nutritional parameters in our population were mild to mediocre, the correlations with the cPENS were predominantly strong. Future studies should compare a scoring system of protein-energy nutritional status with a reference standard of protein-energy nutritional status like total body nitrogen[24] to assess its validity as well as its ability to measure change over time in response to interventions.

In conclusion, we evaluated several composite scores of protein-energy nutritional status based on the consensus of the ISRNM. The proposed cPENS has a strong relation to mortality, but it is of similar strength and magnitude as serum albumin and creatinine. As determination of albumin alone reflects mortality risk similar to multiple nutritional markers combined, our results question the clinical value of the proposed diagnostic criteria for protein-energy wasting[4] with regard to outcome. Future studies should evaluate if a composite score with less readily available nutritional parameters has a superior relation to mortality.

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# The effect of hemodiafiltration on quality of life over time in the Convective Transport Study (CONTRAST): a randomized, controlled trial

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Submitted for publication

## ABSTRACT

**Background.** It is unclear if hemodiafiltration leads to a better quality of life as compared to hemodialysis.

**Objective.** To assess the effect of hemodiafiltration on quality of life as compared to hemodialysis in patients with end-stage renal disease.

**Design.** We analyzed data from the Convective Transport Study (CONTRAST; NCT00205556), a randomized controlled trial on the effect of hemodiafiltration versus hemodialysis on all-cause mortality. The median follow-up for the quality of life part was 2 years.

**Setting.** Dialysis centers in The Netherlands (n=26), Canada (n=2) and Norway (n=1).

**Patients.** 714 patients with end-stage renal disease.

**Intervention.** Online post-dilution hemodiafiltration versus low-flux hemodialysis.

**Measurements.** Quality of life was measured with the Kidney Disease Quality of Life – Short Form (KDQOL-SF). This questionnaire provides data for a physical and mental composite score (PCS and MCS), and describes kidney disease-specific quality of life in 12 domains. The domains have a scale from 0 to 100.

**Results.** There were no significant differences in changes in HRQOL over time between patients treated with hemodialysis (n=358) or hemodiafiltration (n=356). A trend was observed for a worse MCS (-0.5 points per year, 95% confidence interval -1.1 to 0.0, P=0.06) and an improved 'Effects of kidney disease on daily life' (+1.1 (-0.1 to 2.4, P=0.06) in patients on hemodiafiltration versus hemodialysis. The quality of life domain 'patient satisfaction' declined over time in both dialysis modalities (hemodialysis: -2.5, -3.4 to -1.5, P<0.001; hemodiafiltration: -1.4, -2.4 to -0.5, P=0.004).

**Limitations.** Favourable patient selection within the context of a randomized clinical trial.

**Conclusions.** In conclusion, hemodiafiltration compared to hemodialysis did not affect quality of life over time.

## INTRODUCTION

Health-related quality of life (HRQOL) is a multidimensional concept. It comprises a patients' perspective on physical, mental and social domains of health[1]. In a chronic condition like end-stage renal disease, improving patients' HRQOL is considered a relevant treatment goal[2]. The HRQOL of patients with end-stage renal disease has been described to be worse than in patients with congestive heart failure, chronic lung disease or cancer[3]. Besides an important outcome in itself, reduced HRQOL has been related to hospitalisation and mortality[4;5].

Of the various renal replacement therapies, observational studies have suggested that a kidney transplantation offers the most preferable health status in general [6]. However, as the availability of donor kidneys is limited, the effect of contemporary renal replacement therapies on HRQOL is an important issue. Hemodiafiltration (HDF) is a relatively new therapy[7]. It combines diffusion with convection to clear middle molecular weight substances more effectively as compared to hemodialysis (HD)[7;8]. This improved correction of the uremic environment may reduce cardiovascular morbidity and may lead to a preferable health status[9]. Earlier studies on the effect of HDF on HRQOL were inconclusive and based on findings from small (n= 44 to 111) or on non-randomized studies[9-14]. Therefore, the aim of this study was to assess the effect of HDF compared to HD on HRQOL in a large randomized clinical trial.

## METHODS

### Design overview

This randomized analysis is based on data from the Convective Transport Study (CONTRAST). As described previously, CONTRAST is a randomized controlled trial (NCT00205556) that compares the effects of low-flux HD and online HDF on all-cause mortality and cardiovascular events[8]. The study was conducted in accordance with the Declaration of Helsinki and approved by the medical ethics review boards of all participating hospitals. Written informed consent was obtained from all patients prior to enrolment.

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**Setting and participants**

714 Patients were recruited from dialysis centers in The Netherlands (n=26), Canada (n=2) and Norway (n=1). Patients were eligible for inclusion if they were treated two or three times per week with HD for at least two months, with a minimum dialysis urea Kt/V of ≥1.2. Exclusion criteria were age below 18 years, treatment with hemo(dia)filtration or high-flux HD in the six months prior to randomization, a life expectancy less than three months due to non-renal disease, participation in another clinical intervention trial evaluating cardiovascular outcomes and severe incompliance regarding frequency and duration of dialysis treatment [8].

**Randomization and interventions**

Patients were randomized centrally with a 1:1 ratio and stratified per participating center. Online HDF was performed in post-dilution mode with a target dose for substitution fluid of 100 mL/min and high-flux synthetic dialyzers were used. Conventional HD was performed with low-flux dialyzers[8].

**Outcomes and follow-up**

At baseline, standardized forms were used to collect demographic, clinical, and laboratory data. Demographic data included age, gender, race, educational level, and employment status. Clinical characteristics recorded were medical history, including the cause of kidney disease, presence of diabetes mellitus, previous cardiovascular disease, hemodialysis dose (single pool Kt/Vurea), time on dialysis, treatment time in hours, and estimated residual glomerular filtration rate (eGFR). Laboratory values were measured in the different participating hospitals using standard techniques. Study visits were performed at three month intervals. Interdialytic urinary samples were collected in patients with a urinary production of 100 mL per day or more. eGFR was calculated as the mean of creatinine and urea clearances and adjusted for body surface area (mL/min/1.73m$^2$)[15]. Further information regarding the measured characteristics has been reported previously[8].

*Kidney Disease Quality of Life – Short Form (KDQOL-SF)*

HRQOL was assessed at baseline and every subsequent year of follow-up with the validated KDQOL-SF version 1.3 (http://gim.med.ucla.edu/kdqol/downloads/-download.html)[16;17]. This questionnaire covers different domains to face the multidimensional nature of HRQOL. The KDQOL-SF can be split up in a generic part and a disease-specific part. First, the generic part is formed by the SF-36 (Short Form with 36 questions) version 1. The domains of the SF-36 can be summarized in two summary scores, one for physical functioning (Physical Component Summary – PCS) and one for mental functioning (Mental Component Summary – MCS). These summaries are constructed in a way that a score of 50 represents the mean of the general United States population with a standard deviation of 10[18]. Second, the disease-specific part of the KDQOL-SF consists of 44 kidney-disease targeted questions. The responses to these items are condensed in 12 domains (Appendix II). The HRQOL domains have a score from 0 to 100, with higher scores indicating the absence of problems. A difference of 5 points has been proposed to be clinically relevant with regard to individual domains, and a difference of 3 points with regard to the composite scores[18;19].

**Statistical analysis**

Data were analyzed according to an intention-to-treat principle. All variables were reported as proportions, means with standard deviations (SD), or medians with interquartile ranges (IR) when appropriate. Differences in changes in HRQOL domains over time were assessed with multilevel linear regression. The best overall fit of the multilevel linear model was evaluated with the chi-square likelihood ratio test. The residuals of all models had a normal distribution. Differences in subgroups were evaluated using interaction terms. Seven subgroups were evaluated: age, gender, residual renal function (diuresis ≥100 mL/24 hr), dialysis vintage, diabetes, previous cardiovascular disease, and convection volume. The Benjamini and Hochberg False Discovery Rate was used to correct for multiple comparisons[20]. Results were considered statistically significant when $P < 0.05$ (two-tailed comparison). Statistical analyses were performed with SPSS 18 (SPSS inc., Chicago, Illinois, US).

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**Role of the funding source**
CONTRAST is an investigator-initiated trial that was designed, conducted, analyzed, and had data interpreted independently of the financial contributors.

## RESULTS

### Patient characteristics

The baseline characteristics of the patients on HD (N=356) and HDF (N=358) are summarized in Table 1. The mean age was 64 years in both groups (SD HD: 13, HDF: 14). Sixty-five percent of patients on HD were male and 60% of patients on HDF. Figure 1 shows the patient flow over time. Over time, 93% of KDQOL-SF questionnaires were filled out. The median follow-up of these patients was 2.0 years (IR 1.1 – 3.0). The average convection volume over time in patients on HDF was 19 ± 6 (SD) L per session.

**Table 1.** Patient characteristics at baseline.

| | HD (N=356) | HDF (N=358) |
|---|---|---|
| **Demographic** | | |
| Age (years) | 64 ± 13 | 64 ± 14 |
| Gender (% male) | 65 | 60 |
| Caucasian (%) | 83 | 85 |
| **Socio-economic status** | | |
| Employed (%) | 10 | 11 |
| High educational status* (%) | 21 | 20 |
| **Clinical parameters** | | |
| Cause of kidney failure (%) | | |
| Vascular | 27 | 29 |
| Diabetes mellitus | 17 | 21 |
| Nephritis | 24 | 20 |
| Cystic kidney disease | 7 | 7 |
| Other / unknown | 25 | 23 |
| Dialysis vintage (years) | 2.2 (1.0 – 4.0) | 1.8 (1.0 – 3.8) |
| Dialysis frequency (% 3x per week) | 95 | 93 |
| Session time (hours) | 4.0 (3.5 – 4.0) | 4.0 (3.5 – 4.0) |
| spKt/V urea | 1.4 ± 0.2 | 1.4 ± 0.2 |
| eGFR (ml/min/1.73m$^2$)† | 3.2 (1.2 – 5.4) | 3.1 (1.7 – 6.2) |
| BMI (kg/m$^2$) | 26 ± 5 | 25 ± 5 |
| Diabetes (%) | 23 | 26 |
| History of cardiovascular disease (%) | 46 | 42 |
| Hemoglobin (mmol/L) | 7.3 ± 0.7 | 7.4 ± 0.8 |
| Albumin (g/L) | 37 ± 5 | 37 ± 5 |

Mean ± SD or median (interquartile range)
* High educational status: college or university level.
† In 377 patients with diuresis ≥100 mL/24 hr (53%).
HD: hemodialysis; HDF: hemodiafiltration; eGFR: estimated residual glomerular filtration rate.
To convert hemoglobin in mmol/L to g/dL divide by 0.62; albumin in g/L to g/dL, divide by 10.

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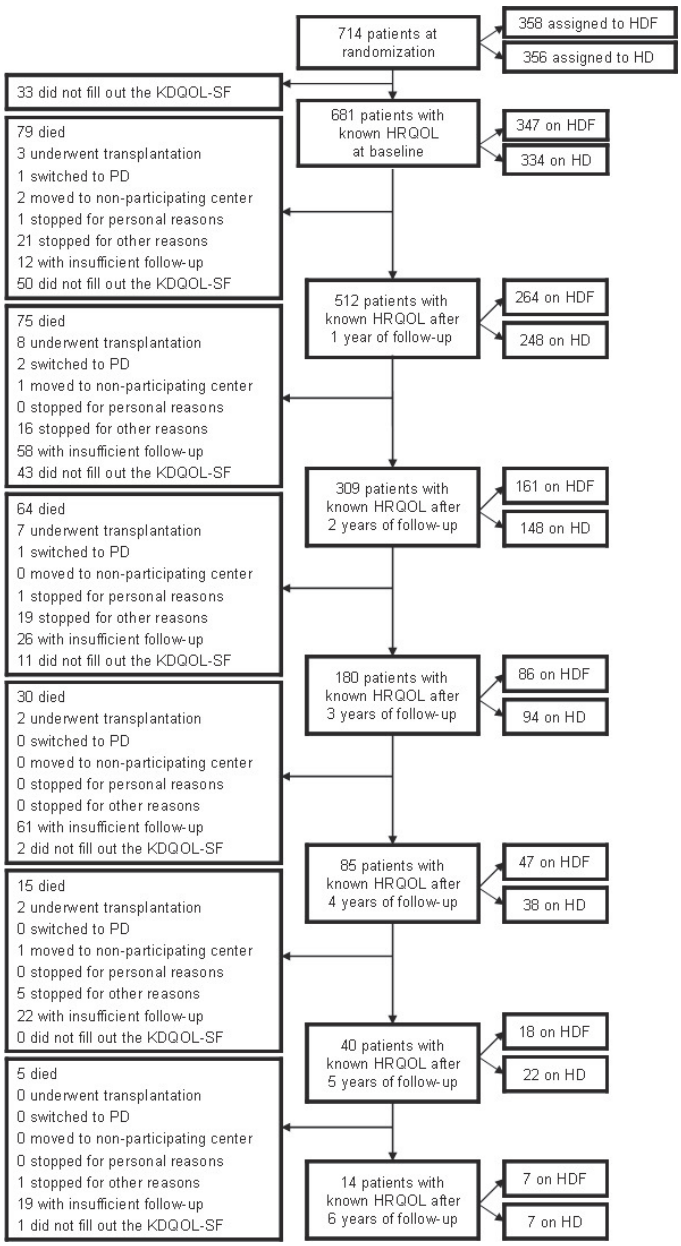


**Figure 1.** Patient flow diagram.
As patients were included at different points in time, potential follow-up time varies per patient.
HDF: hemodiafiltration, HD: hemodialysis, KDQOL-SF: Kidney Disease Quality Of Life – Short Form, HRQOL: health-related quality of life, PD: peritoneal dialysis.

### Quality of life at baseline and over time

Table 2 shows the HRQOL at baseline. The mean PCS was 40 ± 10 in HD patients and 39 ± 11 in HDF patients. The mean MCS was 50 ± 12 in both groups.

**Table 2.** Health-related quality of life at baseline.

| | HD (N=356) | HDF (N=358) |
|---|---|---|
| **Generic domains (SF-36)** | | |
| Physical summary (PCS) | 40 ± 10 | 39 ± 11 |
| Mental summary (MCS) | 50 ± 12 | 50 ± 12 |
| **Kidney disease-specific domains** | | |
| Symptom / problem list | 80 ± 12 | 79 ± 14 |
| Effects of kidney disease on daily life | 72 ± 19 | 71 ± 19 |
| Burden of kidney disease | 46 ± 26 | 45 ± 25 |
| Work status | 0 (0 – 50) | 0 (0 – 50) |
| Cognitive function | 78 ± 20 | 80 ± 18 |
| Quality of social interaction | 83 ± 16 | 81 ± 17 |
| Sleep | 62 ± 21 | 62 ± 20 |
| Social support | 83 (67 – 100) | 83 (67 – 100) |
| Dialysis staff encouragement | 75 (63 – 100) | 75 (63 – 100) |
| Overall health | 55 ± 24 | 54 ± 21 |
| Patient satisfaction | 70 ± 23 | 70 ± 24 |

Mean ± SD or median (interquartile range)
HD: hemodialysis; HDF: hemodiafiltration.
The domains have a range from 0 to 100, with higher scores indicating a preferable health status or a relative absence of problems.

Both in patients on HD and HDF, multiple HRQOL domain scores declined significantly over time (Table 3). The HRQOL domain 'patient satisfaction' declined in both dialysis modalities (HD: -2.5 points per year, 95% confidence interval -3.4 to -1.5, P<0.001; HDF: -1.4, -2.4 to -0.5, P=0.004). One HRQOL domain improved, namely Overall Health in patients on HDF (+ 0.9, 0.1 to 1.7, P=0.03). Over time, there were no significant differences in HRQOL between patients on HDF and HD, although a trend was observed towards a worse MCS (-0.5, -1.1 to 0.0, P=0.06) and an improved 'Effects of kidney disease on daily life' (+1.1, -0.1 to 2.4, P=0.06) in patients on HDF.

Subgroup analyses did not designate patient groups in whom HDF may have a clinical relevant benefit on HRQOL.

**Table 3.** Health-related quality of life over time in patients treated with hemodialysis and hemodiafiltration.

| | HD (N=356) | | HDF (N=358) | | HDF versus HD | |
|---|---|---|---|---|---|---|
| | Δ | P-value | Δ | P-value | Δ | P-value |
| **Generic domains (SF-36)** | | | | | | |
| Physical summary (PCS) | -0.8 (-1.1 to -0.5) | **<0.001** | -0.2 (-0.6 to 0.1) | 0.13 | 0.4 (-0.3 to 1.1) | 0.29 |
| Mental summary (MCS) | 0.1 (-0.3 to 0.5) | 0.78 | -0.5 (-0.8 to -0.1) | **0.01** | -0.5 (-1.1 to 0.0) | 0.06 |
| **Kidney disease-specific domains** | | | | | | |
| Symptom / problem list | -1.1 (-1.8 to -0.4) | **0.003** | -0.6 (-1.2 to 0.0) | 0.07 | 0.4 (-0.5 to 1.4) | 0.33 |
| Effects of kidney disease on daily life | -1.3 (-2.3 to -0.4) | **0.01** | -0.3 (-1.1 to 0.4) | 0.38 | 1.1 (-0.1 to 2.4) | 0.06 |
| Burden of kidney disease | -0.2 (-1.0 to 0.6) | 0.69 | -0.9 (-1.7 to -0.1) | **0.02** | -0.7 (-1.7 to 2.4) | 0.21 |
| Work status | -0.4 (-1.4 to 0.6) | 0.42 | -1.1 (-2.0 to -0.1) | **0.03** | -0.6 (-2.0 to 0.8) | 0.41 |
| Cognitive function | -0.4 (-0.9 to 0.2) | 0.22 | -1.1 (-1.7 to -0.4) | **0.001** | -0.7 (-2.0 to 0.7) | 0.35 |
| Quality of social interaction | -0.1 (-0.9 to 0.6) | 0.71 | -0.4 (-1.2 to 0.4) | 0.36 | -0.2 (-1.3 to 0.9) | 0.68 |
| Sleep | 0.3 (-0.3 to 0.9) | 0.35 | 0.4 (-0.2 to 1.1) | 0.17 | 0.1 (-0.8 to 1.0) | 0.76 |
| Social support | -0.2 (-1.1 to 0.7) | 0.65 | -0.4 (-1.2 to 1.1) | 0.37 | -0.2 (-1.4 to 1.1) | 0.81 |
| Dialysis staff encouragement | -1.0 (-1.8 to -0.1) | **0.02** | 0.0 (-0.7 to 0.8) | 0.96 | 1.0 (-0.1 to 2.1) | 0.09 |
| Overall health | 0.2 (-0.8 to 1.2) | 0.69 | 0.9 (0.1 to 1.7) | **0.03** | 0.7 (-0.5 to 2.0) | 0.25 |
| Patient satisfaction | -2.5 (-3.4 to -1.5) | **<0.001** | -1.4 (-2.4 to -0.5) | **0.004** | 0.0 (0.0 to 0.0) | 0.29 |

Δ: change in health-related quality of life over time per year; HD: hemodialysis; HDF: hemodiafiltration.
The median follow-up was 2.0 years (interquartile range: 1.1 – 3.0).

## DISCUSSION

This study showed that HDF did not affect patients' HRQOL as compared to HD. Although there were changes over time in HRQOL for patients on HDF and HD, these did not result in significant differences over time between both dialysis modalities. There was a trend towards a worse MCS and an improved 'Effects of kidney disease on daily life' in patients on HDF versus HD. As their effect sizes were small and opposite, they implicate no clear benefit for either therapy.

To our knowledge, this is the first large randomized study to analyze the effect of HDF on HRQOL. The results of earlier studies were inconclusive (Table 4): two studies showed an increase in physical HRQOL in patients on HDF[12;14], three found no significant differences between both dialysis modalities[10;11;13]. Furthermore, no clinical meaningful differences in HRQOL have been identified in patients on low- versus high-flux HD[21], or hemofiltration versus HD[22;23]. It should be noted that these studies used different questionnaires to assess HRQOL. Perhaps this might explain why two studies did find a positive effect of HDF on HRQOL where others did not. However, whereas Lin et al[12] used a self-developed form, Shiffl et al[14] applied the Kidney Disease Questionnaire which was also used by Ward et al[11]. Lin et al and Schiffl et al found a positive effect of HDF on physical HRQOL, Ward et al did not.

A difference in HRQOL of 5 points or more has been proposed as being clinically relevant[19]. Such a notion would mean that in our study only the decline in patient satisfaction is likely to have clinical relevance over several years of time. This decline was shown in both dialysis modalities. It is in agreement with previous findings that showed a negative relation with dialysis vintage[24;25]. Patient satisfaction has been related to various factors[24-27], including a positive association with compliance[26] and a negative association with comorbidity[24]. An increase in age seems less relevant, as age has been both positively[28] and negatively[25] related to patient satisfaction.

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**Table 4. Previous studies on hemodiafiltration and health-related quality of life.**

| Reference | Design | Intervention | Number of patients | Follow-up (months) | HRQOL instrument | Effect on HRQOL |
|---|---|---|---|---|---|---|
| Moreno et al.[10] | Cross-sectional | HDF ⇔ HD ⇔ PD | 1013<br>71 on HDF | n/a | KS and SIP | No difference |
| Ward et al.[11] | RCT | HDF ⇔ high-flux HD | 44<br>24 on HDF | ± 12 | KDQ | No difference |
| Lin et al.[12] | RCT | HDF ⇔ high-flux HD | 111* | Unclear | Self-developed | Better physical well-being in HDF (32%) |
| Schiffl et al.[14] | Cross-over | HDF ⇔ high-flux HD | 76 | 2 x 24 | KDQ | Better perception of physical symptoms in HDF (26%) |
| Canaud et al.[13] | Observational | HDF ⇔ High- ⇔ low-flux HD | 2165<br>253 on HDF | ± 21 (HDF) | SF-36 | No difference |

HRQOL: Health-Related Quality Of Life; RCT: Randomized Clinical Trial; HD: Hemodialysis; HF: Hemofiltration; HDF: hemodialfiltration; KDQOL-LF: Kidney Disease Quality Of Life – Long Form(16); KDQ: Kidney Disease Questionnaire(35); KS: Karnofsky Performance Scale(36); SIP: Sickness Impact Profile(37); SF-36: Short Form 36(20).

* Randomization into 4 groups: 3x/wk HD, 3x/wk HDF, and 2 intermediate versions with a 2x versus 1x/wk distribution of HD or HDF.

A limitation of our study is the favourable patient selection within the context of a randomized clinical trial. This might affect changes in HRQOL over time within groups, but it is not likely to affect differences in HRQOL between HDF and HD.

In conclusion, the results from this first large, randomized controlled trial comparing the effect of HDF versus HD on HRQOL, show that HDF had no effect on this important outcome. Several recently completed and still running trial compare HDF and HD on other important outcomes like morbidity and mortality[8;29-33]. Results will be available in the near future.

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# The effect of online hemodiafiltration compared with low-flux hemodialysis on all-cause mortality and cardiovascular events: a randomized controlled trial The CONvective TRansport STudy (CONTRAST)

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Submitted for publication

## ABSTRACT

**Background.** In patients with end-stage renal disease, the effects of online hemodiafiltration on all cause mortality and cardiovascular events are unclear.

**Methods.** In this prospective study, we randomly assigned 714 chronic hemodialysis patients either to online post-dilution hemodiafiltration (N=358) or to continue low-flux hemodialysis (N=356) . The primary outcome measure was all-cause mortality. The main secondary endpoint was the composite of fatal and non-fatal major cardiovascular events, including death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, therapeutic coronary intervention (percutaneous transluminal coronary angioplasty and/or stenting), therapeutic carotid intervention (endarterectomy and/or stenting), and vascular intervention (revascularisation, percutaneous transluminal angioplasty and/or stenting), or amputation.

**Results.** After a mean follow-up of 3.04 years (range 0.4 – 6.6 years), the incidence of all cause mortality was not affected by treatment assignment (online hemodiafiltration 121/1000 person-years, low-flux hemodialysis 127/1000 person-years; hazard ratio 0.95; 95% confidence interval [CI] 0.75 to 1.20. The incidence of fatal and non-fatal cardiovascular events was 127/1000 person-years versus 116/1000 person-years, respectively (hazard ratio 1.07; 95% CI 0.83-1.39). No effects of the intervention on the primary and main secondary endpoints were found in various subgroups. A benefit on all cause mortality was observed in patients who received high volume online hemodiafiltration (hazard ratio upper tertile (›20.3 liters/treatment) 0.56; 95% CI 0.34-0.93.

**Conclusions.** In chronic hemodialysis patients, we observed no beneficial effect of hemodiafiltration on all cause mortality and cardiovascular events compared to low-flux hemodialysis. On-treatment analysis suggested a survival benefit in patients receiving high-volume hemodiafiltration. (Clinicaltrials.gov number NCT 00205556)

## INTRODUCTION

Patients undergoing chronic intermittent hemodialysis have a high risk of cardiovascular morbidity and mortality. Of the potential risk factors involved, retention of uremic toxins in the middle molecular weight range (0.5-40 kiloDalton) might play an important role. During conventional hemodialysis with low-flux membranes, low molecular weight substances (<1.5 kiloDalton) are removed by diffusive transport, while larger uremic toxins accumulate in the body. Therefore, in the past, high-flux membranes have been developed, which enable the removal of larger molecules by convective transport. However, the amount of convective transport is uncertain and uncontrollable. So far, two large randomized controlled trials did not show a distinct clinical benefit of high-flux over low-flux membranes[1;2].

The magnitude of convective transport can be considerably increased by a technique that combines high-flux hemodialysis with the (ultra)filtration of large amounts of plasma water, so-called hemodiafiltration. Obviously, fluid balance can only be maintained if the amount of fluid withdrawn is substituted. In the last decades, the development of sophisticated water treatment systems and effective ultrafilters allowed the 'online' production of sterile substitution fluid at acceptable costs. With modern online hemodiafiltration equipment, high convection and substitution volumes can be reached safely[3], resulting in markedly enhanced removal of middle molecular weight substances[4-7].

Several non-randomized observational studies suggested a survival benefit in patients who are treated with online hemodiafiltration[8-11]. However, small randomized studies failed to show a difference between online hemodiafiltration and standard hemodialysis [summarized in[12]]. Based on the above-mentioned theoretical considerations, the absence of conclusive clinical data, and the growing interest in convective techniques, the CONvective TRAnsport STudy (CONTRAST) was initiated. CONTRAST is a randomized controlled trial, comparing online hemodiafiltration and low-flux hemodialysis with respect to survival and various predefined secondary clinical endpoints.

## METHODS

### Study design

CONTRAST is a randomized controlled trial conducted in twenty-nine dialysis centers in The Netherlands (n=26), Canada (n=2), and Norway (n=1). The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and was approved by both a central medical ethics review board and local ethics committees. Written informed consent was obtained from all patients prior to enrollment. Detailed study methods have been published previously[13].

CONTRAST is an investigator-initiated trial that was designed, conducted and analyzed independently of the financial contributors. Study data were collected and retained by the investigators and were not available for the financial contributors. The writing executive committee, whose membership did not include representatives of the financial contributors, has final responsibility for the interpretation of the data, the preparation of the manuscript and the decision to submit for publication. The executive committee vouches for the validity and completeness of the reported data.

### Patients

Patients with end-stage renal disease undergoing chronic intermittent hemodialysis for at least two months and aged 18 years or above were recruited from June 2004 through December 2009. Primary renal diagnoses were: renal vascular disease (29%), diabetes mellitus (19%), primary glomerulopathy/ glomerulonephritis (12%), interstitial nephropathy (9%), cystic kidney disease (7%), multisystem disease (4%), other (12%) or unknown (8%). Patients were eligible for inclusion if they were treated two or three times per week with low-flux hemodialysis. Exclusion criteria were: treatment with hemo(dia)filtration or high-flux hemodialysis in the six months preceding randomization, a life expectancy less than three months due to non-renal disease, participation in another clinical intervention trial evaluating cardiovascular outcomes and severe incompliance regarding frequency and/or duration of dialysis treatment.

**Treatment and procedures**

Before randomization, all patients had to be stable with a minimum dialysis single-pool Kt/V for urea (spKt/$V_{urea}$) of 1.2. All patients were randomized centrally by a computer-based randomization service (Julius Clinical Research, University Medical Center Utrecht, The Netherlands) into a 1:1 ratio for treatment with online hemodiafiltration or continuation of low-flux HD, stratified per participating center. Treatment times were fixed during follow-up in both treatment arms, unless spKt/$V_{urea}$ was below 1.2.

Online hemodiafiltration was performed in the post-dilution mode with a target convection volume of 6 L/h. This amount was based on a targeted filtration rate ~~of~~ between 25% and 33% of an extracorporeal blood flow rate between 300 and 400 ml/min (so called "filtration fraction"), which appeared achievable in clinical practice. Blood flow rates could be increased in the hemodiafiltration arm to improve convection volumes. For hemodiafiltration, synthetic high-flux dialyzers were used (FX80: 27%, FX100: 11% and Optiflux F200NR: 8% [Fresenius Medical Care, Bad Homburg, Germany]; Polyflux 170H: 25% and Polyflux 210H: 27% [Gambro AB, Stockholm, Sweden] or other dialyzers: 2%). Hemodialysis patients were treated with synthetic low-flux dialyzers (F6HPS: 5%, F8HPS: 45% and Optiflux 18NR: 9% [Fresenius]; Polyflux 14L: 2% and Polyflux 17L: 30% [Gambro], or other: 9%). When hemodiafiltration could temporarily not be performed due to technical reasons, the patients concerned were treated with high-flux membranes. Both hemodiafiltration and hemodialysis were performed with ultrapure dialysis fluids, defined as less than 0.1 colony forming units per mL and less than 0.03 endotoxin units per mL. In a subset of the participating centers, 99% of the samples was within reference quality levels[14]. Routine patient care was performed according to national and international Quality of Care Guidelines.

At baseline, information on demography, history of cardiovascular disease, diabetes mellitus, medication, type of vascular access and duration of dialysis (dialysis vintage) was assessed. At each quarterly visit, information on clinical events, dialysis treatment, medication and laboratory values was recorded. Additionally, blood flow rate, intradialytic weight loss, treatment time, infusion

volume and predialysis blood pressure were assessed. In hemodiafiltration patients, infusion volumes (liters per treatment) were reported as the mean value of three consecutive treatment sessions preceding the quarterly visit. Convection volumes (liters per treatment) were calculated as the sum of the intradialytic weight loss and the substitution volume.

Every three months, blood samples were drawn prior to dialysis, and if appropriate, after the session. Serum beta-2-microglobulin (molecular weight 11.8 kiloDalton) was assessed at baseline and every six months thereafter. All samples were analyzed in the local laboratories of the participating hospitals by standard laboratory techniques. Interdialytic urinary samples were collected during each quarterly visit in patients with a urinary production ≥ 100 mL per day. In these patients, residual kidney function was expressed as estimated glomerular filtration rate (eGFR), calculated by the mean of 24-hour urinary creatinine and urea clearances and adjusted for body surface area (mL/min/1.73m$^2$). The plasma concentrations used for this calculation were the mean of the values before and after dialysis. eGFR was considered zero in patients with a urinary production below 100 mL per day. Dialysis adequacy was expressed as spKt/$V_{urea}$, calculated with the second generation Daugirdas formula[15].

Due to the nature of the intervention, it was not possible to blind the patients, the local study nurses, or the investigators for the treatment assignment.

**Outcome**

The primary study outcome was all-cause mortality. Deaths were reported within 24 hours to the data management center by fax or email. The main secondary endpoint was a composite of fatal and non-fatal cardiovascular events. Cardiovascular events were defined as death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, therapeutic coronary procedure (percutaneous transluminal coronary angioplasty and/or stenting), therapeutic carotid procedure (endarterectomy and/or stenting), and vascular intervention (revascularisation, percutaneous transluminal angioplasty and/or stenting), or amputation. Congestive heart failure was excluded as

cardiovascular event, since the distinction with fluid overload is often difficult to make in patients with end stage renal disease. Hospitalizations, duration of the hospitalizations and main diagnosis (including infections) were recorded during the study period.

Follow-up of patients with respect to mortality and non-fatal cardiovascular events was continued even after they stopped with the randomized treatment because of a renal transplant (n=151), a switch to peritoneal dialysis (n=11), a move to another non-CONTRAST hospital (n=24) or stop of participation for other reasons (n=53). With respect to hospitalization for non-cardiovascular events, patients were followed up until the moment they stopped with the randomized treatment.

**Interim analyses and data monitoring**

An independent Endpoint Adjudication Committee, whose members were not aware of the treatment assignments, reviewed source documentation for all primary outcome events (deaths), as well as non-fatal cardiovascular events and infections.

A separate, independent data and safety monitoring board (DSMB), evaluated the results of sequential interim analyses. Every 2 months, sequential un-blinded analyses were performed on the cumulative database. Based on this design, the DSMB decided whether the data provided enough evidence of either efficacy or futility with respect to the primary outcome and sufficient support to formulate recommendations for the executive committee to continue the trial. Guidelines for early discontinuation have been published previously[16]. In December 2010 the DSMB recommended to stop the trial, as enough evidence was provided for futility, i.e. no clear efficacy of hemodiafiltration above hemodialysis.

**Statistical analyses**

CONTRAST was designed to have a statistical power of 80% to detect a relative risk reduction of 20% or more for online hemodiafiltration as compared to low-flux hemodialysis for the primary outcome, with a two-sided alpha level

of 5%. A 3-year incidence of death from any cause of 44% was expected in HD patients and a relative risk reduction of 20% or more by HDF was assumed. The primary outcome was time-to-death, a relative risk reduction was translated to a hazard ratio of 0.75, which is equal to the ratio of the logarithm of the expected cumulative survival proportion under HDF (1 - 0.352 = 0.648) and the logarithm of the expected cumulative survival proportion under HD (1 - 0.44 = 0.56).

For a sequential design, no fixed sample size estimate can be provided. About 772 patients needed to be enrolled and followed for about three years. In these patients, approximately 250 endpoints were expected to come to a decision. A double sequential triangular test as proposed by Whitehead[17] was employed to monitor accumulating data and test the primary hypothesis.

All primary analyses were conducted according to the intention-to-treat principle. Data for patients were censored at their date of death, date of last visit (for those still alive at the end of the follow-up at December 31, 2010) or date when last known to be alive (for those with unknown vital status). The primary endpoint was analysed cumulatively by sequential analysis[17] using the PEST program version 4.4[18]. Point and interval estimates were adjusted for cumulative testing.

Effects of treatment on secondary study endpoints were estimated with the use of unadjusted Cox proportional-hazards models, involving the time to the first relevant endpoint in any individual patient.

Differences in continuous and dichotomous variables between the two treatment arms during the follow-up period were estimated with linear mixed models (generalized estimating equations [GEE]). The main assumption of the GEE approach is that measurements are assumed to be dependent within subjects and independent between subjects. The correlation matrix representing the within-subject dependencies was estimated using an autoregressive relationship[19]. For this analysis, the interest was in the mean difference over time in risk factor levels between treatment arms. GEE analyses were performed using the on trial measurements adjusted for baseline characteristics.

Homogeneity of treatment effects across subgroups was tested by adding interaction terms to the relevant Cox models. Furthermore, based on the existing literature, we explored whether the treatment effect depended on the amount of convection volume that was achieved in hemodiafiltration patients during the trial. For this purpose, the achieved convection volume was divided in tertiles, which were introduced in a Cox proportional hazards model, with patients treated by low-flux hemodialysis as reference group. In this analysis, adjustments were made for factors which have previously been related to convection volume (age, gender, albumin, and haematocrit)[20], and potential determinants of mortality. All P-values were two-sided, and P-values less than 0.05 were considered significant. No adjustment for multiple statistical testing was made[21]. Analyses were performed with the use of SPSS 17 (SPSS Inc. Headquarters, Chicago, Il, USA).

## RESULTS

### Patient characteristics at baseline

Between June 2004 and December 2009, a total of 714 patients (597 in the Netherlands, 102 in Canada and 15 in Norway) were enrolled and randomly assigned to start online hemodiafiltration (358) or to continue low-flux hemodialysis (356), see figure 3. The two groups were well balanced with respect to baseline characteristics (Tables 1 and 2).

**Table 1. Characteristics of participants at baseline**

| Variable | On-line HDF (n=358) | Low flux HD (n=356) |
|---|---|---|
| Age (year) | 64.1±14.0 | 64.0±13.4 |
| Female sex – no. (%) | 144 (40) | 125 (35) |
| Race – no. (%) | | |
| Caucasian | 304 (85) | 296 (83) |
| Afro-Caribbean | 29 (8) | 29 (8) |
| Asian | 23 (6) | 22 (6) |
| Other | 2 (1) | 9 (3) |
| Region | | |
| Netherlands – no. (%) | 300 (84) | 297 (83) |
| Canada – no. (%) | 51 (14) | 51 (14) |
| Norway – no. (%) | 7 (2) | 8 (2) |
| History of cardiovascular disease – no. (%) | 151 (42) | 162 (46) |
| Diabetes mellitus – no. (%) | 92 (26) | 78 (22) |
| Dialysis vintage (year) | 2.8±2.9 | 3.0±2.8 |
| Systolic blood pressure – mmHg | 147±21 | 148±22 |
| Diastolic blood pressure – mmHg | 75±12 | 76±12 |
| Vascular access | | |
| Arteriovenous fistula – no. (%) | 279 (78) | 288 (81) |
| Graft – no. (%) | 57 (16) | 43 (12) |
| Central catheter – no. (%) | 22 (6) | 25 (7) |
| Duration of a dialysis session – min | 226±26 | 227±22 |
| Blood flow – mL/min | 302±39 | 299±41 |
| Dialysis single pool $Kt/V_{urea}$ | 1.41±0.24 | 1.38±0.19 |
| Residual kidney function – no. (%)* | 186 (52) | 190 (53) |
| Estimated glomerular filtration rate – | | |
| ml/min/1.73m$^2$ ¥ | 2.1±3.4 | 2.0±3.3 |
| median (inter-quartile range) | 0.32 (0-3.30) | 0.30 (0-3.35) |
| Hemoglobin – g/dl | 11.9±1.3 | 11.8±1.2 |
| Phosphorus – mg/dl | 5.12±1.58 | 5.05±1.46 |
| Beta-2-microglobulin – mg/L | 30.7±14.3 | 32.3±13.6 |
| SGA classification | | |
| Well-nourished– no. (%) | 290 (81) | 297 (83) |
| Mild to moderate malnutrition– no. (%) | 68 (19) | 58 (16) |
| Severe malnutrition– no. (%) | 0 (0) | 1 (0) |
| Body mass index after dialysis – kg/m$^2$ | 25.2±5.0 | 25.6±4.6 |
| Albumin – g/L | 36.6±4.5 | 37.0±4.6 |
| Creatinin – mg/dL, pre-dialysis | 9.52±2.94 | 9.94±2.83 |
| Cholesterol – mg/dL | 142±35 | 142±41 |
| Prescribed medication – no. of patients (%) | | |
| Beta blocker | 184 (51) | 193 (55) |
| RAS inhibitor | 179 (50) | 170 (48) |
| Platelet aggregation inhibitor | 111 (34) | 127 (36) |
| 1-OH and 1,25-OH vitamin D | 227 (63) | 254 (72) |
| Statin | 198 (55) | 164 (46) |
| Erythropoiesis Stimulating Agents | 314 (88) | 319 (90) |

Plus-minus values are means ±SD. HDF denotes hemodiafiltration and HD hemodialysis; SGA = subjective global assessment; RAS = renin angiotensin system.
* residual kidney function if diuresis > 100 ml/24h
¥ mean of urea and creatinine clearance in 24h urine collection.

**Table 2.** Additional characteristics of participants at baseline.

| Variable | On-line HDF (n=358) | Low flux HD (n=356) |
|---|---|---|
| Primary renal diagnosis – no (%) | | |
| Renal vascular disease | 104 (29) | 96 (27) |
| Diabetes mellitus | 76 (21) | 60 (17) |
| Glomerulonephritis | 36 (10) | 53 (15) |
| Interstitial nephropathy | 35 (10) | 31 (9) |
| Cystic kidney disease | 27 (7) | 26 (7) |
| Multisystem disease | 15 (4) | 11 (3) |
| Other | 39 (11) | 45 (13) |
| Unknown | 26 (7) | 34 (9) |
| History of cardiovascular disease – no. (%) | 151 (42) | 162 (46) |
| Previous myocardial infarction | 42 (12) | 56 (16) |
| Previous PTCA or CABG | 58 (16) | 58 (16) |
| Previous stroke or TIA | 50 (14) | 59 (16) |
| Previous peripheral artery disease | 62 (17) | 50 (14) |
| Previous amputation | 17 (5) | 13 (4) |
| Medication (see also table 1) – no. (%) | | |
| Calcium antagonist | 109 (30) | 112 (31) |
| Insulin | 70 (20) | 52 (15) |
| Calcium containing phosphate binder | 142 (40) | 154 (43) |
| Sevelamer | 225 (63) | 221 (62) |
| Lanthanum carbonate | 20 (6) | 20 (6) |

HDF denotes hemodiafiltration and HD hemodialysis.

### Treatment characteristics and adherence

Treatment characteristics during the trial are shown in Table 3. During follow-up spKt/$V_{urea}$ increased in patients treated with hemodiafiltration (to 1.53; difference with hemodialysis 0.14, P<0.001). Treatment time increased from 227 to 229 minutes in the hemodialysis group and remained stable in patients treated with hemodiafiltration (226 min; P=0.03 for the difference between the treatment modalities).

As shown in Figure 1, beta-2-microglobulin levels decreased in patients treated with hemodiafiltration (from 30.7 to 26.4 g/L) and increased in hemodialysis patients (from 32.3 to 35.4 g/L; difference between treatment arms 8.9 g/L; P<0.001).

In patients randomized to hemodiafiltration, 2.67 of 2.98 (90%) treatments per week were actually delivered as online hemodiafiltration during the trial. The remaining treatments were delivered as high-flux hemodialysis. The average

convection volume, which includes weight loss, was 19.1 L per treatment session.

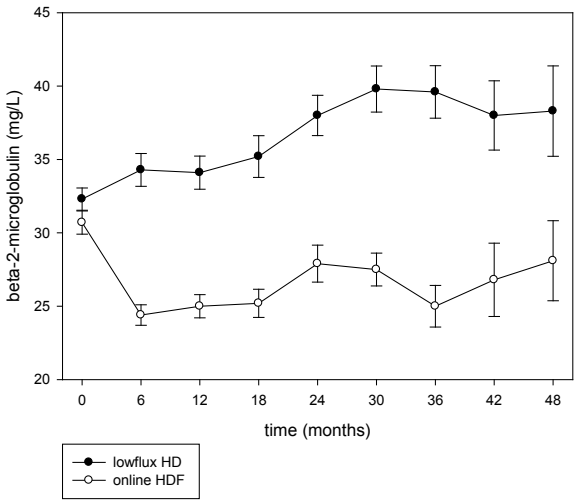
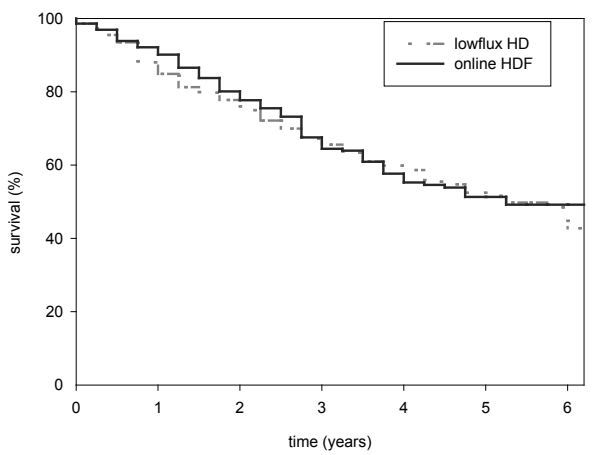



**Figure 1.** Predialysis beta-2-microglobulin levels in patients treated with online hemodiafiltration and low-flux hemodialysis (mean ± SE) using measurements of individuals at those time points.
The difference between beta-2-microglobulin levels for both treatments was significant ($p<0.001$).

A time to death from any cause




| patients at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HD | 356 | 337 | 307 | 269 | 230 | 201 | 169 | 140 | 102 | 83 | 65 | 52 | 32 |
| HDF | 358 | 346 | 324 | 287 | 237 | 203 | 160 | 131 | 103 | 77 | 57 | 44 | 18 |

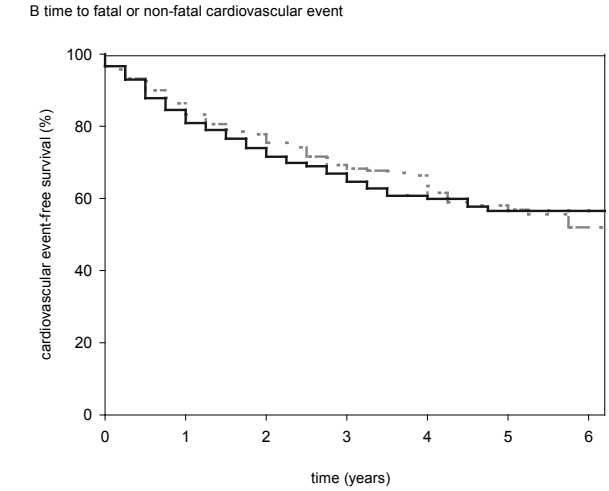



**Figure 2.** Kaplan-Meier curves for time to death from any cause (A) and for time to fatal or non-fatal cardiovascular event (B) based on life table analyses using 3 month time periods.

**Table 3.** Mean characteristics of treatment during follow-up

| | Online HDF | Low-flux HD | Mean difference (SE) | P value for difference |
|---|---|---|---|---|
| Duration of dialysis session – hours | 3.77 (0.01) | 3.81 (0.01) | 0.04 (0.02) | 0.032 |
| Blood flow – mL/min | 329 (4.7) | 310 (3.3) | 19 (5.7) | 0.001 |
| Number of sessions / week | 2.98 (0.01) | 2.96 (0.01) | 0.013 (0.02) | 0.40 |
| Online hemodiafiltration: | | | | |
| - number of sessions/week¥ | 2.67 (0.03) | n.a. | | |
| - convection volume – L/treatment | 19.1 (0.47) | n.a. | | |
| Single-pool Kt/$V_{urea}$ | 1.53 (0.02) | 1.40 (0.02) | 0.14 (0.03) | < 0.001 |
| Beta-2-microglobulin – mg/L | 26.4 (0.37) | 35.4 (0.54) | 8.9 (0.7) | < 0.001 |

Average levels during the trial and mean difference over time between treatment arms obtained through GEE analyses using the on trial measurements with adjustments for baseline measurements. Values are means (SE); n.a. = not applicable

¥ Actual number of sessions per week delivered as online hemodiafiltration during the trial, the other sessions were delivered as high-flux hemodialysis.

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**Primary outcome: all-cause mortality**

After a mean follow-up of 3.04 years (range 0.4 – 6.6 years), the accumulating results met the criterion specified by the sequential analysis plan for termination of the study, see figure 4. The incidence of all cause mortality was not affected by treatment assignment (121/1000 person-years on hemodiafiltration versus 127/1000 person-years on low-flux hemodialysis; [adjusted] hazard ratio 0.95; 95% confidence interval [CI] 0.75 to 1.20, Figure 2A. Both treatment groups had 1085 person-years of follow-up.

**Secondary outcomes**

The incidence of fatal and non-fatal cardiovascular events was 127/1000 person-years in hemodiafiltration patients versus 116/100 person-years in patients treated with low-flux hemodialysis (hazard ratio 1.07; 95% CI 0.83 to 1.39; Figure 2B). There were no significant differences between the two groups in the frequency and incidence of the other secondary cardiovascular endpoints (Table 4). The incidence of renal transplants was similar in both treatment groups.

**Interactions of treatment interventions with baseline factors**

Exploratory analyses for all-cause mortality and the combined fatal and non-fatal cardiovascular events were performed for various subgroups based on age, sex, diabetes, albumin ≤ 40g/L, residual kidney function, vascular access and dialysis vintage.

The hazard ratio for all-cause mortality during treatment with hemodiafiltration was 0.84 (95% CI 0.60 to 1.18) in patients with residual kidney function and 1.06 (95% CI 0.75 to 1.48) in patients without. Similarly, the hazard ratio's were not different between patients with a dialysis vintage above and below the median of 2.0 years (0.96 [95% CI 0.68 to 1.35] and 0.91 [95% CI 0.65 to 1.27], respectively). None of the P-values of the interaction terms was significant (all >0,10).

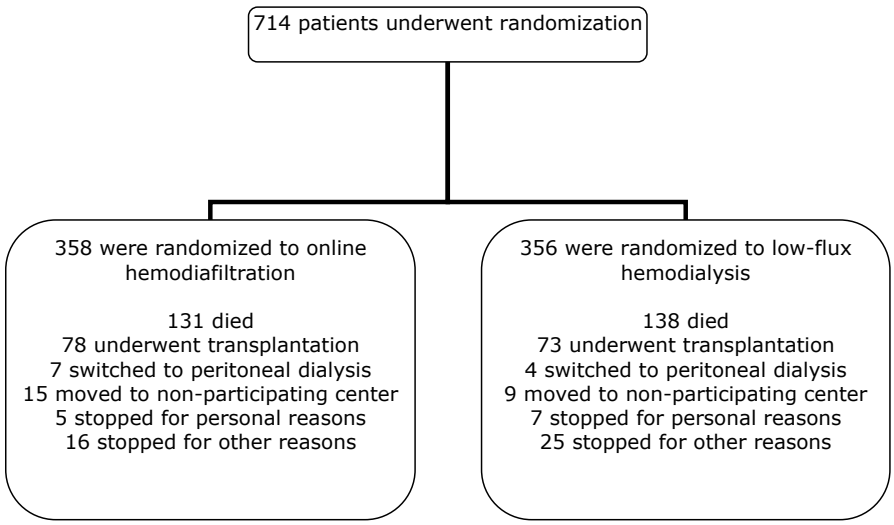


**Figure 3.** Enrolment, randomization, and follow-up of study participants.
For mortality and cardiovascular events, all patients were followed until the end of the study.

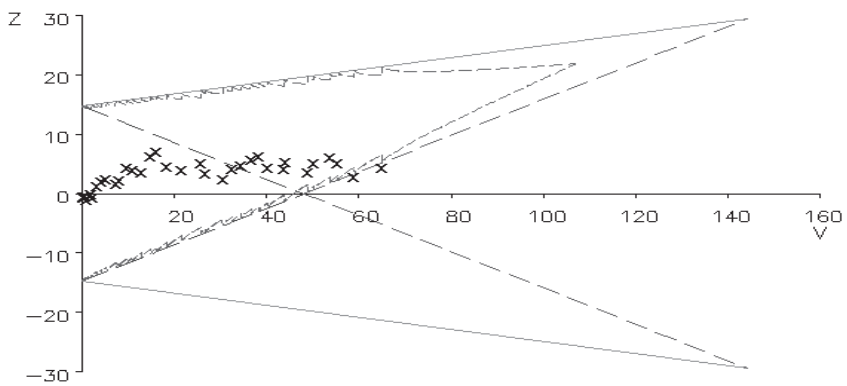


**Figure 4.** Sequential analysis.
Boundaries for double triangular test with $\alpha = 0.05$, power 0.80 and hazard ratio 0.75. Z is the observed number of events in the control group minus the expected number of events given treatment equivalence. V is approximately equal to a quarter of the number of events observed.

**Table 4.** Primary and secondary outcomes

| | Online HDF | | Low-flux HD | | Hazard ratio (95% CI)* |
|---|---|---|---|---|---|
| | Number of events | Person-years of follow-up | Number of events | Person-years of follow-up | |
| All-cause mortality | 131 | 1085 | 138 | 1085 | 0.95 (0.75-1.20) |
| ***Main secondary outcomes*** | | | | | |
| Fatal and non-fatal cardiovascular events | 116 | 916 | 112 | 964 | 1.07 (0.83-1.39) |
| Cardiovascular mortality | 37 | 1085 | 39 | 1085 | 0.80 (0.52-1.24) |
| Non-fatal cardiovascular disease (first event) | 94 | 915 | 87 | 964 | 1.12 (0.83-1.49) |
| Fatal and non-fatal CHD (MI, PTCA, CABG) | 38 | 1000 | 47 | 1022 | 0.81 (0.52-1.23) |
| Fatal and non-fatal stroke | 19 | 1066 | 16 | 1062 | 1.17 (0.60-2.27) |
| Amputation | 21 | 1058 | 16 | 1068 | 1.31 (0.68-2.51) |
| Sudden death | 21 | 1085 | 21 | 1085 | 1.00 (0.55-1.83) |
| Vascular intervention | 59 | 978 | 49 | 1010 | 1.23 (0.84-1.79) |
| Transplantation | 78 | 800 | 73 | 798 | 1.06 (0.77-1.46) |
| Hospital admissions due to infection | 130 | 800 | 110 | 798 | 1.21 (0.94-1.56) |

* obtained through unadjusted Cox proportional hazards models. CHD means coronary heart disease, MI = myocardial infarction, PTCA = percutaneous transluminar coronary angioplasty, CABG = coronary artery bypass graft.

### Convection volume and all cause mortality

The large variation in convection volumes between participating centres enabled an 'on treatment' exploration between the volume of convection and outcome. With respect to all cause mortality a significant inverse trend was observed (P=0.03), which remained after adjustment for potential confounders (see table 5). In the group of patients with the highest convection volume (upper tertile—>20.3L) mortality was considerably lower than in patients randomized to low-flux hemodialysis (hazard ratio 0.54, 95% CI 0.36 to 0.83). This finding remained statistically significant after adjustment for determinants of convection volume and mortality (hazard ratio 0.57, 95% CI 0.37 to 0.88). Correction for body weight, center, and beta-2-microglobulin did not materially alter these findings. A comparable tendency was observed for cardiovascular events (hazard ratio 0.67 95% CI 0.42 to 1.09), which did not reach statistical significance, Table 5.

**Table 5.** Risk of all-cause mortality and fatal and non-fatal cardiovascular events by achieved convection volume in liters per treatment (tertiles).

| | HD | Online HDF | | | |
|---|---|---|---|---|---|
| | | T1 | T2 | T3 | |
| Total mortality | | | | | P for trend |
| Crude | 1.0 | 0.98 (0.69-1.40) | 0.84 (0.57-1.22) | 0.54 (0.36-0.83) | 0.003 |
| Adjusted * | 1.0 | 0.86 (0.59-1.25) | 0.77 (0.52-1.15) | 0.57 (0.37-0.88) | 0.007 |
| Adjusted ** | 1.0 | 0.85 (0.56-1.27) | 0.85 (0.56-1.30) | 0.57 (0.36-0.91) | 0.013 |
| Adjusted *** | 1.0 | 0.89 (0.58-1.35) | 0.78 (0.60-1.47) | 0.63 (0.39-1.02) | 0.056 |
| Fatal and non-fatal CV events | | | | | |
| Crude | 1.0 | 1.30 (0.90-1.89) | 1.27 (0.72-1.58) | 0.77 (0.51-1.16) | 0.238 |
| Adjusted * | 1.0 | 1.31 (0.88-1.95) | 0.95 (0.63-1.43) | 0.72 (0.46-1.13) | 0.173 |
| Adjusted ** | 1.0 | 1.27 (0.83-1.96) | 1.08 (0.69-1.69) | 0.61 (0.38-0.98) | 0.263 |
| Adjusted *** | 1.0 | 1.39 (0.89-2.17) | 1.14 (0.71-1.83) | 0.67 (0.42-1.09) | 0.406 |

Results reported as hazard ratio and 95% confidence interval, from Cox proportional hazards models. Reference is treatment with low-flux hemodialysis (HD). HDF = hemodiafiltration, CV = cardiovascular. Convection volume tertile cutpoints: 15.5 L; 20.3 L.
* adjusted for determinants mortality, i.e age, gender, previous vascular disease, diabetes, previous transplanation, Kt/V, baseline eGFR, baseline albumin, baseline creatinin, baseline haematocrit, use of betablockers, calciumantagonists and angiontensin converting inhibitors at baseline (61 missings, 213 deaths, 185 cardiovascular events)
** like previous, plus adjustment for center differences (61 missings, 213 deaths, 185 cardiovascular events)
*** like previous, plus adjustment for baseline beta-2-microglobulin (110 missings, 198 deaths, 173 cardiovascular events)

## DISCUSSION

In the present study, chronic hemodialysis patients were randomized to treatment with online post-dilution hemodiafiltration or to continuation of low-flux hemodialysis. After a mean follow-up of 3.04 years, treatment with hemodiafiltration did neither result in a lower all-cause mortality nor in a beneficial effect on the composite endpoint of fatal and non-fatal cardiovascular events.

To the best of our knowledge, the present study is the first large scale randomized prospective trial comparing online hemodiafiltration with standard low-flux hemodialysis. Two earlier large randomized studies have addressed the hypothesis that removal of larger uremic toxins would improve survival probability. Both the Hemodialysis (HEMO) study and the Membrane Permeability Outcome (MPO) study compared low-flux hemodialysis with high-flux hemodialysis[22;23]. Neither study showed a difference in mortality risk between the treatment arms.

Convective transport, as quantified by a decrease in beta-2-microglobulin levels, is higher during hemodiafiltration than during high-flux hemodialysis and negligible during low-flux hemodialysis. In our study, the pre-dialysis beta-2-microglobulin levels in the hemodiafiltration group were consistently lower than those in hemodialysis patients. The difference in the present study was more than twice the difference between the high-flux and low-flux arms achieved in the MPO study[24]. Nonetheless, the main outcome of our study does not deviate from the results of both the HEMO and MPO study. Therefore, it appears that the addition of convective transport does not improve survival in chronic dialysis patients, at least not when the average convection volume is 19.1 liters per treatment.

Secondary analyses in the HEMO and MPO studies suggested a survival benefit of high-flux hemodialysis in patients with a dialysis vintage >3.7 years[25], patients with diabetes and patients with a serum albumin ≤40 g/L at baseline[26]. In our study, neither dialysis vintage, nor albumin levels had any influence on the effect of hemodiafiltration on outcome. In a previous analysis

of CONTRAST, we showed that the effect of online hemodiafiltration on beta-2-microglobulin levels was especially present in patients without residual kidney function[27]. However, neither residual kidney function, nor an analysis of other predefined subgroups, such as primary kidney disease, age, co-morbidity and gender modified the effect of treatment in our study.

The lack of an overall beneficial effect of hemodiafiltration on survival might be explained by several factors. First, the positive effect of an increased removal of uremic toxins might be counteracted by the simultaneous loss of essential substances[28], and/or undesirable side effects of the treatment itself [29]. Second, although the Kaplan-Meier curves did not even show a trend for a better outcome, the intervention period (mean 3.04 years) may have been too short for an effect on survival. Third, the positive effect of hemodiafiltration observed in observational studies might be due to the utilization of ultrapure dialysis fluids, which is mandatory for this treatment. The application of contaminated dialysis fluids during conventional hemodialysis might negatively influence patients health[30]. In our study, ultrapure dialysis fluid was used in both treatment arms. Finally, the average convection volume (19.1 L per treatment) was considerably below the target of 24 litres per treatment (6 L per hour). Only a third of the patients achieved a convection volume >20.3 litres.

As the achieved convection volumes showed a substantial range, the relation between convection volume and mortality could be explored. The “on treatment” analysis showed a significant inverse relation between achieved convection volume and mortality risk (P=0.03). Actually, the adjusted hazard ratio for all cause mortality was considerably lower in the group of patients treated with the highest convection volumes (> 20.3 liters, HR 0.56 [95% CI 0.34 to 0.93]) and of borderline significance for cardiovascular events (HR 0.61 [95% CI 0.36 to 1.05]). Although the finding of an association between convection “dose” and outcome is conceptually plausible and in agreement with observational data from the Dialysis Outcomes and Practices Pattern Study (DOPPS)[31], this finding requires further investigation. Very recently, data of another randomized trial comparing hemodialysis with and online hemodiafiltration were presented. In that trial, high convection volumes were associated with a significant survival

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benefit as well (48th Congress of the European Renal Association-European Dialysis Transplant Association, abstract LBCT2).

In DOPPS, a survival benefit was observed in patients with a substitution volume >15 L/session, which, however, did not include net ultrafiltration (i.e. desired weight loss) [32]. Published data linking convection volume to clinical outcome were lacking at the time the study was designed. Our target volume of 24 L/treatment was considered the maximum achievable dose in daily practice, and was merely based on manufacturer's guidelines. The finding that this volume is not achieved in the majority of patients, is a reflection of common practice and as such an important finding. In a previous analysis of CONTRAST, we showed that both the blood flow rate through the extracorporeal circuit and treatment time are potentially modifiable determinants of convection volume[33;34].

Apart from survival, other endpoints might be of relevance as well. Recently, it was shown in a randomized trial that the application of convective therapy was associated with substantial better intra-dialytic hemodynamic stability[35]. Other aspects include effects on quality of life, erythropoietin resistance, vascular stiffness, left ventricular mass, nutritional status and cost-utility[36;37]. All these issues are currently under investigation as predefined secondary endpoints of this study.

The strength of our study is its prospective randomized design and the accurate and concise data collection. The external validity of our study is supported by the fact that the variables age, gender and primary kidney disease of our patients are similar to those in all Dutch patients registered in the RENINE database (www.renine.nl). As this study is event driven, the number of events is sufficient for adequate and valid conclusions. A potential limitation is the inclusion of prevalent patients, as illustrated by a mean dialysis vintage of 2.9 years. Whether the inclusion of incident patients would have resulted in a different outcome cannot be concluded from the present study, although the interaction analysis did not show a different effect in patients with a low dialysis vintage. Finally, as the association between all-cause mortality and high-dose hemodiafiltration was found in an "on-treatment" analysis, this result should be interpreted with caution.

In conclusion, our study showed that treatment with online hemodiafiltration did not result in a reduced mortality or less fatal and non-fatal cardiovascular events as compared to treatment with low-flux hemodialysis. Subgroup analysis yielded no benefits of hemodiafiltration over hemodialysis in patients with diabetes, cardiovascular disease, long dialysis vintage, low albumin or lack of residual kidney function. On treatment analysis suggested a survival advantage in patients receiving the highest convection volumes. These data must be confirmed by other studies in progress[38;39] and/or by a meta-analysis of individual patient records from controlled clinical trials on this topic.

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# 9

# The cost-utility of hemodiafiltration versus hemodialysis in the Convective Transport Study (CONTRAST)

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Submitted for publication

## ABSTRACT

**Context.** Despite the growing interest in hemodiafiltration, there is no information on the costs and cost-utility of this dialysis modality yet.

**Objective.** To study the cost-utility of hemodiafiltration versus hemodialysis.

**Design, Setting and Patients.** Cost-utility analysis using a Markov model. It included data from the Convective Transport Study (CONTRAST), a randomized controlled trial that compared online hemodiafiltration with low-flux hemodialysis. Costs were estimated using a societal perspective. Probabilistic sensitivity analyses were performed to study uncertainty.

**Intervention.** Online hemodiafiltration versus low-flux hemodialysis.

**Main outcome measure.** Costs and quality-adjusted life-years (QALYs).

**Results.** Total annual costs for hemodiafiltration and hemodialysis were €90,921 ± 21,689 and €87,632 ± 17,249 respectively (in 2009 euros). When modeled over a 5-year period, the incremental cost per QALY of hemodiafiltration versus hemodialysis was €120,937. Sensitivity analyses revealed that this amount did not decrease, even under the most favorable assumptions.

**Conclusion.** Based on accepted societal willingness-to-pay thresholds, hemodiafiltration cannot be considered a cost-effective treatment for patients with end-stage renal disease. Apparently, minor additional costs of hemodiafiltration are not counterbalanced by a relevant QALY gain.

## INTRODUCTION

In-center hemodialysis (HD) is one of the most expensive chronic health care interventions. Indeed, the costs per quality-adjusted life year (QALY, a hypothetical year in optimal health) of HD have been recognized as a kind of benchmark for society's willingness to pay for medical technologies[1]. Both survival and quality of life are strongly impaired in patients with end-stage renal disease (ESRD)[2;3]. Their quality of life is for instance lower than in patients with respiratory or coronary disease, arthritis or metastatic colorectal cancer[4]. Dialysis therapies like peritoneal dialysis and home (nocturnal) HD are cost-effective compared to in-center HD[5-9]. A kidney transplantation is the most cost-effective treatment for patients with ESRD, but not all patients are able to undergo a transplantation and treatment availability is low due to a shortage in donor kidneys[9]. Furthermore, not all patients are able to undergo a transplantation[9]. Online hemodiafiltration (HDF) might be a cost-effective alternative to HD[10]. HDF combines diffusion with convection to enhance the clearance of middle molecules. Recently however, large randomized controlled trials revealed that there is no significant benefit in terms of survival associated with HDF[11;12]. Possibly, a positive effect in patient reported outcomes such as quality of life could tip the balance favorably. Conversely, the costs of HDF are also unclear. Accordingly, there is a strong need for an economical evaluation. We therefore aimed to assess the cost-effectiveness of HDF as compared to HD.

## METHODS

### Convective Transport Study (CONTRAST)

The present study was conducted in parallel with the Convective Transport Study (CONTRAST) [11;13]. CONTRAST is a randomized controlled trial that compared online post-dilution HDF with low-flux HD on all-cause mortality. It included 714 patients aged 18 years or above with ESRD undergoing chronic intermittent hemodialysis in twenty-nine dialysis centers located in

The Netherlands (n=26), Canada (n=2), and Norway (n=1). CONTRAST was approximately halfway when the cost-utility analysis started. This means that prospective data on both costs and quality of life were available in 409 of 714 patients. Written informed consent was obtained from all patients prior to randomization. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and was approved by a central and local medical ethics review boards. Detailed information on study design and conduct can be found elsewhere[11;14].

**Model**

The cost-utility of HDF versus HD was analyzed using a Markov model. Cost-utility was determined for three age categories: 18 to 44 years, 45 to 64 and 65 and older. The model included two health states, "ESRD" and "Death", with treatment dependent and independent parameters for costs, utilities and transition probabilities. A probabilistic sensitivity analyses were performed to include parameter uncertainty. A total of 1000 bootstrap replicates were obtained using Microsoft Office Excel 2003. Cycle duration was 3 months as follow-up data were available from the CONTRAST trial for these intervals. The time horizon of the model was 5 years and a sensitivity analysis was performed with a time horizon up to 10 years. In compliance with Dutch guidelines, a discount rate of 4% was applied for costs and 1.5% for outcome[15]. A second sensitivity analysis was performed to evaluate a uniform discount rate, namely 3% for both costs and outcome. Finally, as CONTRAST data suggested that HDF had a beneficial effect on survival if a high convection volume (>20.3 L) was provided[11], a third sensitivity analysis was performed using utility and transition probability measures of HDF patients with a high convection volume.

**Costs and utility**

The cost analysis was performed from a societal perspective. Costs were calculated per 3 months in 2009 euros (1 euro = 1.43 US dollars [2009 exchange rate]). If necessary, cost estimates were indexed to 2009 with the Dutch consumer price indices (http://statline.cbs.nl).

The cost analysis included direct healthcare costs as well as direct and indirect non-healthcare costs. Direct healthcare costs comprised dialysis and other medical staff, material (water installation, dialysis machines and disposables), vascular access, routine diagnostics of patients and dialysis water quality, meals during dialysis, hospitalization, medication and overhead. Direct non-health care costs comprised travel expenses and indirect non-healthcare costs included productivity losses. Productivity losses cover productivity loss with and without absence of paid work and substitution of unpaid, domestic work by family or home care. Dialysis staff involvement in relation to the number of patients was estimated with a cross-sectional analysis in 24 Dutch dialysis centers. A reference price per full-time equivalent for different job levels was obtained from the Dutch guideline for costing research[15]. Reference prices were also available for the visits to the outpatient department, general practitioner, paramedic, psychologist and complementary medicine. The number of patient visits to these health care workers was assessed prospectively with a 3 monthly patient questionnaire. Material costs were provided by a categorical (Dianet) and two university hospitals (University Medical Center Utrecht and VU medical center). The costs of vascular access was calculated as a weighted average of the costs for an arteriovenous fistula, graft or catheter using data from Wijnen et al[16] and Manns et al[17]. The frequency of microbiological and endotoxin testing of (ultra)pure water for dialysis is based on the guideline of the Dutch Nephrology Federation[18]. Prices were provided by the pharmacology department of the VU medical hospital. The frequency of the laboratory diagnostics is based on the guideline of the Dutch Nephrology Federation[19]; the frequency of other diagnostic procedures (chest X-rays and electrocardiograms) on a protocol from the University Medical Center Utrecht. Prices for these diagnostic procedures were obtained from the Dutch Diagnostic Compass issued by the Health Care Insurance Board[20]. The cost for meals during dialysis was estimated to be 200 euros per 3 months, based on 5 euros per meal and 3 dialysis sessions per week. The price of hospitalization is based on reference prices from the Dutch guideline for costing research[15]. Hospitalization and medication use was measured in CONTRAST patients and analyzed per age category. Medication

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use included anemia drugs, anticoagulants and antiplatelets, antihypertensive drugs, Cinacalcet, phosphate binders, Resonium, statins and vitamin D3. Prices were based on the Dutch Pharmacotherapeutical Compass from the Health Care Insurance Board (http://www.fk.cvz.nl/). The Pharmacotherapeutical Compass delivers prices per unit or per time period of standard use. As recommended by the Dutch guideline for costing research, overhead costs were calculated as a percentage (35.5%) of direct healthcare costs that did not yet include overhead[15]. Travel expenses were based on three weekly visits to a dialysis center, using the average distance to a Dutch hospital and reference prices per kilometer of taxi-use as available from the costing guideline[15]. Productivity loss was assessed with a modified version of the Short-Form Health and Labour Questionnaire and valued using the friction cost approach[21;22].
QALY's were calculated by multiplying utilities with survival. Quality of life was assessed 3 monthly with the EQ-5D, offering transfer of quality of life scores of patients to societal utilities for patients' health states using Dutch data[23;24].

## RESULTS

Table 1 depicts the costs of HDF and HD per 3 months in 2009 euros. A detailed description of the different cost units can be found in the appendix on page 223. Total annual costs for HDF and HD were €90,921 ± 21,689 (± SD) and €87,632 ± 17,249 respectively, based on measured costs per quarter. Overall, the higher costs for HDF as compared to HD could mainly be attributed to higher expenses for disposables and a more frequent control of water purity.
Patients participating in the cost-utility data collection were equal at baseline, except for a small but significant difference in spKt/V urea (HDF: 1.45 ± 0.25; HD: 1.39 ± 0.20; P=0.01).

Table 2 shows the utility of ESRD per age category while on HDF or HD, as well as the transition probabilities from ESRD to death per 3 months. Overall utility in patients on HDF was slightly higher as compared to HD and mortality was slightly lower. Table 3 shows the cost-utility of HDF and HD for a patient aged 45 to 65 years, when modeled over a period of 5 years. Over this period, the incremental costs per QALY of HDF versus HD were €120,937 and the incremental costs per life year gained were €192,221. The uncertainty associated with these figures is depicted in Figure 1: the cost-effectiveness plane of HDF versus HD. Figure 2 shows the cost-effectiveness acceptability curve (CEAC). It displays the probability of cost-effectiveness of HDF versus HD for different ceiling ratios, i.e. different thresholds society would be willing to pay for an additional QALY. Results show that only at ceiling ratios over €130,000 per QALY, the probability that HDF is more cost-effective compared to HD surpasses 50%. Based on the small difference in incremental effect, HDF would be cost-effective if its incremental annual cost was lower than €931 or €3,040, respectively based on the usual or upper limit of Dutch society's willingness-to-pay (i.e. €24.500 or €80.000 per QALY)[25].

In patients younger than 45, the incremental costs of HDF versus HD was €34,442 ± 30,587 (± SD) for 0.11 ± 0.33 additional QALYs. In this group, only at ceiling ratios of €350,000 and higher, HDF had a higher probability than HD to be cost-effective. In patients aged 65 and older, the incremental costs of HDF versus HD were €15,869 ± 17,682 for 0.03 ± 0.16 additional QALYs. In these patients, the probability of HDF being cost-effective compared to HD is unlikely, even at ceiling ratios as high as €350,000.

**Table 1.** The costs of hemodiafiltration and hemodialysis per 3 months in 2009 euros.

| | Hemodiafiltration | | Hemodialysis | |
|---|---|---|---|---|
| | Mean | Median | Mean | Median |
| **Direct healthcare costs** | | | | |
| Staff | | | | |
| Dialysis | 7,621 | | 7,621 | |
| Other medical[a] | 347 ± 297 | 188 (119 – 316) | 353 ± 312 | 185 (113 – 320) |
| Material | | | | |
| Water installation | 107 | | 107 | |
| Dialysis machine | 231 | | 231 | |
| Disposables | 2,552 | | 1,895 | |
| Vascular access[b] | 362 | | 362 | |
| Routine diagnostics | | | | |
| Purified water for dialysis | 77 | | 24 | |
| Dialysis patient[c] | 284 | | 284 | |
| Meals | 200 | | 200 | |
| Hospitalization | | | | |
| Overall | 1,566 ± 4,332 | 141 (0 – 1183) | 1,533 ± 3536 | 70 (0 – 1220) |
| Age <45 | 2,452 ± 8,912 | 288 (0 – 1,029) | 935 ± 2,456 | 120 (0 – 807) |
| Age 45 – 64 | 1,995 ± 4,669 | 494 (0 – 2,246) | 1,832 ± 3,311 | 466 (0 – 1,976) |
| Age ≥65 | 2,157 ± 3,898 | 793 (26 – 2,268) | 2,174 ± 4,453 | 795 (61 – 2,516) |
| Medication | | | | |
| Overall | 3,681 ± 1,428 | 3,449 (2,666 – 4,521) | 3,696 ± 1,462 | 3,477 (2,829 – 4,333) |
| Age <45 | 3,871 ± 1,715 | 3,467 (2,765 – 4,798) | 3,731 ± 1,041 | 3,352 (2,981 – 4,371) |
| Age 45 – 64 | 3,847 ± 1,478 | 3,680 (2,666 – 4,705) | 4,017 ± 1,732 | 3,890 (2,836 – 4,835) |
| Age ≥65 | 3,544 ± 1,322 | 3,287 (2,663 – 4,357) | 3,446 ± 1,259 | 3,295 (2,736 – 3,964) |
| Overhead[d] | 4,059 | | 3,807 | |
| **Direct non-healthcare costs** | | | | |
| Travel expenses | 1,365 | | 1,365 | |

| | | | | |
|---|---|---|---|---|
| **Indirect non-healthcare costs** | | | | |
| Productivity loss[e] | 225 ± 1,140 | 0 (0 – 0) | 270 ± 1,064 | 0 (0 – 0) |
| **Total** | | | | |
| Per 3 months | 22,730 ± 5,422 | 21,343 (20,042 – 23,333) | 21,908 ± 4,312 | 20,611 (19,584 – 22,934) |
| Per year | 90,921 ± 21,689 | 85,371 (80,168 – 93,332) | 87,632 ± 17,249 | 82,444 (78,335 – 91,737) |

Costs are depicted as means ± standard deviation and as medians (interquartile range) if available. Most distributions were left-skewed.
1 euro = 1.43 US dollars (2009 exchange rate)
[a] Includes visits to the medical specialist, general practitioner, paramedic, psychologist and alternative healers.
[b] Based on a weighted average of the costs for an arteriovenous fistula, graft or catheter[16;17].
[c] Includes laboratory analyses, electrocardiogram and chest X-ray.
[d] Calculated as a percentage (35.5%) of direct healthcare costs that did not yet include overhead.
[e] Includes productivity loss with and without absence of paid work and substitution of unpaid, domestic work by family or home care.

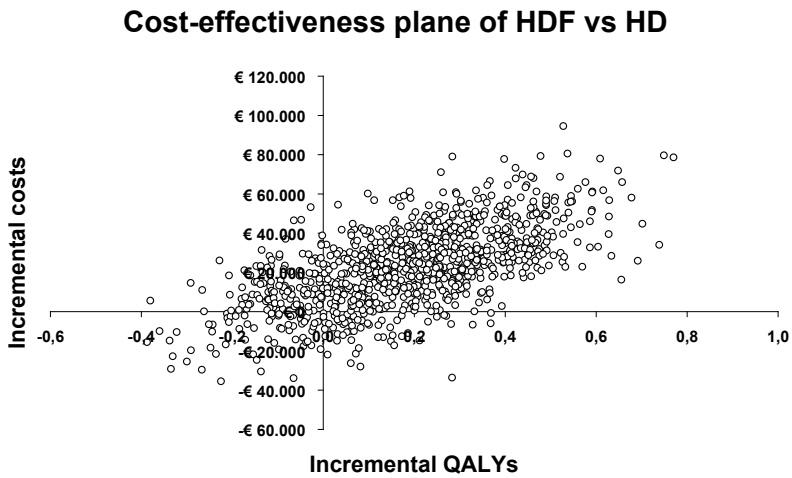


**Figure 1.** Cost-effectiveness plane of hemodiafiltration versus hemodialysis.
The figure shows the cost-utility of hemodiafiltration versus hemodialysis as modeled with 1000 bootstrap replicates for 1000 patients aged 45 to 65 over a 5 year time period. Each dot represents the average for 1000 patients. Whereas sometimes hemodiafiltration is both cheaper and less effective than hemodialysis (the dots in the left lower quadrant), most often hemodiafiltration is more expensive and more effective (the dots in the right upper quadrant).
HDF: hemodiafiltration; HD: hemodialysis; QALY: quality-adjusted life-year.

**Table 2.** Utility and transition probability for death on hemodiafiltration and hemodialysis.

| | Hemodiafiltration | Hemodialysis |
|---|---|---|
| **Utility** | | |
| Overall | 0.74 ± 0.01 | 0.73 ± 0.02 |
| Age <45 | 0.81 ± 0.04 | 0.77 ± 0.06 |
| Age 45 – 64 | 0.76 ± 0.02 | 0.73 ± 0.02 |
| Age ≥65 | 0.72 ± 0.02 | 0.72 ± 0.02 |
| **Transition probability for death per 3 months** | | |
| Overall | 0.0297 ± 0.0026 | 0.0315 ± 0.0027 |
| Age <45 | 0.0044 ± 0.0025 | 0.0019 ± 0.0019 |
| Age 45 – 64 | 0.0192 ± 0.0035 | 0.0221 ± 0.0035 |
| Age ≥65 | 0.0456 ± 0.0047 | 0.0479 ± 0.0050 |

Depicted are means ± standard error.

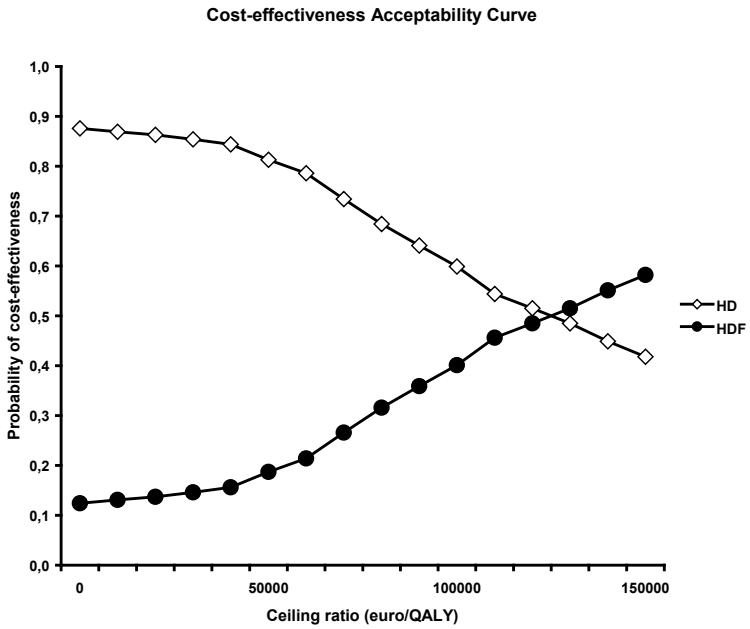


**Figure 2.** Cost-effectiveness acceptability curve of hemodiafiltration versus hemodialysis. This figure shows the probability that HDF or HD is the most cost-effective treatment for different ceiling ratios in patients aged 45 to 64. A ceiling ratio is the price society is willing to pay for a quality-adjusted life year. Overall HDF is more costly and more effective than HD, which means that if the ceiling ratio increases, the probability that HDF becomes the most effective treatment increases.
HDF: hemodiafiltration; HD: hemodialysis; QALY: quality-adjusted life-year.

**Table 3.** Hemodiafiltration and hemodialysis: modelled costs, quality-adjusted life years and survival over 5 years.

| | Hemodiafiltration | Hemodialysis | Hemodiafiltration versus hemodialysis |
|---|---|---|---|
| **Costs (€)** | 348,007 ± 14,886 | 324,972 ± 13,008 | 23,034 ± 20,174 |
| **QALYs** | 3.00 ± 0.14 | 2.82 ± 0.14 | 0.19 ± 0.20 |
| **Life years** | 4.11 ± 0.15 | 3.99 ± 0.14 | 0.12 ± 0.21 |

Depicted are means ± standard deviation based on a patient aged 45 to 65.
The third column shows the incremental cost and effectiveness of hemodiafiltration versus hemodialysis.
QALY: quality-adjusted life year

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**Sensitivity analyses**

For patients aged 45 to 65, three sensitivity analyses were performed. First, if a time horizon of 10 instead of 5 years was applied, the incremental cost for HDF versus HD was €27,064 ± 6,374 with 0,14 ± 0,11 additional QALYs. The probability that HDF would be cost-effective compared to HD surpassed 50% at ceiling ratios above €200,000 per QALY.

Second, a uniform discount rate of 3% for both costs and outcome, resulted in an incremental cost of €18,004 ± 7,545 while on HDF for 0.06 ± 0.07 extra QALYs. The probability of HDF being more cost-effective than HD was higher only at ceiling ratios above €320,000 per QALY.

Third, if only HDF utilities and transition probabilities for patients with a high convection volume (>20.3L) were applied (overall utility: 0.75 ± 0.02 [± SE], overall mortality probability: 0.0217 ± 0.0039 [± SE]), the additional costs of HDF resulted in 0.33 ± 0.16 (± SD) extra QALYs. In this scenario analysis, at a ceiling ratio starting from €130,000 per QALY, HDF is expected to be more cost-effective than HD.

## DISCUSSION

This study showed that, even though the additional costs of HDF seem minor when compared to HD, they are not outweighed by the limited QALY gain. Elaborate sensitivity analyses revealed that society should be willing to pay €120,000 to €350,000 per additional QALY for HDF to become cost-effective compared to HD. These figures by far exceed currently accepted thresholds. In the Netherlands, the average willingness to pay is €24,500 per QALY with a suggested upper limit of €80,000[25]. In the United Kingdom, this threshold is £20,000-£30,000 per QALY and in the United States $50,000-$100,000[26]. Thus HDF exceeds society's willingness to pay for health, even more so because the cost-effectiveness is assessed in comparison with (i.e. investments on top of) a treatment that already is considered to be of borderline cost-effectiveness[1].

The relatively small additional costs of HDF could mainly be attributed to higher expenses for disposables and a more frequent control of dialysis

water purity. In our study all dialysis centers already used ultrapure dialysis fluids for both HDF and HD as recommended, so no additional investments in water purification were required to commence with online HDF. The price of disposables is often open for negotiations with suppliers / manufacturers. Bearing this in mind, HDF could become within currently accepted standards for cost-effectiveness when its incremental costs compared to HD would be below €931 to €3,040. A relatively frequent control of ultrapure water is prescribed in the Netherlands[18]. A less strict regime as recommended by the International Organization for Standardization (ISO)[27], does however not lower HDF costs significantly: €66 per 3 months instead of €77 for the control of purified water. Hence, this would hardly influence the unfavorable incremental cost-effectiveness of HDF compared to HD.

To our knowledge, this study is the first to evaluate the cost-utility of HDF. We furthermore provide an update on the cost-utility of HD from a societal perspective. The last detailed cost-analysis of HD in the Netherlands was published in 1997 by de Wit et al[6]. Converted to 2009 euros, their estimate of prevalent HD cost per year was €85,031, which is comparable to our results (€87,632). This indicates that there were no relevant changes in HD costs between 1997 and 2009. To provide an international reference with regard to recent cost estimates on HD, Table 4 presents the cost data of five recent international cost analyses. Table 5 furthermore provides a reference with regard to international cost-utility estimates of HD. Unfortunately, a strict comparison is hampered due to different viewpoints and cost allocation methods.

Our model has limitations. First, due to selection criteria and repeated measurements, patients in a randomized clinical trial might be healthier and subjected to a higher level of care as compared to patients in general. Whereas this might influence the generalizability of data, it is unlikely to influence the cost-utility of HDF versus HD. Second, as explained in the methods section, the prospective analysis of costs and utility started when the main trial, CONTRAST, was approximately halfway. Participating HDF and HD patients may therefore not be viewed as a random sample as they already survived

up until that time. However, there was only a small difference between HDF and HD participants, namely in Kt/V. As the HEMO study did not find a clear effect of Kt/V on quality of life or survival[28;29] it can be excluded as a potential confounder. The comparison therefore remains valid. Finally, patients and health care professionals could not be blinded for allocation of treatment, which might induce a placebo effect. If any, this might have a positive effect on utility measures in HDF patients.

In conclusion, HDF is not a more cost-effective option to treat ESRD patients than HD. Although the additional costs of hemodiafiltration were limited, they were not compensated for by its marginal positive effect on utility. HDF could become cost-effective when its incremental costs compared to HD will be lowered to a maximum of €3,040.

**Table 4.** The cost of hemodialysis in recent international literature.

| Study | Viewpoint | Country | Price reference year | Cost per year | Cost in 2009 euros | |
|---|---|---|---|---|---|---|
| | | | | | Exchange rate | Power parity[30] |
| Baboolal et al[31] | Service provider | United Kingdom | 2008? | £35,023 | €37,211 | €46,868 |
| Villa et al[32] | Public administration | Spain | 2010 | €37,968 | €37,491[b] | €43,709 |
| Haller et al[9] | Healthcare? | Austria | 2008? | €40,600[a] | €41,087[b] | €40,773 |
| USRDS[2] | Healthcare | United States | 2008 | $77,506 | €56,352 | €66,328 |
| **Mazairac et al** | **Society** | **The Netherlands** | **2009** | **€87,632** | - | - |
| Harris et al[33] | Society | Australia | 2008 | $AU 202,124[c] | €100,893 | €116,947 |
| | | | | $AU 215,354[d] | €107,496 | €124,601 |

USRDS: United States Renal Data System.
[a] Costs for hemodialysis beyond 25 months.
[b] Only adjusted for difference in pricing year using the consumer price index (http://statline.cbs.nl/statweb/)
[c] Patients with a late start of dialysis: estimated glomerular filtration rate of 5-7 mL/min/1.73m$^2$
[d] Patients with an early start of dialysis: estimated glomerular filtration rate of 10-14 mL/min/1.73m$^2$

**Table 5.** The cost-utility of hemodialysis in international literature.

| Study | Viewpoint | Country | Price reference year | Cost per QALY | Cost in 2009 euros | |
|---|---|---|---|---|---|---|
| | | | | | Exchange rate | Power parity[30] |
| McFarlane et al[7] | Healthcare | Canada | 2000-2001 | $CAN 125,845 | €105,183[b] | €109,789[b] |
| **Mazairac et al** | **Society** | **The Netherlands** | **2009** | **€114,335** | - | - |
| Gonzalez-Perez et al[8] | Healthcare | United Kingdom | 2001-2002 | £65,817[c] | €115,566[d] | €105,988[d] |
| Lee et al[1] | Healthcare | United States | 1996-2003 | $129,090 | €118,484[a] | €131,367[a] |
| Harris et al[33] | Society | Australia | 2008 | $AU 405,224[e] | €202,272 | €234,458 |
| | | | | $AU 453,665[f] | €226,452 | €262,485 |

QALY: quality-adjusted life-year.
[a] When the year 2003 is regarded as the price reference year.
[b] When the year 2001 is regarded as the price reference year.
[c] Based on £22.246 per year for 1.69 quality-adjusted life years during 5 years of follow-up.
[d] When the year 2002 is regarded as the price reference year.
[e] Patients with a late start of dialysis: estimated glomerular filtration rate of 5-7 mL/min/1.73m$^2$. Based on $AU 202,124 per year for 2.07 quality-adjusted life years during 4.15 years of follow-up.
[f] Patients with an early start of dialysis: estimated glomerular filtration rate of 10-14 mL/min/1.73m$^2$. Based on $AU 215,354 per year for 1.97 quality-adjusted life years during 4.15 years of follow-up.

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# 10

# General discussion

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The main objective of this thesis was to study costs and outcomes in patients on hemodialysis and hemodiafiltration. The first part of this discussion reflects on outcome in hemodialysis patients, the second part evaluates if online hemodiafiltration leads to a preferable outcome and at what cost.

**Quality of life in hemodialysis patients: in pursuit of optimal patient care.**
It is fortunate that **chapter 2** showed quality of life (QoL) improvement over time, as this outcome is strongly affected in hemodialysis patients in general[1]. However, we demonstrated that physical domains of patients' QoL stayed behind over time compared to mental domains of QoL. Interestingly, **chapter 3** showed that the physical composite score in hemodialysis patients is one of the QoL domains that differed between dialysis centers. This variation indicates room for improvement, at least in some dialysis centers. Based on the results of **chapter 4** however, one can conclude that there are no clear parameters that can guide clinicians to improve patients' QoL. This is an urgent problem, especially because patients value QoL over survival[2]. **Chapter 5** showed the value of protein-energy nutritional status with regard to QoL. However, when one evaluates different composite scores of this entity, it has no better prediction of outcome than its individual components (**chapter 6**).
End-stage renal disease is an illness for which there is no cure. Treatment is palliative, not curative. Hence, an emphasis needs to be placed on optimal patient care. To achieve this, one first needs to realize what optimal patient care actually is. If one tries to reason from the patients' wishes, what do they ordinary wish for? In ancient Egypt, one already had the blessing:


meaning "life, prosperity, health"[3]. Or in later days, "Live and be prosperous", as phrased by Romeo in a play by Shakespeare[4]. People do not only strive to have a long live, they foremost wish it to be pleasant. Optimal patient care includes both survival and QoL, but clinicians usually focus on the first. In patients on hemodialysis however, not only survival is poor. As shown in this thesis, physical QoL is more than a standard deviation below

average. For instance, hemodialysis patients' QoL is lower than in patients with respiratory or coronary disease, arthritis or metastatic colorectal cancer[5]. Patients on hemodialysis face not only the symptoms of end-stage renal disease, but also the demands of an intensive treatment. Over 50% is bothered by fatigue, itching, and muscle cramps[6]. For in-center hemodialysis treatment, patients are required to visit the clinic 3 times per week, 4 hours per day. And after such a dialysis session, patients need about 7 hours to recover[7]. Finally, between all these hours of treatment and recovery, patients need to abide by strict rules on the intake of fluids and food. This not only places a burden on patients, but also on their families and friends.

Realizing the purpose and necessity of optimizing patient care, the next question is how it can be delivered. To improve survival, clinical performance targets are used. These performance targets however do not suffice to improve QoL, as this thesis has shown. One could state that current clinical performance targets contribute to adequate dialysis care, but not to optimal patient care. Hence, there is a need for parameters that may guide clinicians in improving the QoL of their patients. A composite score of protein-energy nutritional status was explored in this thesis, but did not show a surplus value. It is a challenge to devise meaningful target parameters, as QoL is a complex, multidimensional entity that includes physical, mental and social domains[8]. Indeed, clinical factors only explain patients' QoL to a limited extent[9]. To bridge the gap towards meaningful parameters, QoL questionnaires are a valid instrument to gain insight in patients' perceptions. Awareness of these perceptions is key to engage in optimal patient care. Besides the identification of preferences and potential problems, QoL measures can be used to facilitate communications, prioritize problems and monitor changes[10]. Gut-feeling with regard to patients' QoL will not suffice, as there is a discrepancy between clinicians' perceptions of patients' QoL and the perceptions of patients themselves[11]. Subsequently, it seems logic to address the multidimensional challenges of QoL in a multidisciplinary way. Whereas clinicians are guided by clinical parameters, social workers may act on social domains and psychologists or psychiatrists on mental domains. A multidisciplinary group can provide a care strategy that

is both broad and patient-specific, as such a team will not only focus on a clinical approach, but may also implement psychosocial or psychoeducational strategies. Ideally, such care strategies include the patients' environment. Social support has been shown to be a relevant determinant of outcome[12;13]. Again, diagnosis of patients' needs and perceptions remains a prerequisite and it is provided for by the regular use of a validated QoL questionnaire[14]. The acquired data gained by routine measure of patients' QoL and a subsequent discussion in multidisciplinary groups, may stimulate effective care strategies and clinical research towards meaningful performance targets. QoL has been related to compliance, hospitalization and mortality[15-17]. Positive results of a multidisciplinary approach on QoL have been shown in chronic diseases like lower back pain and congestive heart failure[18;19].

The ideal approach to maintain an optimal QoL would off course be to prevent the decline of kidney function and subsequent occurrence of kidney failure. Once the damage is done and patients have end-stage renal disease, a donor kidney is the best treatment available[20-24]. Unfortunately, not all patients are eligible for a kidney transplantation and availability is hampered due to the shortage in donor kidneys. This thesis evaluated hemodiafiltration as an alternative for hemodialysis and its potential is discussed in the second part of this chapter.

**Hemodiafiltration: value for money?**

Hemodiafiltration improves the clearance of middle molecules as compared to hemodialysis[25] and the CONvective TRAnsport STudy (CONTRAST) was developed to evaluate if this leads to an improved outcome in patients with end-stage renal disease[26]. **Chapter 7** indicated that online hemodiafiltration had no effect on QoL as compared to low-flux hemodialysis.

**Chapter 8** showed that the same holds true for survival, except for a possible positive effect of hemodiafiltration in patients who reach a convection volume of more than 20.3L per session. In **chapter 9** it was concluded that based on accepted societal willingness-to-pay thresholds, hemodiafiltration cannot be considered a cost-effective treatment. Although the additional cost of

hemodiafiltration was relatively minor as compared to hemodialysis, it was not counterbalanced by a relevant gain in quality-adjusted life-years (QALY, a hypothetical year in optimal health).

The hypothesis of CONTRAST was that online hemodiafiltration, due to an improved clearance of middle molecular weight substances and so an improved correction of the uremic environment, would decrease cardiovascular damage and thus cardiovascular morbidity and mortality as compared to low-flux hemodialysis[26]. We were able to demonstrate that this is not the case. It is however of interest to further explore the possible dose-response relation between convection volume and all-cause mortality. One should note that the positive effect of a convection volume >20.3 L per session on mortality was shown in an on-treatment analysis of a non-predefined subgroup, implying susceptibility to confounding and multiple testing. Nevertheless, the results of another recent large trial on hemodiafiltration also showed a potential benefit of a high convection volume[27]. Data of both cohorts should be pooled to explore its potential benefit with greater power. Still, this thesis additionally showed that hemodiafiltration is not cost-effective at present cost levels, not even in the subgroup that attained a convection volume of >20.3 L. Although the additional costs of hemodiafiltration are just a few percent compared to hemodialysis, the limited incremental effect is too small to make hemodiafiltration cost-effective. Perhaps incremental costs may be reduced in the future, but due to its small additional value, it will still be a challenge for hemodiafiltration to comply with accepted willingness-to-pay for QALY ratios. In the Netherlands, society is willing to pay €24,500 per QALY with a suggested upper limit of €80,000[28]. In the United Kingdom, this threshold is £20,000-£30,000 per QALY and in the United States $50,000-$100,000[29]. The additional costs of hemodiafiltration versus hemodialysis should than drop below €931 to be cost-effective, or below €3,040 if the suggested upper limit of €80.000 per QALY is used. So do we put a price tag on patients' lives or is only the best good enough, no matter at what cost? Let us explore the latter option. What are the consequences? An example may improve insight in the subject. In 1975, Neuhauser et al[30] evaluated the cost-effectiveness of a faeces

screening regimen for colon cancer in the United States. One really wanted to be sure that no cases were missed, so it was decided that only if 6 sequential stool tests were negative, colon cancer could be ruled out. Neuhauser et al studied the incremental cost-effectiveness of these faeces tests. With 6 stool tests total cost per diagnosis was $176,331. Cost-effectiveness however focuses on the incremental cost-effectiveness and it turned out that the marginal cost per discovered malignancy for the fourth, fifth and sixth stool test was respectively $469,534, $4,724,695 and $47,102,214. So with regard to the sixth stool test, 47 million dollar was needed for a single diagnosis of colon cancer. Both the patient and the treating physician will be glad that colon cancer was diagnosed timely enough to start treatment as a consequence of the screening programme. However, when viewed from a societal perspective, one may wonder if 47 million in healthcare can not be allocated more effectively. Actually, the real cost of any treatment is not the money one has to pay for it, but the value of benefits achievable by another treatment that has been forgone by committing the resources in question to the first treatment[31]. As resources are not infinite, decisions need to be made. If we consider the present evidence regarding hemodiafiltration, we have to conclude it is not cost-effective as compared to hemodialysis. This especially holds true given the fact that our comparator treatment, hemodialysis, with annual treatment costs of €87,632, is already at the far end of societal willingness-to-pay for a QALY[32]. At current price levels, hemodiafiltration further adds to the costs of treatment, without considerable improvements in survival and QoL of patients. Perhaps its surplus costs compared to hemodialysis might decline in the future, but otherwise alternative cost-effective treatments should be pursued. Frequent hemodialysis has a positive effect on both survival en QoL[33], but just like hemodiafiltration it will need a cost reduction to become cost-effective in comparison with traditional hemodialysis[34]. The results for home (nocturnal) dialysis are promising[35;36], but not all patients are eligible to dialyse at home or at night. In years or decades to come, future research will tell if a wearable artificial kidney or even an implantable bioartificial kidney can provide value for money[37;38].

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## Conclusions

To provide optimal patient care in hemodialysis patients, one should strive for both survival and QoL improvement. As there are no clinical meaningful target parameters for the latter, patients' QoL should be routinely measured with a valid questionnaire. This may provide multidisciplinary teams with insight in patient preferences to facilitate current and future care.

To improve care, there may be a clinical advantage of hemodiafiltration as compared to hemodialysis in patients that attain >20.3L of convection volume. However, hemodiafiltration is not cost-effective. Perhaps the surplus costs of hemodiafiltration can be reduced in the future; otherwise cost-effective alternatives for traditional in-center hemodialysis should be pursued.

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## Summary

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**Chapter 1. Introduction.**

Patients with end-stage renal disease can only stay alive with a renal replacement therapy like hemodialysis, peritoneal dialysis or a kidney transplantation. In 2010 approximately 14,690 patients received renal replacement therapy: 5,155 received hemodialysis, 1,137 peritoneal dialysis and 8,398 had a donor kidney.

The quality of life (QoL) of patients on hemodialysis is poor. Patients are not only faced with the symptoms of their disease, but also with a demanding therapy. Patients that receive in-center hemodialysis are connected to a dialysis machine for approximately 3 times per week, 4 hours per day. Excess fluid and toxins are then removed from the blood. Hemodiafiltration is a relatively new variant. This modality improves the clearance of certain toxins, which could have a positive effect on QoL and survival in patients with end-stage renal disease. Earlier studies indeed showed a positive effect of hemodiafiltration on survival, but the results on QoL vary. These studies however had limitations in their design, like a small population or a non-randomized setting. The Convective Transport Study (CONTRAST) was designed as a large randomized trial that could assess the effect of hemodiafiltration as compared to hemodialysis on all-cause mortality and cardiovascular events. 714 Patients participated in 29 dialysis centers in the Netherlands, Norway and Canada. The mean follow-up was 3 years and measurements were performed every 3 months by study nurses. Every year, patients were asked to complete a QoL questionnaire. Besides an evaluation of the effectiveness of hemodiafiltration and hemodialysis, another goal of this thesis was to assess costs of both therapies and combine data on costs and effectiveness in a cost-effectiveness analysis.

**Chapter 2. Changes in quality of life over time – Dutch hemodialysis patients and general population compared.**

Clinical care for hemodialysis patients has improved over time which resulted in a lower mortality. It was however unclear of patients' QoL improved accordingly. To evaluate this, patients' QoL in 2006, as measured in CONTRAST, was compared with patients' QoL in 1995, as measured in the

Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD). In 2006 hemodialysis patients had a higher vitality, less pain, less emotional discomfort and a higher emotional well-being as compared to 1995. The improvement in vitality could partially be explained by a higher hemoglobin level. This study furthermore corrected for concurrent changes in the general population, as improvements in hemodialysis patients' QoL might as well be the result of a general improved well-being. After correcting for these autonomous changes the improvement in patients' QoL decreased, but remained clinical relevant regarding the reduction in pain and emotional discomfort.

**Chapter 3. Differences in quality of life of hemodialysis patients between dialysis centers.**

Most patients on hemodialysis are dialyzed in a center. Several studies have evaluated the relation between clinical variables and QoL, but there is a paucity of information on the role of the dialysis center. In chapter 3 it was shown that there are relevant differences in QoL between dialysis centers, i.e. in the summary score for physical QoL, 'quality of social interaction' and 'dialysis staff encouragement'. This latter domain has been related to compliance. The difference in QoL between centers suggests a room for improvement in some clinics. This study furthermore showed that patients that undergo dialysis in an academic center have a worse QoL than in a general hospital. Patients in a satellite hospital have a better QoL than in a general hospital. It might be reasoned that these latter findings are based on patient selection, which should be a subject of future research.

**Chapter 4. Clinical performance targets and quality of life in hemodialysis patients.**

In hemodialysis, clinical performance targets are used to guide clinicians in providing an adequate treatment. There is however limited scientific evidence on targets used. It is even unclear if attainment of existing targets is related to hemodialysis patients' QoL. In chapter 4, this relationship was studied. Six clinical performance targets, as recommended by the Kidney Disease Outcomes

Quality Initiative (KDOQI), were evaluated: spKt/V (≥1.2), hemoglobin (11 to 13 g/dL), vascular access (arteriovenous fistula), phosphorus (2.3 to 4.5 mg/dL), parathyroid hormone (150-300 pg/mL), and blood pressure (predialysis <140/90 mm Hg and postdialysis <130/80 mm Hg). We were not able to demonstrate any association between these clinical performance targets and QoL. Future research should identify targets that do show a relation. Or, to provide treating physicians with insight in the status and development of patients' QoL over time, it should be measured in a routine fashion using validated QoL questionnaires.

**Chapter 5. Protein-energy nutritional status and kidney disease-specific quality of life in hemodialysis patients.**

Protein-energy wasting is a recently new definition that describes a state of decreased body stores of protein and fat masses. Chapter 5 showed that there is a clear relation between protein-energy nutritional status and disease-specific QoL. In a relatively well-nourished dialysis population, multiple nutritional parameters were not only related to general QoL domains, but also to domains like 'Effects of renal disease on daily life' and the 'Burden of kidney disease'. This underlines the importance of an optimal protein-energy nutritional status in hemodialysis patients and of future research to improve it.

**Chapter 6. A composite score on protein-energy nutritional status predicts mortality in hemodialysis patients no better than its individual components.**

Protein-energy nutritional status needs to be measured with multiple nutritional parameters. When its definition was introduced, the question was posed which composite score could best predict mortality in dialysis patients. In this chapter, various scores were evaluated. It showed that a composite score based on albumin, BMI, creatinine and the nPNA (normalized Nitrogen Appearance, a variable which is closely correlated with protein intake in stable dialysis patients) yielded the strongest relation with mortality. However, some of the individual parameters of the score, notably albumin and creatinine, were

related to mortality with similar strength and magnitude. This questions the clinical value of the proposed diagnostic criteria for protein-energy wasting with regard to mortality. Future studies should evaluate if a composite score with other, less readily available nutritional parameters has a superior relation to mortality.

**Chapter 7. The effect of hemodiafiltration on quality of life over time.**

This chapter evaluated the effect of hemodiafiltration on the QoL of hemodialysis patients. There was a non-significant, opposed trend regarding the effect of hemodiafiltration on two QoL domains: a beneficial effect on the QoL domain 'Effects of kidney disease on daily life' and a detrimental effect on the summary score of mental health. Subgroup analyses did not show a significant effect of hemodiafiltration. In conclusion, the results from CONTRAST, the first large, randomized controlled trial comparing the effect of hemodiafiltration versus hemodialysis on QoL, showed that hemodiafiltration had no effect on this outcome.

**Chapter 8. The effect of online hemodiafiltration compared with low-flux hemodialysis on all-cause mortality and cardiovascular events: a randomized controlled trial.**

**The CONvective TRansport STudy (CONTRAST).**

This chapter describes the results of hemodiafiltration on mortality, the primary end point of CONTRAST. It showed that online hemodiafiltration, as compared to low-flux hemodialysis, did not improve survival. Hemodiafiltration also had no effect on cardiovascular events.

On-treatment subgroup analysis however suggested a survival benefit in patients receiving high-volume hemodiafiltration (>20.3L). This volume, called "convection volume", is the amount of liters of purified water that the patient on hemodiafiltration receives during a dialysis session. It compensates for the fluid that is removed to clean the blood and so gives an indication of the amount of therapy received. Future studies must confirm this potential dose-effect response.

**Chapter 9. The cost-utility of hemodiafiltration versus hemodialysis.**

In health care, resources are scarce which means that difficult choices need to be made on its allocation. If a new therapy is more expensive then a comparator therapy, one should evaluate if these surplus costs are proportional to a beneficial effect. Chapter 9 describes such an economic evaluation of hemodiafiltration versus hemodialysis. Total annual costs for hemodiafiltration and hemodialysis were €90,921 and €87,632 respectively. Despite this relatively small difference in costs, hemodiafiltration was not cost-effective if compared to hemodialysis: its positive effect was too small. Effect in cost-utility analyses is expressed in quality-adjusted life-years (QALY, a hypothetical year in optimal health). Even if the positive effect in the subgroup of patients that received high-volume hemodiafiltration was taken into account, the resulting QALYs were too small to predict that hemodiafiltration will be cost-effective as compared to hemodialysis. The incremental costs per QALY were €120,937 whereas Dutch society is merely willing to pay €24,500 per QALY with a suggested upper limit of €80,000. Due to the small differences in effect of hemodiafiltration compared to standard hemodialysis, it will only become cost-effective if its surplus costs are reduced to €931 (or €3,040 in case of the suggested upper limit).

**Chapter 10. Discussion.**

To provide optimal patient care in hemodialysis patients, one should strive for both survival and QoL improvement. As there are no clinical meaningful target parameters for the latter, patients' QoL should be routinely measured with a valid questionnaire. This may provide multidisciplinary teams with insight in patient preferences to facilitate current and future care.

To improve care, there may be a clinical advantage of hemodiafiltration as compared to hemodialysis in patients that attain >20.3L of convection volume. However, hemodiafiltration is not cost-effective at current price levels. Perhaps the surplus costs of hemodiafiltration can be reduced in the future; otherwise cost-effective alternatives for traditional in-center hemodialysis should be pursued.

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## Samenvatting

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**Hoofdstuk 1. Inleiding.**

Patiënten met terminaal nierfalen kunnen alleen in leven blijven met een nierfunctievervangende therapie zoals hemodialyse, peritoneale dialyse of niertransplantatie. In 2010 werden in totaal 14.690 patiënten met een dergelijke therapie behandeld: 5.155 met hemodialyse, 1.137 met peritoneale dialyse en 8.398 hadden een donornier.

De kwaliteit van leven (KvL) van hemodialysepatiënten is sterk aangetast. Patiënten lijden niet alleen onder de symptomen van hun nierziekte, maar ook onder een veeleisende therapie. Bij hemodialyse in een dialysecentrum dient de patiënt circa 3 keer per week 4 uur verbonden te zijn met een dialyseapparaat. Het bloed van de patiënt wordt hierbij gezuiverd van overtollig vocht en afvalstoffen. Een relatief nieuwe variant van hemodialyse is hemodiafiltratie. Deze methode zorgt voor een betere verwijdering van bepaalde afvalstoffen. Dit zou een positief effect kunnen hebben op de KvL en overleving van patiënten met nierfalen. Bestaande studies tonen een mogelijk gunstig effect op overleving, maar wat betreft KvL zijn de resultaten wisselend. Deze onderzoeken hadden echter beperkingen in hun studieopzet, bijvoorbeeld kleine populaties of een niet gerandomiseerde onderzoekssetting. De Convectieve Transport Studie (CONTRAST) is opgezet als een grote gerandomiseerde studie waarmee een betere uitspraak over de effectiviteit van hemodiafiltratie kan worden gedaan. Hierbij werden patiënten geloot voor behandeling met hemodiafiltratie of hemodialyse. Uiteindelijk namen 714 patiënten deel in 29 dialysecentra in Nederland, Noorwegen en Canada. De patiënten werden gemiddeld 3 jaar gevolgd waarbij elke drie maanden metingen werden verricht door studieverpleegkundigen. Daarbij kregen ze één keer per jaar een KvL vragenlijst voorgelegd. Naast een evaluatie van de effectiviteit van hemodiafiltratie en hemodialyse, was het tevens het doel van dit proefschrift om de kosten van beide therapieën in kaart te brengen en deze tegen de effecten uit te zetten.

**Hoofdstuk 2. Veranderingen in kwaliteit van leven in de tijd – een vergelijking tussen Nederlandse hemodialysepatiënten en de algemene bevolking.**

In de loop der jaren is de klinische zorg voor hemodialysepatiënten verbeterd wat heeft geleid tot een lagere sterfte. Het was echter onduidelijk of de KvL van hemodialysepatiënten er eveneens op vooruit was gegaan. Om dit na te gaan werd de KvL van patiënten uit 2006, zoals gemeten in de CONTRAST studie, vergeleken met de KvL van patiënten uit 1995 in de Nederlandse Coöperatieve Studie naar de Adequaatheid van Dialyse (NECOSAD). In 2006 voelden patiënten zich vitaler, hadden ze minder pijnklachten, minder emotionele hinder en een hoger emotioneel welbevinden dan in 1995. De verbetering in de vitaliteit bleek hierbij deels te kunnen worden verklaard door het hogere hemoglobinegehalte van patiënten. In deze studie werd verder gecorrigeerd voor gelijktijdige veranderingen in de KvL in de algemene bevolking. Mogelijk waren de verbeteringen in de KvL van hemodialysepatiënten namelijk toe te wijzen aan een verbeterd algemeen welbevinden. Na correcties voor deze autonome ontwikkelingen namen de verbeteringen in de KvL van hemodialysepatiënten af, maar bleven ze klinisch relevant wat betreft de verminderde pijnklachten en emotionele hinder.

**Hoofdstuk 3. Verschillen in kwaliteit van leven van hemodialysepatiënten tussen dialysecentra.**

De meeste hemodialysepatiënten ondergaan hun dialyse in een dialysecentrum. In het verleden zijn verschillende onderzoeken gedaan naar de relatie tussen klinische factoren en KvL, maar de rol van het centrum is hierbij onderbelicht gebleven. Uit hoofdstuk 3 kwam naar voren dat er relevante verschillen bestaan in de KvL tussen de dialysecentra, namelijk in de samenvattende score voor fysieke KvL, 'kwaliteit van sociale interactie' en 'aanmoediging door dialyse personeel'. Dit laatste aspect is eerder gerelateerd aan therapietrouw. Het verschil in KvL tussen de centra suggereert dat er in sommige klinieken ruimte is voor verbetering. Verder kwam bij dit onderzoek naar voren dat patiënten in academische centra een slechtere KvL hebben

dan patiënten in streekziekenhuizen. In zelfstandige dialyseklinieken hadden hemodialysepatiënten een betere KvL dan in streekziekenhuizen. Het is aannemelijk dat dit berust op patiëntselectie, maar dat dient vervolgonderzoek uit te wijzen.

**Hoofdstuk 4. Klinische behandeldoelen en kwaliteit van leven in hemodialysepatiënten.**

In de kliniek worden behandeldoelen gebruikt. Men gaat ervan uit dat de behandeling adequaat is indien deze behandeldoelen worden gehaald. Het wetenschappelijk bewijs voor deze aanname is echter beperkt. Het was zelfs onduidelijk of het behalen van bestaande behandeldoelen is gerelateerd aan de KvL van hemodialysepatiënten. In hoofdstuk 4 werd deze relatie geanalyseerd. Zes internationaal toegepaste behandeldoelen zoals geadviseerd door het Amerikaanse 'Kidney Disease Outcomes Quality Initiative' (KDOQI) kwamen aan bod: spKt/V (≥1.2), hemoglobine (11-13 g/dL), vaattoegang (fistel), fosfaatgehalte (2.3-4.5 mg/dL), parathyroïd hormoon (150-300 pg/ml) en bloeddruk (voor dialyse <140/90 mmHg en na dialyse <130/80). Er blijkt geen relatie te zijn tussen deze klinische behandeldoelen en KvL. Toekomstig onderzoek dient behandeldoelen te identificeren die wel gerelateerd zijn aan KvL. Beter nog, om clinici inzicht te verschaffen in de status en ontwikkeling van de KvL van hun patiënten zouden er regulier KvL bepalingen moeten plaatsvinden.

**Hoofdstuk 5. Eiwitenergie voedingsstatus en de ziektespecifieke kwaliteit van leven van hemodialysepatiënten.**

"Eiwitenergie voedingsstatus" is een relatief nieuwe definitie van de voedingsstatus in dialysepatiënten. Hierbij wordt specifiek gekeken naar de eiwit- en energiereserves van de patiënt. Uit hoofdstuk 5 kwam naar voren dat er een duidelijke relatie bestaat tussen eiwitenergie voedingsstatus en ziektespecifieke KvL. In een relatief goed gevoede dialysepopulatie waren meerdere voedingsparameters niet alleen gerelateerd aan algemene KvL domeinen, maar ook aan het 'Effect van de nierziekte op het dagelijks leven'

en het KvL domein 'Last van de nierziekte'. Dit benadrukt het belang van een optimale eiwitenergie voedingsstatus in hemodialysepatiënten alsmede van onderzoek naar de mogelijke verbetering hiervan.

**Hoofdstuk 6. Een samengestelde score van eiwitenergie voedingsstatus voorspelt sterfte in hemodialysepatiënten niet beter dan de individuele componenten van die score.**

Eiwitenergie voedingsstatus dient gemeten te worden met meerdere voedingsparameters. Bij de definitie van de term 'eiwitenergie voedingsstatus' werd de vraag gesteld welke combinatie van de verschillende parameters het beste inzicht geeft in het overlijdensrisico van dialysepatiënten. In dit hoofdstuk werden diverse scoresystemen geëvalueerd. Het bleek dat een score met streefwaarden van albumine, body mass index (BMI), creatinine en nPNA ('normalized Protein Nitrogen Appearance', een factor die bij stabiele patiënten samenhangt met de eiwitinname) het sterkst samenhing met sterfte. Echter, dit scoresysteem leverde geen betere predictie op dan albumine of creatinine alleen. Aangaande de kans op overlijden is het dus de vraag hoe klinisch relevant de definitie van eiwitenergie voedingsstatus is. Toekomstig onderzoek moet uitwijzen of scoresystemen in andere dialysepopulaties of met minder eenvoudig beschikbare voedingsparameters een betere voorspelling geven.

**Hoofdstuk 7. Het effect van hemodiafiltratie op kwaliteit van leven.**

In dit hoofdstuk werd geëvalueerd of hemodiafiltratie in vergelijking met hemodialyse een positief effect heeft op de KvL van patiënten met nierfalen. Bij twee KvL domeinen was een niet significante trend waarneembaar voor een tegengesteld effect, namelijk een gunstig effect van hemodiafiltratie op het domein 'Effecten van de nierziekte op het dagelijks leven' en een ongunstig effect op de samenvattende score voor mentale gezondheid. Uit subgroepanalyses ook kwam geen significant effect van hemodiafiltratie naar voren. Kortom, uit CONTRAST, de eerste grote klinische trial waarin het effect van hemodiafiltratie op KvL werd beschreven, blijkt dat deze behandeling in vergelijking met hemodialyse geen effect heeft op deze uitkomstmaat.

**Hoofdstuk 8. Het effect van online hemodiafiltration in vergelijking met low-flux hemodialyse op sterfte en cardiovasculaire aandoeningen: een gerandomiseerde, gecontroleerde trial. De Convectieve Transport Studie (CONTRAST).**

Dit hoofdstuk beschrijft het resultaat van hemodiafiltratie op overleving, de primaire uitkomstmaat van CONTRAST. Online hemodiafiltratie bleek in vergelijking met low-flux hemodialyse de overleving van patiënten met nierfalen niet te verbeteren. Het had eveneens geen effect op het optreden van cardiovasculaire aandoeningen. Subgroepanalyses gaven aan dat hemodiafiltratie mogelijk wel de kans op overlijden verkleind bij een hoog convectievolume (>20,3L). "Convectievolume" is het aantal liters gezuiverd water dat de hemodiafiltratiepatiënt ontvangt gedurende de behandeling. Het convectievolume compenseert het vocht dat tijdens de behandeling uit het bloed van de patiënt wordt verwijderd en geeft zodoende een indicatie van de hoeveelheid ontvangen therapie (indien meer "verontreinigd" vocht aan de patiënt wordt onttrokken moet ook meer vocht worden gesubstitueerd). Toekomstig onderzoek moet de waarde van deze mogelijke dosis-effectrelatie uitwijzen.

**Hoofdstuk 9. De kosten-utiliteit van hemodiafiltratie versus hemodialyse.**

Door een gebrek aan middelen in de gezondheidszorg dienen vaak lastige keuzes te worden gemaakt over de toewijzing van budgetten. Als een nieuwe therapie duurder is, dient daarom te worden nagegaan of deze extra kosten opwegen tegen mogelijke verbeteringen in de effectiviteit van de nieuwe therapie. Hoofdstuk 9 beschrijft een economische evaluatie van hemodiafiltratie en hemodialyse. De totale jaarlijkse kosten van hemodiafiltratie en hemodialyse waren respectievelijk €90.921 en €87.632. Ondanks dit relatief kleine prijsverschil was hemodiafiltratie in vergelijking met hemodialyse niet kosteneffectief: het positieve effect van hemodiafiltratie was te klein. Het effect wordt bij een kosteneffectiviteitanalyse uitgedrukt in "kwaliteitsjaren", een hypothetisch jaar in optimale gezondheid. Zelfs indien rekening werd gehouden met het positieve effect in de subgroep van patiënten die hoog-volume hemodiafiltratie ontvingen, leverde dit te weinig extra

kwaliteitsjaren in vergelijking met hemodialyse voor kosten-effectiviteit. De extra kosten van hemodiafiltratie per kwaliteitsjaar waren namelijk €120.937, terwijl de maatschappij maar €24.500 per extra kwaliteitsjaar wil betalen waarbij €80.000 is gesuggereerd als limiet. Vanwege het minimale verschil in effect met hemodialyse kan hemodiafiltratie pas kosteneffectief worden indien de meerkosten ervan ten opzichte van hemodialyse worden gereduceerd naar €931 (of €3.040 indien men uitgaat van wat de maatschappij maximaal wil betalen).

**Hoofdstuk 10. Discussie**

Indien men hemodialysepatiënten optimaal wil behandelen, moet men streven naar zowel een langer levensduur als een betere KvL. Aangezien er ter behoeve van KvL geen klinisch relevante behandeldoelen bestaan, zou de KvL van patiënten routineus gemeten dienen te worden met een valide vragenlijst. Het aldus verkregen inzicht kan door multidisciplinaire teams worden gebruikt om de huidige en toekomstige zorg te verbeteren.

Om de zorg te verbeteren, is er in vergelijking met hemodialyse mogelijk een positief effect van hemodiafiltratie in patiënten die >20,3L convectievolume per sessie halen. Hemodiafiltratie is echter niet kosteneffectief bij huidige prijsniveaus. Eventueel kunnen de meerkosten van hemodiafiltratie worden verkleind, maar anders moeten alternatieven voor de traditionele centrumhemodialyse worden nagestreefd die wel kosten-effectief zijn, bijvoorbeeld thuis- of nachtelijke dialyse.

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# 11

# Appendix I: CONTRAST Investigators

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**Canada:** Georges-L Dumont Regional Hospital, Moncton – M Dorval; CHUM St Luc Hospital, Montréal – R Lévesque; **The Netherlands:** Academic Medical Center, Amsterdam – MG Koopman; Catharina Hospital, Eindhoven – CJAM Konings; Dialysis Clinic Noord, Beilen – WP Haanstra; Dianet Dialysis Centers, Utrecht – M Kooistra and B van Jaarsveld; Fransiscus Hospital, Roosendaal – T Noordzij; Gelderse Vallei Hospital, Ede – GW Feith; Haga Hospital, The Hague – M van Buren; Isala Clinics, Zwolle – JJG Offerman; Jeroen Bosch Hospital, 's Hertogenbosch – EK Hoogeveen; Maasland Hospital, Sittard – F de Heer; Maasstad Hospital, Rotterdam – PJ van de Ven; Martini Hospital, Groningen – TK Kremer Hovinga; Medical Center Alkmaar, Alkmaar – WA Bax; Onze Lieve Vrouwe Gasthuis, Amsterdam – JO Groeneveld; Oosterschelde Hospital, Goes – ATJ Lavrijssen; Rijnland Hospital, Leiderdorp – AM Schrander-Van der Meer; Rijnstate Hospital, Arnhem – LJM Reichert; Slingeland Hospital, Doetinchem – J Huussen; St Elisabeth Hospital, Tilburg – PL Rensma; St Fransiscus Gasthuis, Rotterdam – Y Schrama; University Medical Center St Radboud, Nijmegen – HW van Hamersvelt; University Medical Center Utrecht, Utrecht – WH Boer; VieCuri Medical Center, Venlo – WH van Kuijk; VU University Medical Center, Amsterdam – MG Vervloet; Zeeuws-Vlaanderen Hospital, Terneuzen – IMPMJ Wauters. **Norway:** Haukeland University Hospital, Bergen – I Sekse.

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# 11

## Appendix II:
## KDQOL-SF, the kidney disease-specific scales

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**Table 1.** The Kidney Disease Quality of Life – Short Form (KDQOL-SF): the kidney disease-specific scales.

| Domains | Meaning | |
|---|---|---|
| | Low | High |
| Symptom / problem list | Extremely bothered by dialysis-related symptoms such as muscle cramps, pruritus, anorexia and/or access problems | Not at all bothered |
| Effect of kidney disease on daily life | Extremely bothered by fluid and dietary restriction, by an inability to travel and dependency on doctors | Not at all bothered |
| Burden of kidney disease | Extremely bothered by the time consumed by dialysis, its intrusiveness and degree burden on family | Not at all bothered |
| Work status | Unemployed due to health | Employed, health not an issue |
| Cognitive function | Affected all of the time by inability to concentrate, confused with poor reaction time | Not at all affected |
| Quality of social interaction | Continual irritation and failure to get along with people with virtual isolation | No problem, socially interactive |
| Sexual function | Experiencing severe problems with enjoyment and arousal | No problems |
| Sleep | Very poor sleep with day time somnolence | No problem with sleep |
| Social support | Very dissatisfied | Satisfied with level of social support |
| Dialysis staff encouragement | High perceived encouragement and support | Low perceived encouragement and support |
| Overall health | Rates health as worst possible | Rates health as best possible |
| Patient satisfaction | Very poor | The best |

Modified from: Carmichael P, Popoola J, John I, Stevens PE, Carmichael AR. Assessment of quality of life in a single centre dialysis population using the KDQOL-SF questionnaire. *Qual Life Res* 2000; 9: 195-205



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# 11

# Appendix III: Results cost study hemodialysis and hemodiafiltration

**Table 1.** Dialysis staff costs per 3 months in 2009 euros for hemodiafiltration and hemodialysis.

| Health care professional | FTE per patient[a] | Salary[b] | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Academic per month | General per month | Additional costs (%) | | Total per month | Total per patient | |
| | | | | Premium | Other[c] | | Per month | Per 3 months |
| **Nephrologist** | 0.040 | 12,576 | 12,772 | n/a[b] | n/a[b] | 12,751.61 | 510.02 | 1,530.07 |
| **Nurse** | 0.399 | 2,815 | 2,840 | 10 | 39 | 4,338.16 | 1,731.79 | 5,195.37 |
| **Dietician** | 0.012 | 2,815 | 2,840 | n/a | 39 | 3,943.78 | 48.51 | 145.53 |
| **Social Worker** | 0.020 | 3,106 | 3,199 | n/a | 39 | 4,432.39 | 88.65 | 265.94 |
| **Technician** | 0.027 | 2,815 | 2,840 | 10 | 39 | 4,338.16 | 118.31 | 354.94 |
| **Secretary** | 0.015 | 2,101 | 2,063 | n/a | 39 | 2,873.38 | 43.10 | 129.30 |
| **Total** | | | | | | | | 7,621.16 |

FTE: full-time equivalent; Academic: academic hospital; General: general hospital.
[a] Mean FTE per patient on hemodialysis and hemodiafiltration as measured in 24 Dutch dialysis centers for the nephrologists, nurses, dieticians and social workers. The FTE of the secretary and technician was based on one center.
[b] The salary of the nephrologist was based on the Dutch costing guideline[1] and already includes additional costs. Other salaries were based on salary scales in job advertisements. Wages of academic and general hospitals were averaged based on the rate of 11% of Dutch patients who dialyzed in academic centers versus 89% in general hospitals.
[c] Holiday pay, social insurance, etcetera.

**Table 2.** Costs of other medical staff per 3 months in 2009 euros.

| Health care provider | Costs per visit (€)[a] | Hemodiafiltration | | | Hemodialysis | | |
|---|---|---|---|---|---|---|---|
| | | Visits (N) | Cost (€) | | Visits (N) | Cost (€) | |
| | | | Median | Mean | | Median | Mean |
| General practitioner | 28 | 0.1 (0.0 – 0.6) | 3.5 (0.0 – 17.5) | 14.6 ± 25.7 | 0.1 (0.0 – 0.7) | 3.3 (0.0 – 18.7) | 14.4 ± 26.4 |
| Medical specialist | 71[b] | 2.0 (1.4 – 3.0) | 142.0 (101.2 – 213.0) | 190.2 ± 160.7 | 2.0 (1.0 – 3.0) | 142.0 (71.0 – 213.0) | 177.1 ± 169.9 |
| Paramedic | 34[c] | 0.0 (0.0 -0.5) | 0.0 (0.0 – 17.0) | 32.2 ± 87.6 | 0.0 (0.0 – 0.6) | 0.0 (0.0 – 19.2) | 48.5 ± 139.2 |
| Psychologist, etc. | 87[d] | 0.0 (0.0 – 0.0) | 0.0 (0.0 – 0.0) | 8.6 ± 44.3 | 0.0 (0.0 – 0.0) | 0.0 (0.0 – 0.0) | 16.3 ± 105.7 |
| Alternative healer | 34[e] | 0.0 (0.0 – 0.0) | 0.0 (0.0 – 0.0) | 2.0 ± 16.2 | 0.0 (0.0 – 0.0) | 0.0 (0.0 – 0.0) | 1.0 ± 6.0 |
| **Total** | | | 188.2 (118.9 – 315.5) | 346.5 ± 297.2 | | 184.6 (112.6 – 320.4) | 353.0 ± 311.9 |

Costs are depicted as medians (interquartile range) or means ± standard deviation. Distributions were left skewed.
The number of visits was assessed with a patient questionnaire.
[a] Based on the Dutch guideline for cost research[1].
[b] The cost of a visit to the medical specialist in an academic and general hospital (€129 and €64 respectively) was averaged based on the rate of 11% of Dutch patients who dialyzed in academic centers versus 89% in general hospitals.
[c] Average of the costs for a visit to the physiotherapist, physical therapist, occupation therapist and speech therapist.
[d] Average of the costs of the visit to a psychologist and psychiatrist.
[e] The same costs were taken as for a paramedic, as no clear data was available.

**Table 3.** Costs of the water purification installation per patient per 3 months in 2009 euros.

| Dialysis center | Purchase (€) | Maintenance | Number of dialysis per year | Cost per dialysis (€) | Cost per 3 months[b] (€) |
|---|---|---|---|---|---|
| Dianet Utrecht | 250,000 | 10,493 | 13,000 | 2.73 | 106.48 |
| UMCU | 135,000 | Unknown | 7,000 | 2.74[a] | 106.78 |
| **Average** | | | | | 106.63 |

UMCU: University Medical Center Utrecht
[a] Maintenance costs of the UMCU were estimated using Dianet Utrecht as a reference.
[b] Based on 3 dialyses per week.

**Table 4.** Costs of dialysis machines per patient per 3 months in 2009 euros.

| Dialysis center | Purchase (€) | Number of machines | Number of dialysis per year | Cost per dialysis (€) | Cost per 3 months[a] (€) |
|---|---|---|---|---|---|
| Dianet Utrecht | 23,000 | 30 | 13,000 | 5.31 | 207.00 |
| UMCU | 23,000 | 20 | 7,000 | 6.57 | 256.29 |
| **Average** | | | | | 231.64 |

UMCU: University Medical Center Utrecht
[a] Based on 3 dialyses per week.

**Table 5.** Cost dialysis disposables per patient per 3 months in euros.

| Dialysis center | Treatment | Disposables type[a] | | Total | |
|---|---|---|---|---|---|
| | | Direct | Additional | Per dialysis | Per 3 months[b] |
| Dianet Utrecht | Hemodialysis | 31.99 | 18.58 | 50.57 | 1,972.25 |
| | Hemodiafiltration | 42.69 | 19.90 | 62.52 | 2,438.37 |
| VUmc | Hemodialysis | 28.00 | [c] | 46.59[d] | 1,816.84 |
| | Hemodiafiltration | 48.44 | [c] | 68.28[d] | 2,665.41 |
| **Average** | Hemodialysis | 30.00 | 18.58 | 48.58 | 1,894.54 |
| | Hemodiafiltration | 45.57 | 19.90 | 65.43 | 2,551.89 |

VUmc: Vu medical center, Amsterdam.
[a] Direct disposables include the artificial kidney and blood lines. Additional disposables include supporting material like disinfectant, bandages and clamps.
[b] Based on 3 dialyses per week.
[c] Unknown.
[d] Cost of additional disposables in the VUmc were estimated using the costs of Dianet Utrecht as a reference.

**Table 6.** Costs of vascular access per patient per 3 months.

| | Number (%) of patients in CONTRAST at baseline | Cost (€) | | | |
|---|---|---|---|---|---|
| | | Per vascular access | | Average | |
| | | Annual | Per 3 months | Annual | Per 3 months |
| **AVF** | 567 (80) | 847.15 | 211.79 | 677.72 | 169.43 |
| **AVG** | 97 (14) | 2,592.32 | 648.08 | 362.93 | 90.73 |
| **Catheter** | 46 (6) | 6,832.05 | 1,708.01 | 409.92 | 102.48 |
| **Overall** | | | | 1,450.57 | **362.64** |

CONTRAST: Convective Transport Study; AVF: arteriovenous fistula; AVG: arteriovenous graft.
Costs are based on data from Wijnen et al[2] and Manns et al[3].
[a] The so called share in costs for vascular access was based on the percentage of vascular access types in patients under study.

**Table 7.** Costs of purified water control per patient per 3 months in 2009 euros.

| | Frequency per 3 months[a] | | Per test[b] | Cost (€) Per 3 months[c] | |
|---|---|---|---|---|---|
| | HDF | HD | | HDF | HD |
| **Bacterial count and endotoxins** | 1.29 | 0.41 | 59.46 | 76,75 | 24,14 |
| **Total organic carbon** | 0.01 | 0.01 | 34.67 | 0,17 | 0,17 |
| **Total** | | | | **76.93** | **24.32** |

HDF: hemodiafiltration, HD: hemodialysis
[a] Control frequencies are based on the guideline of the Dutch Nephrology Federation[4].
[b] Prices were provided by the pharmacology department of the VU medical center in Amsterdam.
[c] Costs per patient per 3 months were based on the average of 55 patients per center in the Netherlands and 3 patients per dialysis machine.

**Table 8.** Cost of routine diagnostics in the dialysis department per 3 months.

| Test | Frequency[a] | Price (€) | | Cost 2009 (€) |
|---|---|---|---|---|
| | | 2003 | 2009 | |
| **Laboratory analysis** | | | | |
| - Sodium | 6 | 1.41 | 1.55 | 9.30 |
| - Potassium | 6 | 1.41 | 1.55 | 9.30 |
| - Urea | 6 | 1.41 | 1.55 | 9.30 |
| - Creatinin | 3 | 1.41 | 1.55 | 4.65 |
| - Calcium | 3 | 5.55 | 6.09 | 18.27 |
| - Phosphate | 3 | 1.41 | 1.55 | 4.65 |
| - Hemoglobin | 3 | 11.08 | 12.17 | 36.51 |
| - Bicarbonate[b] | 3 | 1.41 | 1.55 | 4.65 |
| - Residual renal function | 1 | 6.60 | 7.25 | 7.25 |
| - Kt/V[c] | 1 | 1.41 | 1.55 | 1.55 |
| - Alkaline phosphatase | 1 | 1.41 | 1.55 | 1.55 |
| - GGT | 1 | 1.41 | 1.55 | 1.55 |
| - PTH | 1 | 8.31 | 9.12 | 9.12 |
| - Albumin | 1 | 1.41 | 1.55 | 1.55 |
| - HbA1c | 1 | 6.65 | 7.30 | 7.30 |
| - Glucose | 1 | 1.41 | 1.55 | 1.55 |
| - Ferritin | 1 | 8.31 | 9.12 | 9.12 |
| - Transferrin saturation | 1 | 5.55 | 6.09 | 6.09 |
| - CRP | 1 | 3.88 | 4.26 | 4.26 |
| - Platelets | 1 | 1.41 | 1.55 | 1.55 |
| - White blood cell count | 1 | 1.41 | 1.55 | 1.55 |
| - Bilirubin | 0.5 | 1.41 | 1.55 | 0.78 |
| - ALT | 0.5 | 1.41 | 1.55 | 0.78 |
| - AST | 0.5 | 1.41 | 1.55 | 0.78 |
| - HbsAg | 0.5 | 11.83 | 12.99 | 6.50 |
| - Hepatitis B antibody titre | 0.5 | 13.67 | 15.01 | 7.51 |
| - Cholesterol | 0.5 | 1.41 | 1.55 | 0.78 |
| - HIV antibodies | 0.25 | 13.67 | 15.01 | 3.75 |
| - Hepatitis C antibodies | 0.25 | 9.66 | 10.61 | 2.65 |
| - HDL-cholesterol | 0.25 | 2.77 | 3.04 | 0.76 |
| - LDL-cholesterol | 0.25 | 6.07 | 6.66 | 1.67 |
| - Triglycerides | 0.25 | 1.89 | 2.08 | 0.52 |
| Laboratory order tariff | 6 | - | 12.90 | 77.40 |
| **Chest X-ray** | 0.5 | 43.92 | 48.22 | 24.11 |
| **Electrocardiogram** | 0.25 | 20.58 | 22.60 | 5.65 |
| **TOTAL** | | | | **284.26** |

The frequency of the laboratory diagnostics is based on is based on the guideline of the Dutch Nephrology Federation[5]; the frequency of other diagnostic procedures (chest X-rays and electrocardiograms) on a protocol from the University Medical Center Utrecht. Prices were obtained from the Dutch Diagnostic Compass 2003 issued by the Health Care Insurance Board[6].

[a] Per 3 months.

[b] Approximation, price not mentioned in the Diagnostic Compass.

[c] 2 urea measurements minus 1 default measurement.

**Table 9.** Hospitalization costs per 3 months in 2009 euros.

| | Hemodiafiltration | | Hemodialysis | | Total | |
|---|---|---|---|---|---|---|
| | Median | Mean | Median | Mean | Median | Mean |
| **Duration (days)** | | | | | | |
| - total during study | 9 (0 – 34) | 27 ± 48 | 11 (0 – 35) | 27 ± 42 | 10 (0 – 34) | 27 ± 45 |
| - per 3 months | 1 (0 – 4) | 4 ± 9 | 1 (0 – 5) | 5 ± 11 | 1 (0 – 5) | 4 ± 10 |
| Age < 45 | 0 (0 – 2) | 2 ± 5 | 1 (0 – 2) | 5 ± 20 | 0 (0 – 2) | 4 ± 15 |
| Age 45 – 64 | 1 (0 – 4) | 4 ± 7 | 1 (0 – 5) | 4 ± 10 | 1 (0 – 4) | 4 ± 9 |
| Age ≥ 65 | 2 (0 – 6) | 5 ± 10 | 2 (0 – 5) | 5 ± 9 | 2 (0 – 5) | 4 ± 9 |
| **Costs (€)** | | | | | | |
| - total during study | 4,113 (114 – 15,538) | 12,524 ± 21,954 | 5,027 (0 – 15,995) | 12,390 ± 19,104 | 4,570 (0 – 15,563) | 12,457 ± 20,560 |
| - per 3 months | 570 (5 – 2,024) | 1,920 ± 3,887 | 578 (0 – 2,071) | 2,140 ± 4,958 | 578 (0 -2,059) | 2,030 ± 4,454 |
| Age < 45 | 120 (0 – 807) | 935 ± 2,456 | 288 (0 – 1,029) | 2,452 ± 8,912 | 198 (0 – 937) | 1,762 ± 6,792 |
| Age 45 – 64 | 466 (0 – 1,976) | 1,832 ± 3,311 | 494 (0 – 2,246) | 1,995 ± 4,669 | 473 (0 – 1,985) | 1,906 ± 3,972 |
| Age ≥ 65 | 795 (61 – 2,516) | 2,174 ± 4,453 | 793 (26 – 2,268) | 2,157 ± 3,898 | 794 (54 – 2,302) | 2,165 ± 4,165 |

Depicted are medians (interquartile range) and means ± standard deviation. Distributions were left-skewed.
The price of one day in the hospital is based on the reference price of the Dutch guideline for cost research[1] (€457 per day).

**Table 10.** Medication costs per 3 months in 2009 euros.

| | Hemodiafiltration | | Hemodialysis | | Total | |
|---|---|---|---|---|---|---|
| | Median | Mean | Median | Mean | Median | Mean |
| Anemia drugs | 118 (53 – 270) | 260 ± 470 | 110 (54 – 258) | 266 ± 462 | 114 (53 – 262) | 263 ± 466 |
| Anticoagulants and antiplatelets | 90 (38 – 218) | 141 ± 137 | 95 (37 – 235) | 143 ± 128 | 92 (37 – 227) | 142 ± 133 |
| Antihypertensive drugs | 31 (15 – 56) | 40 ± 32 | 31 (14 – 57) | 60 ± 33 | 31 (14 – 56) | 40 ± 32 |
| Cinacalcet | 176 (114 – 383) | 318 ± 292 | 260 (107 – 623) | 388 ± 336 | 236 (111 – 523) | 353 ± 313 |
| Phosphate-binding drugs | 127 (52 – 327) | 216 ± 219 | 118 (51 – 332) | 218 ± 226 | 122 (52 – 331) | 217 ± 223 |
| Resonium | 88 (45 – 201) | 113 ± 83 | 87 (37 – 164) | 108 ± 79 | 87 (40 – 184) | 111 ± 81 |
| Statins | 63 (32 – 98) | 69 ± 44 | 50 (27 – 97) | 63 ± 45 | 59 (30 – 98) | 66 ± 44 |
| Vitamin D3 | 76 (32 – 156) | 114 ± 119 | 71 (32 – 155) | 104 ± 100 | 74 (32 – 156) | 109 ± 110 |
| **Total per patient** | 3449 (2666 – 4521) | 3681 ± 1428 | 3477 (2829 – 4333) | 3696 ± 1462 | 3467 (2741 – 4427) | 3689 ± 1444 |
| Age < 45 | 3467 (2765 – 4798) | 3871 ± 1715 | 3352 (2981 – 4371) | 3731 ± 1041 | 3528 (2943 – 4452) | 3806 ± 1434 |
| Age 45 – 64 | 3680 (2666 – 4705) | 3847 ± 1478 | 3890 (2836 – 4835) | 4017 ± 1732 | 3840 (2776 – 4804) | 3939 ± 1619 |
| Age ≥ 65 | 3287 (2663 – 4357) | 3544 ± 1322 | 3295 (2736 – 3964) | 3446 ± 1259 | 3287 (2690 – 4107) | 3498 ± 1292 |

Depicted are medians (interquartile range) and means ± standard deviation. Distributions were left skewed.
Based on standard prices of the Dutch Pharmacotherapeutical Compass (http://www.fk.cvz.nl/), which delivers prices per unit or per time period of standard use.

**Table 11.** Travel expenses per patient per 3 months in 2009 euros.

| Average dialysis frequency per week | Average distance to the hospital | Costs (€) | | |
|---|---|---|---|---|
| | | Taxi fare | One-way taxi costs | Per patient per 3 months |
| 3 | 7.0 kilometers | €3.50 + €2.00 per kilometer | 17.50 | 1,365 |

The average distance to the hospital and the taxi fare were based on the reference price of the Dutch guideline for cost research[1]. Based on interviews with dialysis nurses it was assumed that there were no relevant transportation costs by ambulance (€243 per ordered single journey) or private or public transport (€1.40 per single journey).

**Tabel 12.** Productivity loss per patient per 3 months in euros.

| | Hemodiafiltration | | Hemodialysis | | Total | |
|---|---|---|---|---|---|---|
| | Median | Mean | Median | Mean | Median | Mean |
| Productivity loss due to absence at paid work | 0.0 (0.0 – 0.0) | 6.1 ± 95.2 | 0.0 (0.0 – 0.0) | 2.2 ± 40.6 | 0.0 (0.0 – 0.0) | 4.2 ± 73.3 |
| Productivity loss without absence at paid work | 0.0 (0.0 – 0.0) | 50.0 ± 547.6 | 0.0 (0.0 – 0.0) | 5.6 ± 85.4 | 0.0 (0.0 – 0.0) | 27.8 ± 392.7 |
| Costs of substitution of domestic work | 0.0 (0.0 – 0.0) | 468.4 ± 994.3 | 0.0 (0.0 – 0.0) | 262.3 ± 1061.2 | 0.0 (0.0 – 0.0) | 215.2 ± 1028.5 |
| **Total** | 0.0 (0.0 – 0.0) | 224.6 ± 1139.8 | 0.0 (0.0 – 0.0) | 270.0 ± 1063.7 | 0.0 (0.0 – 0.0) | 247.2 ± 1102.0 |

Depicted are medians (interquartile range) and means ± standard deviation. Distributions were left-skewed.
Productivity loss was assessed with a modified version of the Short-Form Health and Labour Questionnaire[7].
The substitution costs of unpaid hours were €9.11 per hour and the costs of paid hours were €33.66 per hour[7].

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# 11

## Dankwoord

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*Honor est in honorante* - MHD Praetor

Als eerste gaat mijn dank uit naar de patiënten van CONTRAST voor het herhaald invullen van de vele vragenlijsten. Bedankt dat ik jullie levens vanuit meerdere hoeken mocht bestuderen. Een onmisbare link daarbij waren de vele enthousiaste studieverpleegkundigen van CONTRAST. Naast de directe patiëntenzorg, zorgden jullie voor een berg aan wetenschappelijke data. Volledig belangeloos hebben jullie je jarenlang door dit droge cijferwerk heen geworsteld. Ik ben jullie veel dank verschuldigd. Tot slot horen uiteraard ook de CONTRAST onderzoekers in dit rijtje thuis. Bedankt voor de bijdrage die jullie met je centra aan het project hebben geleverd.

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krultang…) in vond je telkens weer tijd om mijn plannen en stukken te voorzien van waardevolle, praktische adviezen. En ik was me volledig bewust van de luxe dat ik, naast begeleid te worden door een epidemioloog en nefroloog, ook frequente begeleiding mocht genieten van de gezondheidseconome die als laatste de kosten-utiliteit van dialyse heeft bestudeerd.

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Albert

# 11

## Curriculum Vitae

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Albert Mazairac was born on April 15th 1982 in 's-Hertogenbosch, The Netherlands. After graduating secondary school at Gymnasium Bernrode in Heeswijk-Dinther, he started his medical studies at Maastricht University in 2000. He obtained his medical degree in 2006 and worked as a resident in Internal Medicine in the Rode Kruis Ziekenhuis in Beverwijk. In 2008 he started his PhD research at the department of Nephrology in the University Medical Center Utrecht under supervision of Professor M.L. Bots, Dr. P.J. Blankestijn and Dr. G.A. de Wit. He also received guidance from other members of the Executive Committee of the CONvective TRAnsport STudy (CONTRAST). At the American Society of Nephrology Review 2009, he received an award for presenting one of the best Dutch abstracts. He followed a Master of Science in Clinical Epidemiology at Utrecht University which he graduated in 2010 and successfully participated in the educational unit 'Cost-effectiveness Modeling Methods' of the Health Science Research Master of the Maastricht University. In 2011, he started his specialist training in Radiology at the VU Medical Center in Amsterdam (Professor C. van Kuijk).

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