Intradialytic hypotension

Prevalence, Definitions & Impact on Quality of Life

Johanna Kuipers

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Chapter 1

Introduction

Introduction

Dialysis

Dialysis is a life-saving treatment for people with end stage renal disease (ESRD). It was implemented on a large scale in patient care in the late 60`s and early 70`s of the 20th century century[1]. Given the fact that no cure is available for ESRD, kidney transplantation is the best possible renal replacement therapy, however due to shortness of donor organs and high comorbidity in patients with ESRD this is not always possible [2]. Dialysis is a form of renal function replacement treatment to remove the waste products and excess fluid. In 2017 almost 6500 Dutch patients are being treated with dialysis[3]. Approximately 14% of patients is treated with peritoneal dialysis and 86% with haemodialysis. Life expectancy in patients undergoing dialysis is relatively limited. Half of the patients that start dialysis between the ages of 45 and 65 years, die within 5 years[4].

The characteristics of patients undergoing dialysis have changed dramatically over the years. Where first relatively young patients with glomerulonephritis or polycystic kidney disease were treated, the patient group now includes older multi-morbid people with diabetes mellitus or hypertension as the cause of kidney failure[5].

Dialysis seriously impairs the quality of life due to a high symptom burden. Most patients have a fluid restriction and a strict diet with low sodium and potassium. They have an increased cardiovascular risk and their general condition often deteriorates over time[6]. The haemodialysis treatment schedule and treatment itself also has a great impact on the daily lives of patients. The treatment is mostly thrice weekly for 4 hours and causes large changes in the composition of the blood over a short period of time. The removal of the excess fluid can lead to intradialytic hypotension which is often symptomatic and persists for some time after the treatment was completed [4].

Intradialytic hypotension

During haemodialysis, fluid is withdrawn from the circulation by the artificial kidney. At the same time the excess fluid moves from the interstitial tissue back into the circulation. The rate at which the fluid is withdrawn from the circulation (the ultrafiltration rate) is almost always higher than the rate at which the fluid moves from the interstitial tissue into the circulation (refill rate). This disbalance causes a decline in blood volume and often a decrease in blood pressure[7]. Cardiovascular compensating mechanisms such as venous and arterial vasoconstriction, redistribution of blood from peripheral and splanchnic vascular beds to the central blood compartment and increases in heart rate and cardiac contractility help to maintain blood pressure during hypovolemia[8]. The presence of cardiac dysfunction[9], autonomous neuropathy[10] and use of cardiovascular medication[11] limit the effectiveness of these compensating mechanisms and intradialytic hypotension can occur[11-12]. Other patient and treatment-related factors such as age, female gender, diabetes mellitus, Hispanic origin, longer dialysis vintage,

higher body mass index, lower pre-dialytic SBP and a relatively high dialysate temperature, may also play a role in the failure of these compensating mechanisms[13-14].

Intradialytic hypotension (IDH) is considered one of the most frequent complications of haemodialysis treatment and is associated with increased cardiovascular morbidity and mortality[15]. Various reviews report that up to 50% of haemodialysis sessions are complicated by IDH[13-16-22]. However, studies on the prevalence of IDH are relatively scarce[23-26].

Over the years, dialysis techniques have improved and there is more awareness of strategies to prevent IDH, e.g. by lowering the dialysate temperature[27-28] and monitoring and restricting of relative blood volume changes[29]. At the same time, the average age of dialysis patients as well as the proportion of patients with significant co-morbidities such as diabetes mellitus and heart failure have increased[30-31].

A complicating factor in the analysis of IDH is that many different definitions of hypotension are used in the literature. These vary from liberal definitions that only require a minimum fall (e.g. 20 or 30 mmHg) in systolic blood pressure (SBP)[32-34] to strict definitions that require the combination of a clinical event and a nursing intervention in addition to a minimum fall in blood pressure[11-35-36].

Variability in Blood Pressure and interdialytic weight gain

Patients on a thrice-weekly haemodialysis scheme are generally more fluid overloaded at the start of the first dialysis session of the week compared with the second and third session of the week. This is caused by the longer interdialytic interval before the first dialysis session of the week, which results in a higher interdialytic weight gain (IDWG). These variations in fluid status over the week may have major consequences for blood pressure dynamics before and during the individual dialysis sessions because extracellular volume is a major determinant of BP in dialysis patients [37-39]. Thus it is conceivable that the more pronounced fluid overload at the start of the first HD session translates to higher pre-dialysis blood pressures compared with the subsequent haemodialysis sessions of the week. However, this was never studied.

At the same time, IDWG is increasingly being recognized as an indicator of nutritional status[40-42]. Malnutrition is considered as a major complication among haemodialysis patients and can result in increased morbidity and mortality[43-44]. Several studies demonstrated that a greater IDWG is related to overall increase intake and is thus (directly) associated with improved nutritional status[41-42-45].

Quality of Life

In the past 10-15 years, there has been an increasing awareness that patient survival might not be the one relevant outcome factor for patients who have a chronic disease. Quality of Live (QOL) has taken a more prominent place in research, and has been investigated in patients with chronic diseases, such as ESRD who depend on dialysis[46-47]. It has become increasingly important to not only provide the patients with the best medical and nursing care, but also to understand what significantly influences their QOL.

Several studies have investigated QOL in dialysis patients. Especially the physical components of QOL have been shown to be worse among dialysis patients in comparison with the general population[48], pre-dialysis CKD patients[49] and patients with other chronic diseases like congestive heart failure, diabetes, depression and even cancer[50]. An improvement in QOL of dialysis patients was seen after renal transplantation: six months after transplantation, the mean health-related quality of life scores of almost all components of QOL had improved compared to pre-transplantation and remained improved throughout the two years of follow up[51-52].

IDH is often accompanied by symptoms such as nausea, dizziness, light-headedness, fatigue, and muscle cramps, affecting the daily lives of haemodialysis patients[53] and, therefore, likely influences QOL. Pathophysiology of IDH and the methods to avoid this complication have been extensively investigated[54-55]. Also the association between IDH and mortality has been studied by several groups, Flythe *et.al.* showed that an absolute nadir systolic blood pressure <90 mmHg was most potently associated with mortality[55]. Caplin *et.al.* studied the burden and duration of haemodialysis-associated symptoms with a survey but did not study the association between symptoms and QOL[53]. As far as we know, there is no research on the association between intradialytic symptoms and QOL.

The impact of dialysis on the lives of patients and their family members can be overwhelming[56]. The nephrology nurses have long-term relationships with HD patients and often are familiar with the daily lives of patients. A better understanding of the factors that influence QOL of patients can help the nursing staff to support the patient in improving their QOL. This might lead to better motivated patients and better adherence to their treatment[57]. Therefore, better knowledge on the association between QOL and haemodialysis treatment related factors like IDH and the impact on QOL can help to improve the QOL of patients.

Aim and outline of this thesis

The major aim of this thesis is to get a better insight in the multifactorial issues surrounding IDH and to contribute in finding a definition that can be used to best describe IDH also capturing the patient- experienced burden of IDH on QOL.

Patients on a trice weekly haemodialysis schedule have higher pre-dialysis weights and higher ultrafiltration rates at the first compared with the second and third dialysis session of the week. In **chapter 2** we questioned whether these variations in excess weight and ultrafiltration rate are associated with a consistent difference in pre-, intra- and post-dialysis blood pressure behaviour between the first and the subsequent dialysis session of the week. In **chapter 3** we aimed to identify the major determinants of a high IDWG and its association with nutritional parameters. The major goal of the study described in **chapter 4** was to assess the prevalence of IDH in our population and to identify patient and treatment factors that are associated with its presence. In **chapter 5** we describe a systemic literature review and meta-analysis on studies that investigated the prevalence of IDH and provide an insight in the wide variation of definitions that are being used. In **chapter 6** we studied whether the occurrence of IDH according to the European Best Practice Guideline (EBPG) on haemodynamic instability as well as its 3 components, i.e. a fall in SBP of ≥20 mmHg, the occurrence of clinical events, and nursing interventions has an influence on the perception of QOL in HD patients. In **Chapter 7** we discuss the results of the studies presented and highlight ideas for future research.

REFERENCES

1. Https://www.nierstichting.nl/over-de-nierstichting/missie/visiestrategie/inspirator/.
2. Kievits F, Van Maanen H. Preëmptieve niertransplantatie onbenut. *Ned Tijdschr Geneeskd*. 2009;153(C107).
3. Https://Www.nefrovisie.nl/renine/nefrodata.
4. Https://www.nierstichting.nl/professionals/factsheets/.
5. Jager,K.J., Ocak,G., Drechsler,C., et al. The EQUAL study: A european study in chronic kidney disease stage 4 patients. *Nephrol Dial Transpl*. 2012;27(suppl_3):iii27-iii31.
6. Janssen D, Spruit MA, Wouters E, Schols J. Daily symptom burden in end-stage chronic organ failure: A systematic review. *Palliat Med*. 2008;22(8):938-948.
7. Dasselaar JJ. *Relative blood volume measurements during hemodialysis: Merits and limitations.* Rijksuniversiteit Groningen; 2007.
8. Ettema EM. *Hemodynamic stability during hemodialysis: A role for vasopressin?* Rijksuniversiteit Groningen; 2016.
9. van der Sande FM. The hemodynamic effect of different ultrafiltration rates in patients with cardiac failure and patients without cardiac failure: Comparison be tween isolated ultrafiltration and ultrafiltration with dialysis.*Clin Nephrol*. 1998-11;50(5):301-8.
10. Shafi Tariq T. Autonomic dysfunction as a mechanism of intradialytic blood pres sure instability. *Semin Dial*. 2017;30(6):537-544.
11. Kooman J, Basci A, Pizzarelli F, et al. EBPG guideline on haemodynamic instability. *Nephrol Dial Transplant.* 2007;22 Suppl 2:ii22-ii44.
12. Chou JA. A brief review of intradialytic hypotension with a focus on survival. *Semin Dial*. 2017;30(6):473-480.
13. Sands J, Usvyat LA, Sullivan T, et al. Intradialytic hypotension: Frequency, sources of variation and correlation with clinical outcome. *Hemodial Int.* 2014;18:415-422.
14. Selby NM, McIntyre CW. A systematic review of the clinical effects of reducing di alysate fluid temperature. *Nephrol Dial Transplant*. 2006;21(7):1883-1898.
15. Stefánsson BV, Brunelli SM, Cabrera C, et al. Intradialytic hypotension and risk of cardiovascular disease. *Clin J Am Soc of Nephrol.* 2014-12-5;9(12):2124-32.

16. Davenport A. Can advances in hemodialysis machine technology prevent intradialytic hypotension? *Semin Dial*. 2009;22(3):231-236.

17. Dubin R, Owens C, Gasper W, Ganz P, Johansen K. Associations of endothelial dysfunction and arterial stiffness with intradialytic hypotension and hypertension. *Hemodial Int.* 2011;15(3):350-358.

18. Perazella MA. Pharmacologic options available to treat symptomatic intradialytic hypotension. *Am J Kidney Dis.* 2001;38(4 Suppl 4):S26-S36.

19. Passauer J, Büssemaker E, Gross P. Dialysis hypotension: Do we see light at the end of the tunnel? *Nephrol Dial Transplant.* 1998;13(12):3024-3029.

20. Daugirdas JT. Pathophysiology of dialysis hypotension: An update. *Am J Kidney Dis.* 2001;38(4, Supplement 4):S11-S17.

21. Daugirdas JT. Preventing and managing hypotension. *Semin Dial*. 1994;7(4):276-283.

22. Zucchelli P, Santoro A. Dialysis-induced hypotension: A fresh look at pathophysiol ogy. *Blood Purif*. 1993;11(2):85-98.

23. Tislér A, Akócsi K, Hárshegyi I, et al. Comparison of dialysis and clinical characteris tics of patients with frequent and occasional hemodialysis-associated hypotension. *Kidney Blood Press Res*. 2002;25(2):97-102.

24. Converse RL, Jacobsen TN, Jost CM, et al. Paradoxical withdrawal of reflex vaso constriction as a cause of hemodialysis-induced hypotension. *J Clin Invest*. 1992;90(5):1657-1665.

25. Hossli S. Clinical management of intradialytic hypotension: Survey results. *Nephrol Nurs J.* 2005;32(3):287-91.

26. Oliver MJ, Edwards LJ, Churchill DN. Impact of sodium and ultrafiltration profiling on hemodialysis-related symptoms. *J Am Soc Nephrol.* 2001;12(1):151-156.

27. Chesterton LJ, Selby NM, Burton JO, McIntyre CW. Cool dialysate reduces asymp tomatic intradialytic hypotension and increases baroreflex variability. *Hemodial Int.* 2009;13(2):189-196.

28. Jefferies HJ, Burton JO, McIntyre CW. Individualised dialysate temperature im proves intradialytic haemodynamics and abrogates haemodialysis-induced myo cardial stunning, without compromising tolerability. *Blood Purif*. 2011;32(1):63-68.

29. Franssen CFM, Dasselaar J, Sytsma P, Burgerhof JGM, Jong de PE, Huisman RM. Automatic feedback control of relative blood volume changes during hemodialysis improves blood pressure stability during and after dialysis. *Hemodial Int.* 2005;9(4):383-392.

30. Davenport A, Cox C, Thuraisingham R. Blood pressure control and symptomatic intradialytic hypotension in diabetic haemodialysis patients: A cross-sectional sur vey. *Nephron.Clinical practice*. 2008;109(2):c65-c71.

31. Mc Causland FR, Brunelli SM, Waikar S. Dialysis dose and intradialytic hypotension: Results from the HEMO study. *Am J Nephrol*. 2013;38(5):388-396.

32. Zimmerman CY, Ladefoged A, Søren SN. Can haemodialysis-induced hypotension be predicted? *Nephron*. 2002;92(3):582-588.

33. Schreiber MJ. Setting the stage. *Am J Kidney Dis.* 2001;38(4, Supplement 4):S1-S10.

34. Shimizu K, Kurosawa T, Sanjo T. Effect of hyperosmolality on vasopressin secretion in intradialytic hypotension: A mechanistic study. *Am J Kidney Dis.* 2008;52(2):294-304.

35. Prakash S, Garg AX, Heidenheim AP, House A. Midodrine appears to be safe and effective for dialysis-induced hypotension: A systematic review. *Nephrol Dial Transplant.* 2004;19(10):2553-2558.

36. Bossola M, Laudisio A, Antocicco M, et al. Intradialytic hypotension is associated with dialytic age in patients on chronic hemodialysis. *Ren Fail*. 2013;35(9):1260-1263.

37. Hall JE. Pressure-volume regulation in hypertension. *Kidney int. Supplement*. 1996-6;55:35-41.

38. Koomans HA. The importance of plasma protein for blood volume and blood pressure homeostasis. *Kidney Int*. 1986-11;30(5):730-5.

39. Ventura JE. Volume sensitivity of blood pressure in end-stage renal disease. *Nephrol Dial Transplant*. 1997-3;12(3):485-91.

40. Kalantar-Zadeh K. Fluid retention is associated with cardiovascular mortality in patients undergoing long-term hemodialysis. *Circulation*. 2009-2-10;119(5):671-9.

41. López-Gómez JM. Interdialytic weight gain as a marker of blood pressure, nutrition, and survival in hemodialysis patients. *Kidney Int.* 2005-1(93):63-8.

42. Testa A. The other side of the coin: Interdialytic weight gain as an index of good nutrition. *Am J Kidney Dis*. 1998-5;31(5):830-4.

43. Araújo de IC. Nutritional parameters and mortality in incident hemodialysis patients. *J Ren Nutr.* 2006-1;16(1):27-35.

44. Herselman M. Protein-energy malnutrition as a risk factor for increased morbidity in long-term hemodialysis patients. *J Ren Nutr.*. 2000-1;10(1):7-15.

45. Sherman RA. Interdialytic weight gain and nutritional parameters in chronic hemodialysis patients. *Am J Kidney Dis*. 1995-4;25(4):579-83.

46. Merkus MP, Jager KJ, Dekker FW, Boeschoten EW, Stevens P, Krediet RT. Quality of life in patients on chronic dialysis: Self-assessment 3 months after the start of treatment. *Am J Kidney Dis*. 1997;29(4):584-592. doi: https://doi.org/10.1016/S0272-6386(97)90342-5.

47. Mingardi G, Cornalba L, Cortinovis E, Ruggiata R, Mosconi P, Apolone G. Health-re lated quality of life in dialysis patients. A report from an italian study using the SF-
36 health survey. *Nephrol Dial Transplant*. 1999;14(6):1503.

48. Molsted S, Prescott L, Heaf J, Eidemak I. Assessment and clinical aspects of health-related quality of life in dialysis patients and patients with chronic kidney disease. *Nephron Clin Pract*. 2007;106(1):c24-33.

49. Perlman RL, Finkelstein FO, Liu L, et al. Quality of life in chronic kidney disease (CKD): A cross-sectional analysis in the renal research institute-CKD study. *Am J Kidney Dis*. 2005;45(4):658-666.

50. Mittal SK. Self-assessed physical and mental function of haemodialysis patients. *Nephrol Dial Transplant*. 2001-7;16(7):1387-94.

51. Laupacis A, Keown P, Pus N, et al. A study of the quality of life and cost-utility of renal transplantation. *Kidney Int*. 1996;50(1):235-242.

52. Jofre R, López-Gómez JM, Moreno F, Sanz-Guajardo D, Valderrábano F. Changes in quality of life after renal transplantation. *Am J Kidney Dis*. 1998;32(1):93-100.

53. Caplin B, Kumar S, Davenport A. Patients' perspective of haemodialysis-associated symptoms. *Nephrol Dial Transplant*. 2011;26(8):2656-2663.

54. Tisler A, Akocsi K, Borbas B, et al. The effect of frequent or occasional dialysis associated hypotension on survival of patients on maintenance haemodialysis. *Nephrol Dial Transplant*. 2003;18(12):2601-2605.

55. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol*. 2014.

56. White Y. The biopsychosocial impact of end-stage renal disease: The experience of dialysis patients and their partners. *J Adv Nurs*. 1999-12;30(6):1312-20.

57. Barnett T. Fluid compliance among patients having haemodialysis: Can an educational programme make a difference? *J Adv Nurs*. 2008-2;61(3):300-6.

Chapter 2

Variability of pre-, intra-, and post-dialytic blood pressures in the course of a week: a study in Dutch and US chronic hemodialysis patients

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ABSTRACT

Background: Patients with thrice-weekly hemodialysis have higher pre-dialysis weights and ultrafiltration rates at the first compared with subsequent dialysis sessions of the week. We hypothesized that these variations in weight and ultrafiltration rate are associated with a systematic difference in blood pressure.
Study Design: Observational study.
Setting and Participants: During three months we prospectively collected hemodynamic data of 4007 hemodialysis sessions from 124 Dutch patients. A similar analysis was performed in 789 US patients comprising 6060 hemodialysis sessions.
Factor: First versus subsequent hemodialysis sessions of the week.
Outcomes: Blood pressure.
Measurements: Blood pressure, weight, and ultrafiltration rate were analyzed separately for the first, second, and third dialysis session of the week. Comparisons were made with linear mixed models.
Results: In Dutch patients pre-dialysis weight and ultrafiltration rate were significantly greater at the first compared with subsequent hemodialysis sessions of the week ($p<0.001$). Pre-dialysis systolic and diastolic blood pressures were higher at the first than at subsequent sessions of the week ($p<0.001$). Pre-dialysis blood pressure differences persisted throughout the session: Systolic and diastolic blood pressures were on average 5.0 and 2.5 mmHg higher during the first compared to the third session of the week. Post-dialysis blood pressure followed a comparable pattern ($p<0.001$). Blood pressure differences between the first and subsequent days of the week persisted after adjustment for possible confounders. Results in the US cohort were materially identical despite differences in patient characteristics and treatment practice between the two cohorts.
Limitations: Dry weight was not assessed by objective methods.
Conclusion: Blood pressure of patients on a thrice-weekly dialysis schedule varies systematically over the week. Pre-dialysis blood pressure is highest at the first hemodialysis session of the week, most likely due to greater interdialytic weight gain. Intra- and post-dialytic blood pressures are also highest at the first session of the week despite higher ultrafiltration rates.

INTRODUCTION

Patients on a thrice-weekly hemodialysis (HD) scheme are generally more fluid overloaded at the start of the first dialysis session of the week compared with the second and third session of the week. This is caused by the longer interdialytic interval before the first dialysis session of the week, which results in a higher interdialytic weight gain. These variations in fluid status over the week may have major consequences for blood pressure (BP) dynamics before and during the individual dialysis sessions.

Extracellular volume is a major determinant of BP in dialysis patients[1-3]. Thus it is conceivable that the more pronounced fluid overload at the start of the first HD session might translate to higher pre-dialysis BPs compared with the subsequent HD sessions of the week. At the same time, higher ultrafiltration rates have to be prescribed at the first compared with the subsequent sessions of the week in order to end the HD session at target weight[4]. Since ultrafiltration rate is a major determinant of hemodynamic stability during HD[5-7] variations in ultrafiltration rate may result in differences in BP behavior between the first and subsequent sessions of the week.

In this study we tested the hypothesis that differences in pre-dialysis volume status and ultrafiltration rate between the first and subsequent HD sessions of the week are associated with a systematic variation in pre-dialysis BP and intra-dialytic BP course. For this purpose, we prospectively collected the hemodynamic data of 4007 dialysis sessions from 124 Dutch patients and analyzed the course of BP, weight, ultrafiltration rate, and the incidence of dialysis hypotension separately for the first, second and third dialysis session of the week. To assess the generalizability of our results we performed a similar analysis in a cohort of 789 dialysis patients from six United States (US) dialysis centers that are part of the Renal Research Institute (RRI).

METHODS

Patients: Dutch study population

Adult (≥18 years) patients from the Dialysis Center Groningen and the dialysis unit of the University Medical Center Groningen were eligible for this study when they fulfilled the following criteria: 1. Maintenance bicarbonate HD for >3 months; 2. Three times a week 4 hours HD schedule. The only exclusion criterion was absence of informed consent. The study was performed in accordance with the principles of the Declaration of Helsinki.

Study protocol: Dutch study population

During 3 months, we prospectively collected the hemodynamic data of all HD sessions from participating patients. Each session was evaluated for pre- and post-HD weight, pre-, intra- and post-dialytic BP and heart rate (HR), ultrafiltration volume, and ultrafiltration rate. BP and HR were measured with an automated oscillometric monitor before HD, at 10, 30, 60, 120, and 180 minutes intra-HD, at the end of the HD session (240 minutes), and 10 minutes post-HD.

Patients were either dialyzed at Monday, Wednesday and Friday or at Tuesday, Thursday and Saturday. Monday and Tuesday were defined as the first, Wednesday and Thursday as the second, and Friday and Saturday as the third session of the week. All parameters were analyzed separately for the first, second and third session of the week. HD sessions during hospitalization were excluded from the analysis.

Prescriptions regarding target weight and antihypertensive medications were made by the nephrologist during weekly visits. Target weight was evaluated clinically (peripheral edema, signs of pulmonary congestion, intra- and extra-dialytic BP course, muscle cramps) and by (changes of) the cardiopulmonary radiological aspect. Excess weight at the start of HD was defined as the difference between pre-dialysis weight and target weight. The prescribed ultrafiltration volume was calculated by adding the estimated intra-dialytic fluid intake (usually 750 ml) to the excess weight. For all analyses, however, the exact ultrafiltration volume as 'delivered' by the dialysis apparatus was used. Ultrafiltration rate was calculated by dividing the ultrafiltration volume by dialysis session length and target weight. No saline was routinely administered to the patient during connection to the extracorporeal circuit. Individual treatment times were not changed in the course of the study.

Dialysis hypotension was defined as a decrease in systolic BP ≥30 mmHg in combination with systolic BP drop to <90 mmHg. We restricted this definition to BP since detailed per treatment information on symptoms and interventions were not available in the US cohort. Presence of residual renal function was indicated by a urinary volume of ≥500 ml per day.

Dialysis settings: Dutch Study population

All patients were dialyzed 3 times a week for 4 hours with low-flux polysulphone hollow-fiber dialysers, F8 or F10 (Fresenius Medical Care, Bad Homburg, Germany). Dialysis settings were identical for the first, second, and third session of the week. Blood flow ranged between 250 and 350 ml/min. Dialysate flow was 500 or 700 ml/min. Blood flow and dialysate flow were kept constant throughout the study period in the individual patient. All patients were dialyzed with a constant ultrafiltration rate. Dialysate temperature was 36.0 or 36.5 °C and was kept constant during the study period for the individual patient. Dialysate composition was as follows: sodium 139 mmol/l, potassium 1.0 to 3.0 mmol/l, calcium 1.5 mmol/l, magnesium 0.5 mmol/l, chloride 108 mmol/l, bicarbonate 34 mmol/l, acetate 3 mmol/l, and glucose 1.0 g/l. Patients received a light meal and 2 cups of coffee or tea during HD.

US study population

US patients were studied during the same 3-month calendar period using identical methodology as for the Dutch study population with some exceptions as outlined below. US patients were analyzed as part of standard operating procedures with BP recordings automatically collected by the computer system used in the RRI clinics. Consequently, BP and HR recordings were obtained not at pre-specified time points (as it was done in the Dutch study population) but as instructed by operational guidance which suggests measuring BP approximately every 30 minutes or when a patient experiences symptoms. The computer system that was used to collect intradialytic BPs was implemented about half way into the study period, so fewer treatments per patient were available in the US population.

Because US population was treated as part of standard clinic practice and patients were not enrolled into a study, it is possible that patients' treatment times varied slightly from treatment to treatment. Furthermore, adjustments to blood and dialysate flow might have been made from treatment to treatment. Contrary to the Dutch population, patients were not dialyzed with constant ultrafiltration rate, in fact, in most cases, ultrafiltration rate was lowered in the last 15-30 minutes of the treatment. Dialysate temperature was between 35.0 and 37.0 °C. Dialysate composition differed: sodium 137 to 140 mmol/l, potassium 1.0 to 3.0 mmol/l, calcium 1.0 to 1.75 mmol/l, magnesium 0.8 to 1.0 mmol/l, chloride 101 to 107 mmol/l, bicarbonate 33 to 38 mmol/l, acetate 4 to 8 mmol/l, and glucose 1.0 g/l. Patients received no meals from the clinic but were allowed to bring their own meals to the dialysis unit.

Statistical analysis

Data were analyzed using SPSS version 19 (SPSS Inc., Chicago, IL, USA), R version 2.15.1, and SAS version 9.3 (SAS Institute Inc. Cary, NC, USA). Comparisons between the Dutch and US population were made with t-test for continuous variables and chi-square

test for categorical variables. Comparisons of weight, BP, ultrafiltration volume and rate between the first, second and third day of the week were made with linear mixed models with fixed and random effects accounting for inter- and intra-patient variability. In separate analyses, pre- and post-dialysis parameters were adjusted for factors that may affect BP: age, gender, dialysis vintage, diabetic status, body mass index, residual renal function, co-morbidity of ischemic heart disease, co-morbidity of congestive heart failure, dialysate composition (magnesium, calcium, and sodium concentrations), albumin-corrected plasma calcium level, plasma phosphorus level, and number of different cardiovascular drugs (angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, beta-blocker, calcium channel blocker) used by the patient. These data were collected at the start of the study period, except for calcium and phosphate levels, which were measured twice during the study period and averaged. For linear mixed models, treatment day, age, gender, dialysis vintage, diabetic status, body mass index, residual renal function, co-morbidity of ischemic heart disease and congestive heart failure, dialysate composition, albumin-corrected plasma calcium, plasma phosphorus level, and number of cardiac drugs were treated as fixed variables. Random variables were patient specific intercept and day when patient was treated. Linear mixed models were also used to adjust for a possible effect of pre-dialysis systolic BP on post-dialysis systolic BP[6].

BPs for Dutch patients were measured at pre-specified time points whereas BPs for US patients were not measured at pre-specified time points. For a proper comparison of the Dutch and US populations, we used the percentage of dialysis session elapsed. To investigate the trend of BP and HR over percent of total treatment time, we computed means and standard deviations at pre-specified time points for Dutch patients. For US patients, we fitted cubic spline models and constructed confidence intervals for the mean functions. The R package ASSIST was used to fit cubic spline models where the smoothing parameter was selected by the generalized maximum likelihood method[8].

RESULTS

Characteristics of the Dutch and US patient cohorts are shown in Table 1.

Patients: Dutch Study population

Hundred twenty-four patients participated in this study. Mean (±SD) hemoglobin and albumin levels were 10.7±1.2 g/dL and 39±3.2 g/L, respectively. eKt/V was 1.37±0.3 per session. HD access was an arterio-venous fistula or PTFE graft in 77% of patients and a tunneled central venous catheter in 23% of patients. A total of 4007 hemodialysis sessions were analysed. The average number of HD sessions analyzed per patient was 32.

Table 1.
Patient characteristics.

	Dutch population (N=124)	US population (N=789)	P-value
Age (year)	64.1 ± 15.7	60.7±15.4	0.05
Number of males, n (%)	69 (56)	426 (54)	0.43
Dialysis vintage (months), median (25th - 75th percentile)	24 (3 - 60)	26 (8 - 55)	0.21
Number of diabetics, n (%)	31 (27)	323 (41)	<0.01
Body Mass index (kg/m²)	25.2 ± 4.8	28.4 ± 7.9	<0.01
Number of patients with central venous catheter as dialysis access, n (%)	28 (23)	134 (17)	0.23
Number with residual renal function	26 (21)	47 (6)	<0.01
Dialysis treatment time (min)	236 ± 12	208 ± 29	<0.01
Cardiovascular history*, n (%)	48 (39)	237 (30)	0.03
Primary renal disease, n (%)			<0.01
Hypertension	32 (26)	213 (27)	
Diabetes	19 (15)	220 (28)	
Glomerulonefritis	17 (14)	32 (4)	
Obstructive uropathy	17 (14)	47 (6)	
ADPKD	10 (8)	16 (2)	
IgA nephropathy	6 (5)	24 (3)	
Other diagnoses	13 (10)	134 (17)	
Unknown	10 (8)	0 (0)	
Medication used n (%)			
Beta-blocker	72 (58)	410 (52)	<0.01
CCB	31 (25)	158 (20)	<0.01
ACE-I/ ARB	24 (19)	95 (12)	<0.01
Hemoglobin (g/dL)	10.7 ± 1.2	11.1 ±1.2	<0.01
Albumin (g/L)	39 ± 3.2	38 ± 4.1	0.05
eKt/V	1.37 ± 0.3	1.51 ± 1.9	0.41

All values are presented as mean (standard deviation) unless otherwise indicated. Abbreviations: ADPKD, adult dominant polycystic kidney disease; CCB, calcium channel blocker; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NS, not significant. *Cardiovascular history: any history of ischemic heart disease, congestive heart failure, stroke or peripheral vascular disease.

Patients: US study population

Seven hundred and eighty nine patients were studied. US patients were younger, more often male, and had a longer dialysis vintage compared with the Dutch population (Table 1). The proportion of patients with diabetes (41% versus 27%; P<0.01) was significantly higher and the proportion of patients with residual renal function was significantly lower (6% versus 21%; P<0.01) in the US compared with the Dutch population. Dialysis treatment time was significantly shorter in the US population

compared with the Dutch population (208±29 versus 236±12 minutes; P<0.01). Hemoglobin was slightly but significantly higher in the US population compared with the Dutch population (Table 1). eKt/V did not differ significantly from the Dutch population (Table 1). HD access was an arterio-venous fistula or PTFE graft in 83% of patients and a tunneled central venous catheter in 17% of patients. A total of 9560 hemodialysis sessions were analyzed while 6060 sessions were studied where all three treatment day data was available per patient. The average number of HD sessions analyzed per patient was 12.

Pre- and post-dialysis weight and ultrafiltration volume: Dutch Study population

As shown in Table 2a, pre-dialysis weight was 0.58 and 0.73 kg higher at the first compared with the second and third session of the week, respectively (p<0.001). Post-dialysis weight was 0.24 and 0.28 kg higher at the first compared with the second and third session of the week, respectively (p<0.001). The excess weight at the start of HD was significantly higher at the first compared with the second and third session of the week (both p<0.001). Total ultrafiltration volume and ultrafiltration rate were significantly (both p<0.001) higher during the first compared with the second and third session of the week (Table 2a). Differences in pre-dialysis weight, excess weight at the start of HD, and ultrafiltration volume and rate between the first and the subsequent days of the week remained significant after multivariable adjustment (Supplementary file S1).

Blood pressure and heart rate: Dutch Study population

As shown in Table 2a, pre-dialysis systolic and diastolic BP were significantly higher (p<0.001) and HR was significantly lower (p<0.001) at the first compared with the second and third session of the week. BP fell during each dialysis day but the pre-dialysis differences persisted throughout the dialysis session. At most time points during the treatment, systolic and diastolic BPs were significantly higher at the first compared with the other two dialysis sessions of the week (Figure 1 left). Post-HD systolic and diastolic BPs were significantly higher (p<0.001) and HR was significantly lower (p<0.01) after the first compared with the other two sessions of the week (Table 2a). Differences in pre- and post-dialysis BPs between the first and subsequent days of the week remained significant after multivariable adjustment (Supplementary file S1).

Differences in pre-dialysis (Figure 2, left panel) and post-dialysis (Figure 3, left panel) systolic and diastolic BP and pre-dialysis HR between the first and the other HD sessions of the week were consistent throughout the 3-month study period. The same was observed for the intra-dialytic BPs (data not shown).

Frequency of dialysis sessions with a BP drop of ≥30 mmHg was more pronounced on the first treatment of the week; however, no significant difference in dialysis hypotension was observed (Table 2a).

Pre- and post-dialysis weight and ultrafiltration volume: US Study population

In agreement with the Dutch data, pre-dialysis weight was 0.44 and 0.53 kg higher at the first compared with the second and third session of the week, respectively (Table 2b; p<0.001). Post-dialysis weight was 0.25 and 0.32 kg higher at the first compared with the second and third session of the week, respectively (p<0.001). The excess weight at the start of HD was significantly higher at the first compared with the second and third session of the week (both p<0.001), which is the same as seen in the Dutch population. Similar findings for ultrafiltration volume and rate were observed in US as in the Dutch study population. No differences, however, were observed between second and third HD treatments of the week. Differences in pre-dialysis weight, excess weight at the start of HD, and ultrafiltration volume and rate between the first and subsequent days of the week remained significant after multivariable adjustment (Supplementary file S2).

Blood pressure and heart rate: US Study population

As in the Dutch population, US patients had higher pre-dialysis systolic and diastolic BPs at the first compared with the second and third session of the week (Table 2b). No significant differences were observed in pre-dialysis HR between the first and the second treatment, but significant differences between first and third treatment were observed (Table 2b). BP fell during each dialysis day but the pre-dialysis differences persisted throughout the entire dialysis session. At most time points during the treatment, systolic and diastolic BPs were significantly higher at the first compared with the other two sessions of the week (Figure 1 right). Differences in pre- and post-dialysis BPs between the first and subsequent days of the week remained significant after multivariable adjustment, except for the difference in pre-dialysis diastolic BP between the first and third session of the week which lost its significance (Supplementary file S2).

As shown in Figure 2 and Figure 3 (right panels), for the US cohort differences in pre- and post-dialysis systolic and diastolic BPs between the first and the other session of the week were consistent throughout the 3-month study period but less consistent and less pronounced than in the Dutch population. Contrary to the Dutch patients, differences in HR between days of the week were not observed.

Contrary to the Dutch study population, frequency of systolic BP drops ≥30 mmHg was more pronounced on the third HD day. Less hypotensive episodes occurred on the first HD day compared to second (p<0.05) and third HD day of the week (NS) (Table 2b).

Table 2a.

Weight, ultrafiltration volume and ultrafiltration rate, blood pressure, and heart rate: Dutch study population.

	First HD of the week (N=1322)	Second HD of the week (N=1353)	Third HD of the week (N=1332)	First vs second HD of the week	First vs third HD of the week	Second vs third HD of the week
Pre-dialysis weight (kg)	75.9 (72.9-78.8)	75.3 (72.4-78.3)	75.2 (72.2-78.1)	0.58 *** (0.52 to 0.64)	0.73 *** (0.68 to 0.79)	0.15 *** (0.10 to 0.21)
Post-dialysis weight (kg)	73.8 (70.9-76.7)	73.5 (70.6-76.5)	73.5 (70.6-76.4)	0.24 *** (0.16 to 0.32)	0.28 *** (0.21 to 0.36)	0.04 (-0.03 to 0.12)
Excess weight at the start of the HD session (kg)	2.5 (2.4-2.7)	2.0 (1.8-2.1)	1.8 (1.7-2)	0.57 *** (0.52 to 0.62)	0.71 *** (0.66 to 0.76)	0.14 *** (0.09 to 0.19)
Total UF volume (ml)	2651 (2527-2775)	2303 (2179-2426)	2220 (2097-2344)	348.3 *** (306.0 to 390.6)	430.9 *** (388.5 to 473.4)	82.6 *** (40.4 to 124.8)
UF rate (ml/kg/h)	9.4 (9-9.9)	8.2 (7.7-8.7)	7.9 (7.4-8.4)	1.26 *** (1.09 to 1.43)	1.54 *** (1.37 to 1.71)	0.28 ** (0.11 to 0.45)
Pre-dialysis systolic blood pressure (mmHg)	149.6 (145.6-153.6)	144.6 (140.6-148.6)	143.4 (139.4-147.4)	4.95 *** (3.74 to 6.16)	6.19 *** (4.97 to 7.4)	1.23 * (0.03 to 2.44)
Post-dialysis systolic blood pressure (mmHg)	134.9 (130.9-138.8)	131.6 (127.7-135.5)	132.2 (128.3-136.1)	3.26 *** (1.86 to 4.66)	2.64 *** (1.23 to 4.05)	-0.62 (-2.02 to 0.78)
Pre-dialysis diastolic blood pressure (mmHg)	74.1 (72-76.3)	72.4 (70.2-74.6)	71.6 (69.4-73.7)	1.75 *** (1.03 to 2.47)	2.6 *** (1.88 to 3.31)	0.84 * (0.13 to 1.56)
Post-dialysis diastolic blood pressure (mmHg)	68.8 (66.8-70.9)	67.4 (65.3-69.4)	67.3 (65.2-69.3)	1.46 *** (0.7 to 2.22)	1.57 *** (0.8 to 2.33)	0.1 (-0.66 to 0.86)
Pre-dialysis heart rate (bpm)	74.2 (72.4-75.9)	75.5 (73.7-77.3)	75.9 (74.1-77.6)	-1.32 *** (-1.88 to -0.76)	-1.68 *** (-2.24 to -1.11)	-0.36 (-0.92 to 0.2)
Post-dialysis heart rate (bpm)	76.4 (74.3-78.5)	77.4 (75.3-79.5)	77.3 (75.2-79.4)	-1.06 ** (-1.79 to -0.33)	-0.96 * (-1.7 to -0.21)	0.11 (-0.63 to 0.84)
Systolic blood pressure fall >30 mmHg (%)	46.2	40.8	43.0	5.4 ** (2.0 to 8.9)	3.2 (-0.2 to 6.7)	-2.2 (-5.7 to 1.3)
Dialysis hypotension (%)	7.4	6.6	7.2	0.8 (-1.1 to 2.74)	0.2 (-1.8 to 2.1)	-0.7 (-2.6 to 1.3)

All values are presented as mean (95% confidence interval) using linear mixed effect model (unadjusted data). Abbreviations: HD, hemodialysis; UF, ultrafiltration; bpm, beats per minute.

* Denotes p<0.05, ** denotes p<0.01, and *** denotes p<0.001.

Table 2b.

Weight, ultrafiltration volume and ultrafiltration rate, blood pressure, and heart rate: US study population.

	First HD of the week (N=2190)	Second HD of the week (N=1949)	Third HD of the week (N=1921)	First vs second HD of the week	First vs third HD of the week	Second vs third HD of the week
Pre-dialysis weight (kg)	83.3 (81.6-85)	82.9 (81.1-84.6)	82.8 (81-84.5)	0.44 *** (0.3 to 0.57)	0.53 *** (0.39 to 0.66)	0.09 (-0.05 to 0.23)
Post-dialysis weight (kg)	80.9 (79.2-82.6)	80.6 (78.9-82.4)	80.6 (78.9-82.3)	0.25 *** (0.16 to 0.34)	0.32 *** (0.23 to 0.41)	0.08 (-0.02 to 0.17)
Excess weight at the start of the HD session (kg)	3.0 (2.7-3.3)	2.6 (2.3-2.9)	2.6 (2.3-2.9)	0.76 *** (0.68 to 0.83)	0.65 *** (0.57 to 0.72)	-0.11 ** (-0.19 to -0.04)
Total UF volume (ml)	2496 (2420-2573)	2246 (2168-2323)	2258 (2180-2335)	250.70 *** (200.0 to 301.4)	238.45 *** (187.7 to 289.2)	-12.25 (-64.6 to 40.1)
UF rate (ml/kg/h)	10.6 (10.3-10.9)	9.7 (9.4-10)	9.9 (9.6-10.2)	0.90 *** (0.74 to 1.06)	0.77 *** (0.61 to 0.93)	-0.13 (-0.29 to 0.04)
Pre-dialysis systolic blood pressure (mmHg)	146.2 (144.6-147.9)	144 (142.4-145.7)	144.8 (143.2-146.5)	2.19 *** (1.13 to 3.25)	1.37 * (0.31 to 2.42)	-0.82 (-1.92 to 0.27)
Post-dialysis systolic blood pressure (mmHg)	136.7 (135.1-138.3)	135.2 (133.6-136.8)	135.4 (133.8-137)	1.50 ** (0.43 to 2.57)	1.34 * (0.27 to 2.42)	-0.15 (-1.26 to 0.95)
Pre-dialysis diastolic blood pressure (mmHg)	76.3 (75.3-77.3)	75.3 (74.3-76.3)	75.6 (74.6-76.6)	1.03 ** (0.37 to 1.69)	0.67 * (0.01 to 1.33)	-0.36 (-1.04 to 0.32)
Post-dialysis diastolic blood pressure (mmHg)	71.8 (70.9-72.7)	71.1 (70.1-72)	71.1 (70.2-72.1)	0.77 * (0.12 to 1.42)	0.69 * (0.04 to 1.34)	-0.08 (-0.75 to 0.59)
Pre-dialysis heart rate (bpm)	74.8 (73.9-75.7)	75.1 (74.2-76)	75.4 (74.5-76.3)	-0.32 (-0.83 to 0.19)	-0.60 * (-1.10 to -0.09)	-0.28 (-0.80 to 0.25)
Post-dialysis heart rate (bpm)	77.2 (76.2-78.1)	77.4 (76.5-78.4)	78 (77.1-79)	-0.29 (-0.89 to 0.3)	-0.87 ** (-1.47 to -0.27)	-0.58 (-1.20 to 0.04)
Systolic blood pressure fall >30 mmHg (%)	48.4	46.8	50	1.65 (-0.99 to 4.3)	-1.55 (-4.2 to 1.09)	-3.20 * (-5.94 to -0.47)
Dialysis hypotension (%)	15.6	17.7	17.2	-2.13 * (-4.14 to -0.11)	-1.61 (-3.63 to 0.41)	0.52 (-1.57 to 2.6)

All values are presented as mean (95% confidence interval) using linear mixed effect model (unadjusted data). Abbreviations: HD, hemodialysis; UF, ultrafiltration; bpm, beats per minute. * Denotes p<0.05,
** denotes p<0.01, and *** denotes p<0.001.

Figure 1.
Courses of intra-dialytic systolic blood pressure, diastolic blood pressure, and heart rate. For the Dutch cohort on the left, each line joints mean values of the first, second and third hemodialysis sessions at pre-specified time points. For the US cohort on the right, each line represents cubic spline estimate of the mean function for the first, second and third hemodialysis sessions. Shaded area around each line represents 95% confidence intervals.

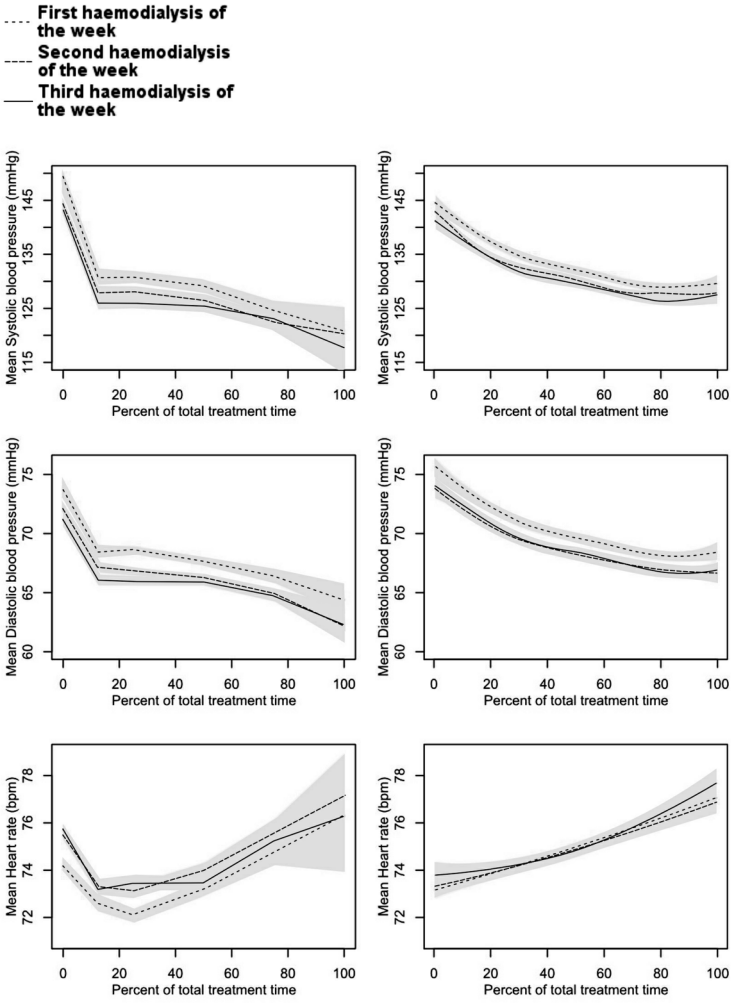


Figure 2.

Pre-dialysis systolic and diastolic blood pressure, and heart rate throughout the study period in the Dutch study population (left) and US study population (right). Each line represents the mean value of the 124 Dutch patients (left) and 789 US patients (right). The error bars represent the 95% confidence interval.

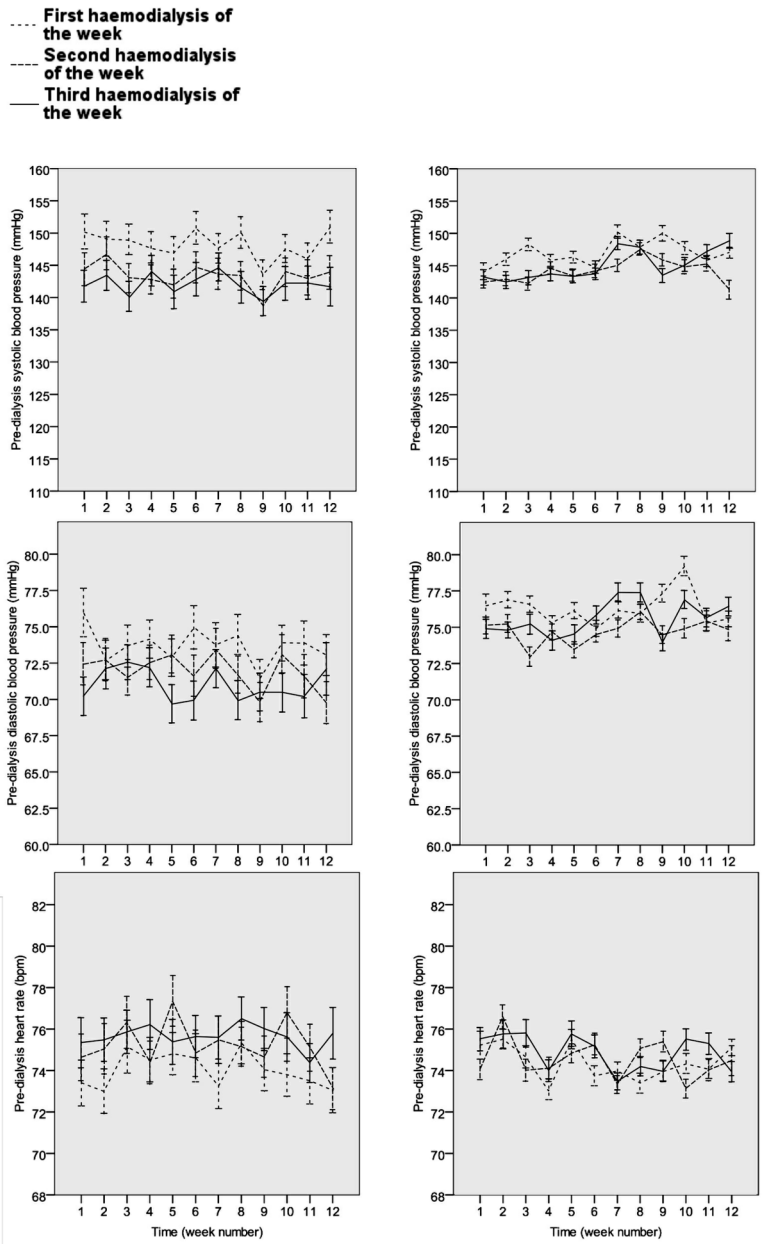
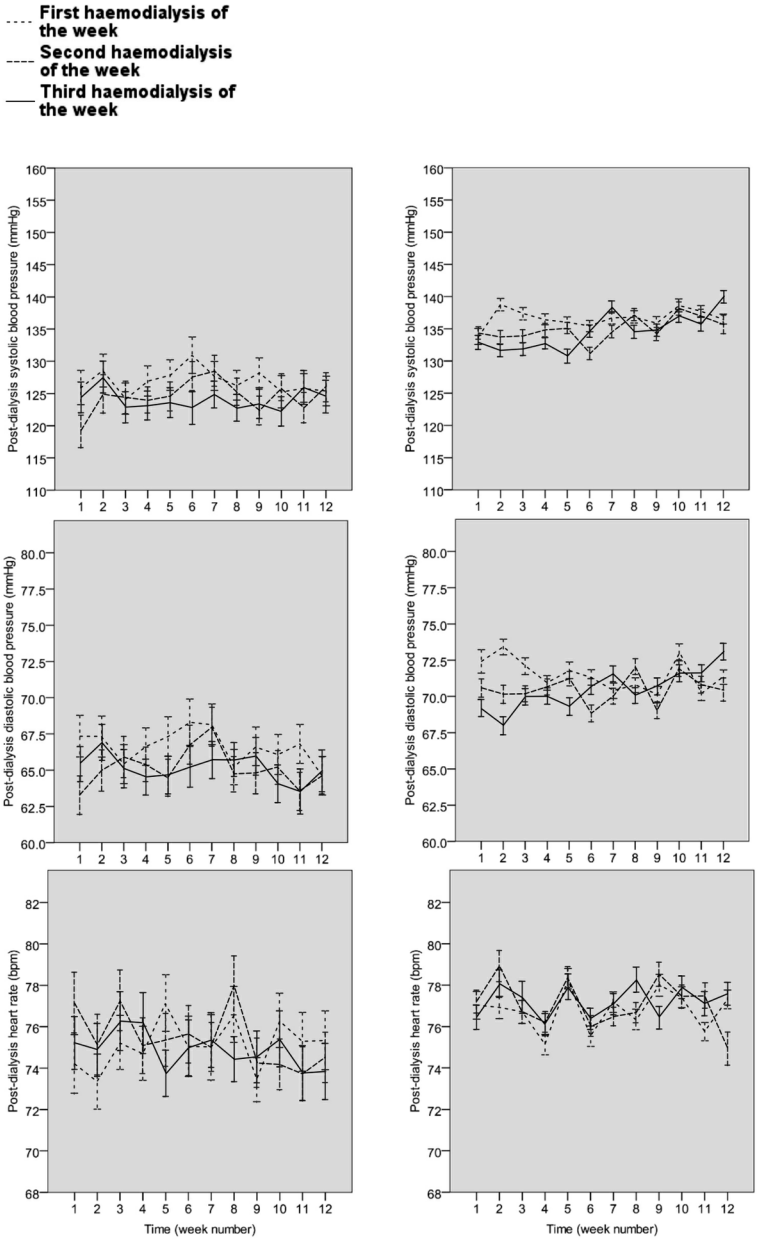


Figure 3.

Post-dialysis systolic and diastolic blood pressure, and heart rate throughout the study period in the Dutch study population (left) and US study population (right). Each line represents the mean value of the 124 Dutch patients (left) and 789 US patients (right). The error bars represent the 95% confidence interval.



Interaction between pre-dialysis and post-dialysis blood pressure

Since pre-dialysis systolic BP influences the BP course during the subsequent dialysis session[6] we performed an additional analysis in which we used linear mixed model to adjust for the effect of pre-dialysis systolic BP on post-dialysis systolic BP in addition to the other adjustments. When adjusted for these factors, differences in post-dialysis systolic BP disappeared in the US population and there was still a significant difference between first and second day of the week in the Dutch population (Supplementary file S3).

DISCUSSION

In this study we addressed the question whether variations in pre-dialysis fluid status and ultrafiltration rate in patients on a thrice-weekly dialysis scheme translate to a systematic difference in BP behaviour between the first and subsequent dialysis session of the week. We found that pre-dialysis systolic and diastolic BPs were significantly higher at the first compared with the two other dialysis sessions of the week. A second, unexpected, finding was that intra- and post-dialytic BPs were also significantly higher during the first compared with the other dialysis sessions of the week despite higher ultrafiltration rates.

It is well established that fluid status is a major determinant of BP in dialysis patients[1-3]. Since patients on a thrice-weekly HD scheme are more fluid overloaded after the longest interdialytic interval it is not surprising that pre-dialysis BP was significantly higher at the first compared with the other sessions of the week. Additionally, volume-independent mechanisms may contribute to the higher BP at the start of the first HD session of the week, e.g. by accumulation of uremic substances with vasopressor activity and/or a higher sympathetic tone after the long interdialytic interval.

The ultrafiltration rate is considered to be a major determinant of hemodynamic stability during HD[5-6] and higher ultrafiltration rates are associated with increased cardiovascular morbidity and mortality[9]. The present study shows that intra- and post-dialysis BPs were higher at the first compared with the other dialysis sessions of the week despite higher ultrafiltration rates. Koomans *et al* and Wizeman *et al* have shown that the more fluid overloaded the patient, the smaller is the observed decrease in relative blood volume per unit of ultrafiltration volume[8-9]. This is explained by a higher refill rate from the interstitial tissues in a more fluid overloaded state[8-9]. As such, the higher degree of fluid overload at the first dialysis session of the week facilitates plasma refill and may explain that the BP fall during the first dialysis session did not exceed the BP decrease during the other sessions of the week despite a significantly higher ultrafiltration rate. Additionally, post-dialysis weight was significantly lower at the second and third session compared with the first sessions of the week indicating that patients were

closer to target weight. This may also have contributed to lower intra- and post-dialytic BP at the second and third session of the week compared with the first session of the week.

In this study, interesting differences in patient characteristics and treatment practice between the US and the Dutch study population were observed. In particular, the proportion of patients with diabetes was higher in the US population whereas the proportion of patients with residual renal function was higher in the Dutch population. The average dialysis treatment time was significantly shorter in the US and this explains the higher ultrafiltration rate in the US compared with the Dutch population. Notably, differences in BP between the first and subsequent sessions of the week were comparable in the two populations despite these variations in patient and treatment characteristics.

The US cohort demonstrated significantly higher rates of dialysis hypotension (15.6%, 17.7% and 17.2% of treatments at the first, second, and third session of the week, respectively) than the Dutch cohort (7.4%, 6.6% and 7.2% of treatments at the first, second, and third session of the week, respectively) despite similar percentages of treatments with systolic BP declines ≥30 mmHg. The etiology of this difference remains unclear, however may relate to differences in ultrafiltration rate, dialysate temperature, the proportion of patients with diabetes, or other undetermined differences in patient characteristics or practice patterns between the US and Dutch centers.

Our findings may have relevance for the observation that the mortality rate in dialysis patients varies over the week and is influenced by the dialysis schedule[12-15]. A higher BP at the first dialysis day of the week may be one of the cardiovascular stressors that contribute to the higher cardiovascular event rate at the first dialysis day of the week. Our data support the claim that it is time to revisit the thrice-weekly conventional HD approach[15]. However, whether alternate-day hemodialysis reduces the differences in BP between the first and subsequent sessions of the week remains to be studied.

A limitation of this study is that we did not use objective methods to assess dry weight. Therefore, we cannot exclude that a proportion of patients was not at their true dry weight at the end of dialysis and this may have affected the BP level. However, this could not explain differences in BP between the different sessions of the week. A second limitation is the use of dialysis machine-measured BP which is subject to differing calibrations that may introduce bias. Bias in BP measurements could also be introduced by underlying vascular disease or prior access surgeries. This may be particularly relevant to the US population who had a higher percentage of diabetic patients. A third limitation is that we did not have detailed information on interventions for hemodynamic instability and treatment-to-treatment adaptations of dry weight that may affect BP behavior. Interventions during hemodialysis, however, would not affect the conclusion that pre-dialysis BP and weight are highest on the first treatment day of the week.

Finally, detailed information on (changes in) cardiovascular medication dosage, dialyzability, and long- versus short-acting status was not available.

In conclusion, this international multi-center study shows that pre-dialysis BP is highest at the first dialysis session of the week, probably due to more pronounced fluid overload. Despite significantly higher ultrafiltration rates, intra- and post-dialysis BP are also highest during the first session of the week compared with the subsequent dialysis sessions of the week.

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REFERENCES

1. Hall JE, Guyton AC, Brands MW. Pressure-volume regulation in hypertension. *Kidney Int.* 1996;55(6):S35-41.

2. Koomans HA, Braam B. The importance of plasma protein for blood volume and blood pressure homeostasis. *Kidney Int.* 1986;30(5):730-735.

3. Ventura JE, Sposito M. Volume sensitivity of blood pressure in end-stage real disease. *Nephrol Dial Transplant.* 1997;12(3):485-491.

4. Dasselaar JJ, de Jong PE, Huisman RM, Franssen CFM. Influence of ultrafiltration volume on blood volume changes during hemodialysis as observed in day-of-the-week analysis of hemodialysis sessions. *ASAIO J.* 2007;53(4):479-484.

5. Daugirdas JT. Pathophysiology of dialysis hypotension: an update. *Am J Kidney Dis.* 2001;38(4 Suppl 4): S11-S17.

6. Dinesh K, Kunaparaju S, Cape K, Flythe JE, Feldman HI, Brunelli SM. A model of systolic blood pressure during the course of dialysis and clinical factors associated with various blood pressure behaviors. *Am J Kidney Dis.* 2011;58(5):794-803.

7. Davenport A. Can advances in hemodialysis machine technology prevent intradialytic hypotension? *Semin Dial.* 2009;22(3):231-236.

8. Wang Y. Smoothing Splines: Methods and Applications. New York: Champman and Hall; 2011.

9. Flythe JE, Kimmel SE, Brunelli SM. Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. *Kidney Int.* 2011;79(2):250-257.

10. Koomans H, Geers A, Mees EJ. Plasma volume recovery after ultrafiltration in patients with chronic renal failure. *Kidney Int.* 1984;26(6):848–854.

11. Wizemann V, Leibinger A, Mueller K, Nilson A. Influence of hydration state on plasma volume changes during ultrafiltration. *Artif Organs* 1995;19(5):416–419.

12. Foley RN, Gilbertson DT, Murray T, Collins AJ. Long interdialytic interval and mortality among patients receiving hemodialysis. *New Engl J Med.* 2011;365(12):1099-1107.

13. Zhang H, Schaubel DE, Kalbfleisch JD, et al. Dialysis outcomes and analysis of practice patterns suggests the dialysis schedule affects the day-of-the week mortality. *Kidney Int.* 2012;81(11):1108-1115.

14. Prabhalvalkar SM, Mullan RN, Cunningham GC, Harron CJ. Association between dialysis schedule and mortality in maintenance hemodialysis. *Kidney Int.* 2012;82(9):1034-1035.

15. Liu J, Foley RN. Alternate-day dialysis may be needed for hemodialysis patients. *Kidney Int.* 2012;81(11):1055-1057.

Supplementary file S1.

Weight, ultrafiltration volume and rate, blood pressure, and heart rate, adjusted analysis#: Dutch study population.

	First HD of the week (N=1322)	Second HD of the week (N=1353)	Third HD of the week (N=1332)	First vs second HD of the week	First vs third HD of the week	Second vs third HD of the week
Pre-dialysis weight (kg)	75.4 (72.7-78.1)	74.8 (72.1-77.5)	74.7 (72.0-77.3)	0.58 *** (0.53 to 0.64)	0.73 *** (0.68 to 0.79)	0.15 *** (0.10 to 0.21)
Post-dialysis weight (kg)^	73.3 (70.6-75.9)	73.0 (70.4-75.7)	73.0 (70.4-75.6)	0.24 *** (0.16 to 0.32)	0.28 *** (0.21 to 0.36)	0.04 (-0.03 to 0.12)
Excess weight at the start of the HD session (kg)	2.5 (2.3-2.6)	1.9 (1.8-2.1)	1.8 (1.6-1.9)	0.57 *** (0.51 to 0.63)	0.71 *** (0.65 to 0.76)	0.14 *** (0.08 to 0.19)
Total UF volume (ml)	2634 (2527-2741)	2284 (2177-2391)	2205 (2098-2312)	350.0 *** (306.3 to 393.7)	429.0 *** (385.2 to 472.9)	79.0 *** (35.6 to 122.5)
UF rate (ml/kg/h)	9.5 (9.1-9.9)	8.2 (7.8-8.6)	7.9 (7.5-8.3)	1.28 *** (1.11 to 1.45)	1.56 *** (1.39 to 1.73)	0.28 ** (0.11 to 0.45)
Pre-dialysis systolic blood pressure (mmHg)	149.4 (145.6-153.3)	144.7 (140.8-148.5)	143.4 (139.6-147.3)	4.76 *** (3.53 to 5.99)	5.97 *** (4.75 to 7.2)	1.22 (0 to 2.43)
Post-dialysis systolic blood pressure (mmHg)	134.6 (130.9-138.3)	131.3 (127.6-135.0)	132.0 (128.3-135.7)	3.26 *** (1.82 to 4.71)	2.63 *** (1.18 to 4.09)	-0.63 (-2.07 to 0.81)
Pre-dialysis diastolic blood pressure (mmHg)	73.7 (71.7-75.7)	72.0 (70-74)	71.3 (69.3-73.2)	1.71 *** (0.97 to 2.45)	2.44 *** (1.7 to 3.18)	0.73 (0 to 1.46)
Post-dialysis diastolic blood pressure (mmHg)	68.3 (66.5-70.1)	66.8 (65-68.6)	66.8 (65-68.6)	1.51 *** (0.73 to 2.29)	1.49 *** (0.7 to 2.28)	-0.02 (-0.80 to 0.76)
Pre-dialysis heart rate (bpm)	73.8 (72.2-75.4)	75.1 (73.5-76.8)	75.6 (74-77.2)	-1.33 *** (-1.91 to -0.76)	-1.78 *** (-2.36 to -1.2)	-0.45 (-1.02 to 0.12)
Post-dialysis heart rate (bpm)	76.0 (74-78)	77.1 (75.1-79.1)	77.1 (75-79.1)	-0.31 (-0.91 to 0.29)	-0.9 ** (-1.5 to -0.3)	-0.59 (-1.21 to 0.03)
Systolic blood pressure fall >30 mmHg (%)	46.2	41.8	43.4	4.47 * (0.85 to 8.09)	2.78 (-0.83 to 6.4)	-1.69 (-5.28 to 1.91)
Dialysis hypotension (%)	7.4	6.7	7.4	0.71 (-1.31 to 2.73)	-0.01 (-2.04 to 2.01)	-0.73 (-2.74 to 1.28)

All values are presented as mean (95% confidence interval) using linear mixed effect model.

#All parameters except pre-dialysis and post-dialysis weight were adjusted for age, gender, dialysis vintage, diabetic status, body mass index, residual renal function, co-morbidity of ischemic heart disease, co-morbidity of congestive heart failure, dialysate composition (magnesium, calcium, and sodium concentrations), albumin-corrected plasma calcium level, plasma phosphorus level, and the number of different cardiovascular drugs. Pre-dialysis and post-dialysis weights were adjusted for all these factors except body mass index.

Abbreviations: HD, hemodialysis; UF, ultrafiltration; bpm, beats per minute.

* Denotes p<0.05, ** denotes p<0.01, and *** denotes p<0.001.

Supplementary file S2.

Weight, ultrafiltration volume and rate, blood pressure, and heart rate, adjusted analysis#: US study population.

	First HD of the week (N=2190)	Second HD of the week (N=1949)	Third HD of the week (N=1921)	First vs second HD of the week	First vs third HD of the week	Second vs third HD of the week
Pre-dialysis weight (kg)	82.9 (81.3-84.5)	82.5 (80.9-84.1)	82.4 (80.8-84)	0.44 *** (0.30 to 0.58)	0.53 *** (0.39 to 0.66)	0.09 (-0.05 to 0.23)
Post-dialysis weight (kg)^	80.5 (78.9-82.1)	80.3 (78.7-81.9)	80.2 (78.6-81.8)	0.25 *** (0.16 to 0.34)	0.32 *** (0.23 to 0.41)	0.08 (-0.02 to 0.17)
Excess weight at the start of the HD session (kg)	2.8 (2.8-2.9)	2.1 (2-2.2)	2.2 (2.1-2.3)	0.76 *** (0.68 to 0.83)	0.65 *** (0.57 to 0.72)	-0.11 ** (-0.18 to -0.03)
Total UF volume (ml)	2506 (2442-2570)	2256 (2191-2321)	2267 (2202-2333)	250.1 *** (199.6 to 300.6)	239.1 *** (188.5 to 289.7)	-11.0 (-63.2 to 41.1)
UF rate (ml/kg/h)	10.7 (10.5-11.0)	9.8 (9.6-10.1)	10.0 (9.7-10.2)	0.9 *** (0.74 to 1.06)	0.77 *** (0.61 to 0.93)	-0.14 (-0.30 to 0.03)
Pre-dialysis systolic blood pressure (mmHg)	146.0 (144.4-147.5)	143.7 (142.2-145.3)	144.6 (143-146.1)	2.25 *** (1.19 to 3.30)	1.39 ** (0.34 to 2.45)	-0.85 (-1.94 to 0.24)
Post-dialysis systolic blood pressure (mmHg)	136.4 (134.9-137.9)	134.9 (133.3-136.4)	135.1 (133.5-136.6)	1.58 ** (0.51 to 2.65)	1.37 * (0.30 to 2.44)	-0.21 (-1.32 to 0.89)
Pre-dialysis diastolic blood pressure (mmHg)	76.1 (75.2-77.0)	75.1 (74.2-75.9)	75.5 (74.6-76.4)	1.05 ** (0.40 to 1.71)	0.64 (-0.02 to 1.3)	-0.41 (-1.10 to 0.27)
Post-dialysis diastolic blood pressure (mmHg)	71.6 (70.8-72.5)	70.8 (70-71.7)	71.0 (70.1-71.8)	0.81 * (0.16 to 1.46)	0.67 * (0.02 to 1.32)	-0.14 (-0.81 to 0.53)
Pre-dialysis heart rate (bpm)	74.8 (74-75.7)	75.2 (74.3-76)	75.4 (74.6-76.3)	-0.34 (-0.85 to 0.17)	-0.62 * (-1.13 to -0.11)	-0.28 (-0.80 to 0.25)
Post-dialysis heart rate (bpm)	77.1 (76.2-78.0)	77.4 (76.5-78.4)	78.0 (77.1-78.9)	-0.31 (-0.91 to 0.29)	-0.90 ** (-1.50 to -0.30)	-0.59 (-1.21 to 0.03)
Systolic blood pressure fall >30 mmHg (%)	48.1	46.4	49.6	1.73 (-0.90 to 4.37)	-1.5 (-4.14 to 1.13)	-3.24 * (-5.96 to -0.51)
Dialysis hypotension (%)	15.4	17.6	17.0	-2.17 * (-4.18 to -0.15)	-1.61 (-3.63 to 0.40)	0.55 (-1.53 to 2.64)

All values are presented as mean (95% confidence interval) using linear mixed effect model.

#All parameters except pre-dialysis and post-dialysis weight were adjusted for age, gender, dialysis vintage, diabetic status, body mass index, residual renal function, co-morbidity of ischemic heart disease, co-morbidity of congestive heart failure, dialysate composition (magnesium, calcium, and sodium concentrations), albumin-corrected plasma calcium level, plasma phosphorus level, and the number of different cardiovascular drugs. Pre-dialysis and post-dialysis weights were adjusted for all these factors except body mass index.

Abbreviations: HD, hemodialysis; UF, ultrafiltration; bpm, beats per minute.

* Denotes p<0.05, ** denotes p<0.01, and *** denotes p<0.001.

Supplementary file S3.

Post-dialysis blood pressure in the Dutch and US population, adjusted for pre-dialysis systolic blood pressure#.

Dutch data:

	First HD of the week	Second HD of the week	Third HD of the week	First vs second HD of the week	First vs third HD of the week	Second vs third HD of the week
Post-dialysis systolic blood pressure (mmHg)	133.7 (130.7-136.7)	131.2 (128.2-134.2)	132.3 (129.3-135.3)	2.46 **	1.38	-1.08

US data:

	First HD of the week	Second HD of the week	Third HD of the week	First vs second HD of the week	First vs third HD of the week	Second vs third HD of the week
Post-dialysis systolic blood pressure (mmHg)	136.0 (134.8-137.3)	135.2 (133.9-136.5)	135.1 (133.8-136.4)	0.88	0.94	0.06

#Adjusted for age, gender, vintage, diabetic status, BMI, residual renal function, comorbidity of ischemic heart disease, comorbidity of congestive heart failure, dialysate composition (magnesium, calcium, and sodium), plasma calcium, plasma phosphorus, number of cardiovascular drugs, and pre-dialysis systolic blood pressure.

** Denotes p<0.01

Chapter 3

Causes and consequences of interdialytic weight gain

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ABSTRACT

Background: Higher interdialytic weight gain (IDWG) is associated with higher predialysis blood pressure and increased mortality. IDWG is also increasingly being recognized as an indicator of nutritional status. We studied in detail the associations of various patient factors and nutritional parameters with IDWG.
Methods: We collected data during one week for IDWG and hemodynamic parameters in 138 prevalent adult haemodialysis patients on a thrice-weekly haemodialysis schedule. A multivariate linear regression analysis was employed to identify factors that are associated with IDWG.
Results: The mean (±SD) age was 62.5 (±18.2) years, 36% were female, 36% had diuresis, and 23% had diabetes. Patients in the highest IDWG tertile were significantly younger, more frequently male, and had a significantly higher subjective global assessment score (SGA). A higher IDWG as a percentage of body weight (%IDWG) was associated with a younger age, greater height and weight, absence of diuresis, and lower postdialysis plasma sodium levels. The model with these five parameters explained 37% of the variance of %IDWG. Predialysis, intradialysis, and postdialysis diastolic blood pressure was significantly higher in the highest tertile of IDWG.
Conclusion: The most important associations of %IDWG are age, height, weight, diuresis, and postdialysis sodium. Patients with the highest IDWG have significantly higher diastolic blood pressures.

BACKGROUND

Interdialytic weight gain (IDWG) is the result of salt and water intake between two haemodialysis sessions. IDWG is used as a parameter for fluid intake while taking the daily urine output into account[1-2] A higher IDWG is associated with higher predialysis blood pressure[2-3], greater intradialytic reductions in blood pressure as a result of higher ultrafiltration rates[4], and increased mortality[5-7].

At the same time, IDWG is increasingly being recognized as an indicator of nutritional status[8-9-10-11]. Malnutrition is considered as a major complication among haemodialysis patients and can result in increased morbidity and mortality[12-13] Causes of malnutrition in dialysis patients are multi-factorial and include reduced appetite and food intake[12-14-15], protein-energy wasting as a result of chronic inflammation[16], and reduced physical activity[17]. Several studies demonstrated that a greater IDWG is directly associated with improved nutritional status[2-10-11]. Usvyat et al. recently showed that IDWG began to decline a year before death indicating that a decrease in IDWG has short-term adverse prognostic significance[18]. Thus, on the one hand, higher IDWG is associated with adverse effects such as higher blood pressure, however, on the other hand, higher IDWG may be associated with favourable effects such as better nutritional status.

The goal of this study was to identify the most important associations of a high IDWG in an effort to disentangle its ambiguous associations. To achieve this, we meticulously examined a cohort of 138 patients on a thrice-weekly haemodialysis schedule.

METHODS

Participants and Study design

We retrospectively collected data from 138 haemodialysis patients scheduled for thrice weekly haemodialysis who were older than 18 years and had been undergoing haemodialysis treatment for at least three months. Since IDWG tends to fall before death[18] and this may confound the relationship between IDWG and nutritional status in patients with a short life expectancy, we excluded patients who died within 6 months after collection of the data. We used data of IDWG, various nutritional parameters, and hemodynamic measurements during one week from the patients' records in November 2012. The study was performed in accordance with the principals of the Declaration of Helsinki and guidelines for Good Clinical Practice.

Dialysis regimens and Dietary consultation

Dialysis treatment consisted of conventional haemodialysis or home haemodialysis thrice weekly for four to five hours with blood flows and dialysate flows of 250-350 ml/min and 500-700 ml/min, respectively. All patients were dialyzed with low-flux polysulphone dialyzers and a constant dialysate conductivity of 13.9 mS/cm. The dialysate composition was as follows: sodium 139 mmol/l, potassium 1.0 or 2.0 mmol/l, calcium 1.5 mmol/l, magnesium 0,5 mmol/l, chloride 108 mmol/l, bicarbonate 34 mmol/l, acetate 3 mmol/l, glucose 1.0 g/l. Low-molecular-weight heparin was used as an anticoagulant.

Dry weight was evaluated clinically (peripheral oedema, signs of pulmonary congestion, intra- and interdialytic blood pressure course, muscle cramps) in combination with the predialysis cardiothoracic ratio on a chest X-ray as a surrogate marker of hydration status.

All patients had regular contact with the dietician every four to six weeks according to usual clinical practice. During these visits, the nutritional status was evaluated, and changes in weight, laboratory results, and appetite were monitored.

Measurements

For all of the patients, we collected demographic data including age, gender, level of education, and patient characteristics such as dialysis vintage, weight, and height. Body mass index (BMI) was calculated as: postdialysis weight (kg)/length $(m)^2$. Cardiovascular history was defined as any history of ischemic heart disease, congestive heart failure, stroke or peripheral vascular disease, and hypertension. Residual renal function was defined as diuresis ≥200 ml/day. Equilibrated Kt/V was calculated from pre- and postdialysis plasma urea concentration according to the second generation logarithmic Daurgirdas equation[19].

The nutritional status of the patients was assessed with various parameters: the seven-point subjective global assessment (SGA), serum albumin, dry body weight, body height, BMI, and protein catabolic rate (PCR). The SGA has been described and validated in dialysis patients in the Netherlands Cooperative Study on the Adequacy of Dialysis[20]. A score of '1' indicates severe protein energy wasting, and a score of '7' indicates a normal nutritional status. Blood samples were collected in heparin-coated tubes from the arterial line at the initiation and at the end of the first haemodialysis session of the study week in order to determine sodium and albumin levels. Plasma sodium was measured with the indirect method of ion-selective electrode on a Roche Modular (Hitachi, Tokyo, Japan).

IDWG was calculated as predialysis weight minus the postdialysis weight of the previous haemodialysis session. Since body weight may influence nutritional and fluid intake, the results are also shown for IDWG as a percentage of dry body weight (%IDWG)[9]. The ultrafiltration rate was calculated by dividing the ultrafiltration volume (ml) by the length of time of the dialysis session (hours) and target dry weight (kg). Blood pressure was measured with an automatic oscillometric monitor that is incorporated in the haemodialysis apparatus. The results of IDWG, ultrafiltration volume and rate, and blood pressure for the three haemodialysis sessions in the study week were averaged.

Statistical Analyses

Data are reported as mean±SD for continuous variables with normal distributions and numbers (percent) for categorical data. Demographic characteristics, laboratory data, and blood pressures were categorized into tertiles of IDWG and %IDWG. Differences between tertiles were analysed with ANOVA followed by Tukey's honest post hoc test. For categorical data, the Pearson Chi-Square test and the Generalized Cochran Mantel-Haenszel Test were used.

A multivariate linear regression analysis was utilized to identify patient factors including various nutritional parameters that were associated with IDWG and/or %IDWG. IDWG or %IDWG was entered as a response variable. The following possible explanatory variables were entered into the model: age, gender, weight, height, Kt/V, dialysis vintage, diuresis, diabetes, SGA, nPCR, serum albumin, and predialysis and postdialysis plasma sodium concentration (Figure 1). Next, to identify variables significantly contributing to IDWG, the Bayesian Information Criterion (BIC) for model selection was used[21]. Statistical analyses were performed with SPSS version 20 (SPSS inc., IBM company, USA) and statistical programming language R (R Development Core Team)[22]. Two-tailed P-values <0.05 were considered statistically significant.

Figure 1.
Schematic representation of possible causes and consequences of IDWG.

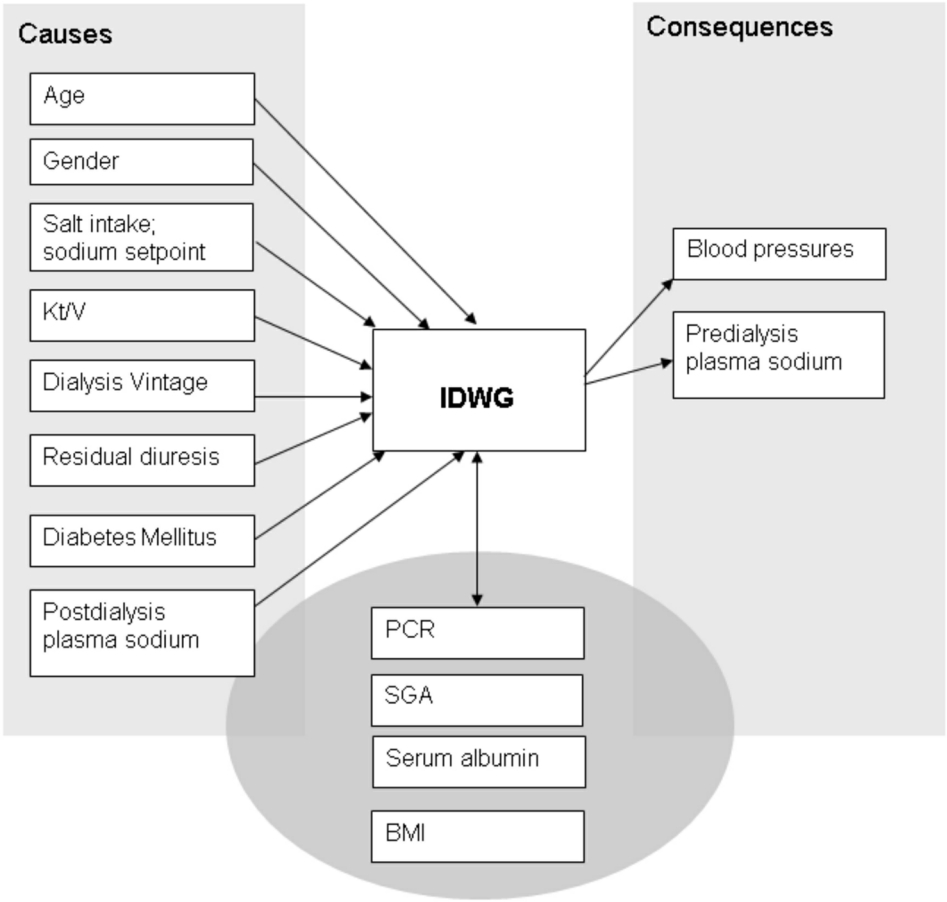


Table 1.
Patient characteristics for the total group and according to tertiles of absolute IDWG.

	Haemodialysis (n=138)	Tertile 1 <1.48L (n=46)	Tertile 2 1.48-2.09L (n=46)	Tertile 3 ≥2.09L (n=46)	P
Age (years)	62.5±18.2	68.0±17.6	63.9±17.4	55.7±17.7	0.004
Gender (female)	50 (36%)	23 (50%)	20 (43%)	7 (15%)	0.001*
Level of education	(n=135)				0.824
No education / elementary school	23 (17%)	9 (20%)	5 (11%)	9 (20%)	
Secondary school / high school	65 (47%)	22 (48%)	21 (46%)	22 (48%)	
Secondary vocational school	34 (25%)	10 (22%)	13 (28%)	11 (24%)	
Higher professional education / university	13 (9%)	3 (7%)	6 (13%)	4 (9%)	
Dry body weight (kg)	74.5±14.7	73.4±13.9	70.6±14.8	79.6±14.1	0.009*
Height (cm)	172±10.0	169±10.0	170±8.9	177±9.3	0.000*
Body mass index (kg/m²)	25±4.3	25.5±4.2	24.2±4.6	25.3±3.9	0.305
Kt/V	4.39±0.80	4.36±0.90	4.48±0.72	4.32±0.80	0.617
Dialysis vintage (years)	3.5±3.5	3.2±3.5	3.0±2.8	4.2±4.1	0.193
Weekly dialysis duration (h/week)	12.0±0.9	11.5±0.94	12.0±0.67	12.5±0.70	0.000*
Residual diuresis	49 (36%)	24 (52%)	15 (33%)	10 (22%)	0.008*
Diabetes Mellitus	32 (23%)	6 (13%)	13 (28%)	13 (28%)	0.136
Cardiovascular history	95 (69%)	31 (67%)	35 (76%)	29 (63%)	0.388
Nutritional status					
Subjective Global Assessment (SGA)	5.5±1.4	5.43±1.50	5.11±1.52	6.07±1.04	0.004*
SGA category					0.219
Severe malnutrition (SGA 1-2)	8 (6%)	4 (9%)	3 (7%)	1 (2%)	
Mild malnutrition (SGA 3-5)	45 (33%)	15 (33%)	19 (41%)	11 (24%)	
Good nutritional state (SGA 6-7)	85 (62%)	27 (59%)	24 (52%)	34 (74%)	
PCR (g/day)	69.0±19.6	65.3±18.1	66.9±21.7	74.6±17.9	0.051
nPCR (g/kg/day)	0.93±0.24	0.91±0.22	0.95±0.25	0.94±0.23	0.683
Albumin (g/l)	39.8±3.4	39.4±3.3	39.5±3.0	40.4±3.9	0.281
Predialysis plasma sodium (mmol/l)	138±3.6	138.5±3.0	137.8±3.8	137.5±3.9	0.433
Postdialysis plasma sodium (mmol/l)	138±2.3	138.5±1.9	137.2±2.3	137.8±2.6	0.024*
Treatment characteristics					
Absolute IDWG	1.79±0.9	0.82±0.53	1.79±0.20	2.75±0.54	0.000*
%IDWG (% of dry body weight)	2.44±1.2	1.16±0.83	2.64±0.54	3.52±0.74	0.000*
UF rate (ml/h/kg dry body weight)	7.5±2.3	4.9±2.2	8.1±2.0	9.5±2.3	0.000*

Abbreviations: SGA: subjective global assessment, (n)PCR: (normalized) protein catabolic rate, IDWG: Interdialytic weight gain, UF: ultrafiltration.
P values: differences in means between the 3 groups tested by ANOVA.

RESULTS

Patient characteristics

Patient characteristics are depicted in Table 1. The mean (±SD) age was 62.5 (±18.2) years, 36% were female, 36% had diuresis, and 23% had diabetes. Patients in the highest IDWG tertile were significantly younger (P=0.004), more frequently male (P=0.001), taller (P<0.0001), heavier (P=0.009), and had a significantly higher SGA (P=0.004) compared with patients in the other tertiles (Table 1). Similar results were obtained for %IDWG (data not shown).

IDWG and possible explanatory variables.

In the multivariate linear regression model with optimizing BIC, the response variable IDWG was significantly associated with the explanatory variables height, age, the presence of residual diuresis, and postdialysis sodium levels. The model incorporating these four variables explained 35% of the variance of absolute IDWG (Table 2). The response variable %IDWG was significantly associated with the presence of residual diuresis, age, weight, height, and post-dialysis sodium levels. The model with these five variables explained 37% of the variance of the %IDWG (Table 3). Height was positively associated with absolute IDWG and %IDWG. Weight was positively associated with %IDWG. Age had a negative effect on IDWG whereby one year of older age resulted in a decrease of 0.016 kg and 0.023% in absolute IDWG and %IDWG, respectively. The presence of residual diuresis was associated with a significantly lower IDWG and %IDWG. Postdialysis sodium levels had a negative association with both IDWG and %IDWG: higher postdialysis sodium levels were associated with lower IDWG and %IDWG. Since this was an unexpected finding, we analysed the course of pre- to postdialysis plasma sodium concentration per tertile (Supplementary file 1). Patients in the middle and highest IDWG tertiles had a lower plasma sodium concentration, both pre- and postdialysis, compared with patients in the lowest IDWG tertile (Table 1). However, differences between the IDWG tertiles were only significant for postdialysis sodium concentration (Table 1). The other tested dependent variables (Kt/V, dialysis vintage, diabetes, SGA, serum albumin, and predialysis plasma sodium level) did not significantly contribute to explaining the variance of absolute IDWG or %IDWG.

Table 2.
Multivariate linear regression analysis with model building strategy Bayesian Information Criterion (BIC) – factors that are associated with absolute IDWG.

					95% CI	
	Estimate	**SE**	**T**	**P**	**Lower**	**Upper**
Height (cm)	0.031	0.006	4.91	0.000	0.019	0.044
Age (years)	-0.016	0.003	-4.52	0.000	-0.023	-0.009
Diuresis (yes)	-0.658	0.133	-4.94	0.000	-0.921	-0.395
Postdialysis plasma sodium (mmol/l)	-0.068	0.027	-2.50	0.014	-0.122	-0.014

IDWG was entered as a response variable, the other parameters as explanatory variables.
The variance of absolute IDWG is explained for 35% by the explanatory variables.
Abbreviations: SE: standard error, CI: confidence interval.

Table 3.
Multivariate linear regression analysis with model building strategy Bayesian Information Criterion (BIC) – factors that are associated with %IDWG.

					95% CI	
	Estimate	**SE**	**T**	**P**	**Lower**	**Upper**
Diuresis (yes)	-0.887	0.177	-5.02	0.000	-1.236	-0.537
Age (years)	-0.023	0.005	-5.05	0.000	-0.032	-0.014
Weight (kg)	0.024	0.007	-3.43	0.000	-0.037	-0.010
Height	0.032	0.010	3.12	0.002	0.012	0.052
Postdialysis plasma sodium (mmol/l)	-0.102	0.036	-2.82	0.006	-0.173	-0.030

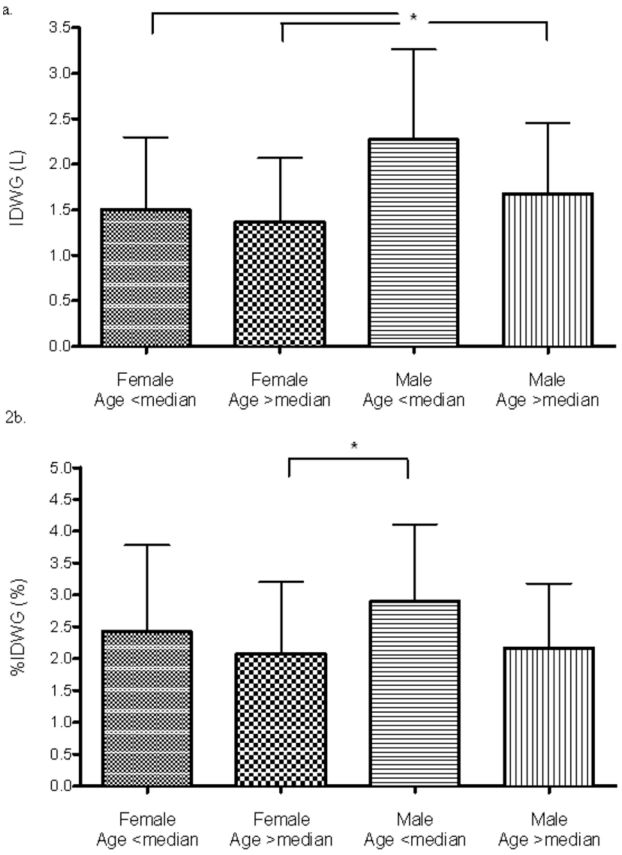
Relative IDWG was entered as a response variable, and the other parameters as explanatory variables.
The variance of %IDWG is explained for 37% by the explanatory variables.
Abbreviations: SE: standard error, CI: confidence interval.

Effect of gender and age

Table 1 shows that patients with the highest IDWG (tertile 3) were younger and more frequently male. As demonstrated in Figure 2a, younger males (median age ≤ 65 years (yr)) indeed had a significantly higher IDWG compared with younger females (median age ≤ 69.5 yr, P=0.002), older females (median age > 69.5 yr, P=0.000), and older males (median age > 65 yr, P=0.008). For %IDWG, there was only a significant difference between younger males (median age ≤ 65 yr) and older females (median age > 69.5 yr, P=0.030) (figure 2b).

Figure 2.

The combined effect of age and gender on absolute IDWG (upper panel) and %IDWG (lower panel).



Error bars indicate standard deviation. * Indicates a significant difference.

IDWG and blood pressure

Pre-, intra- and postdialysis systolic blood pressure did not vary significantly between tertiles of IDWG. Predialysis, intradialysis, and postdialysis diastolic blood pressure (DBP) was significantly higher in the highest IDWG tertile compared with the lowest tertile (Table 4, Figures 3a and 3b). For %IDWG, predialysis and intradialysis DBP was significantly higher in the highest %IDWG tertile compared with the lowest tertile (Table 5, Figure 3c and 3d).

Table 4.

Differences in blood pressures between tertiles of absolute IDWG.

	Tertile 1 IDWG <1.48 L (N=46)	Tertile 2 IDWG 1.48 – 2.09 L (N=46)	Tertile 3 IDWG ≥2.09 L (N=46)	P#	Tertiles	95% CI for differences between tertiles
SBP (mm/Hg) predialysis	143.3±22.3	143.4±25.4	149.5±24.6	0.367	1 – 2 3 – 2 3 – 1	[-12.01 – 11.82] [-5.77 – 18.06] [-5.68 – 18.16]
DBP (mm/Hg) predialysis	67.4±12.6	65.6±12.0	74.9±15.5	0.003*	1 – 2 3 – 2 3 – 1	[-4.90 – 8.37] [2.64 – 15.91]* [0.90 – 14.17]*
SBP (mm/Hg) intradialysis	133.1±21.3	132.0±26.3	135.6±23.4	0.766	1 – 2 3 – 2 3 – 1	[-10.77 – 13.05] [-8.40 – 15.70] [-9.68 – 14.69]
DBP (mm/Hg) intradialysis	64.1±12.4	61.9±12.8	72.6±16.1	0.001*	1 – 2 3 – 2 3 – 1	[-4.70 – 9.10] [3.65 – 17.62]* [1.37 – 15.49]*
SBP (mm/Hg) postdialysis	142.7±24.4	135.7±27.0	134.3±26.2	0.250	1 – 2 3 – 2 3 – 1	[-5.8 – 19.80] [-14.24 – 11.35] [-21.24 – 4.35]
DBP (mm/Hg) postdialysis	66.4±12.6	62.0±10.3	70.5±14.4	0.006*	1 – 2 3 – 2 3 – 1	[-1.81 – 10.57] [2.31 – 14.69]* [-2.07 – 10.31]

Abbreviations: IDWG: interdialytic weight gain, CI: confidence interval; SBP: systolic blood pressure. DBP: diastolic blood pressure.

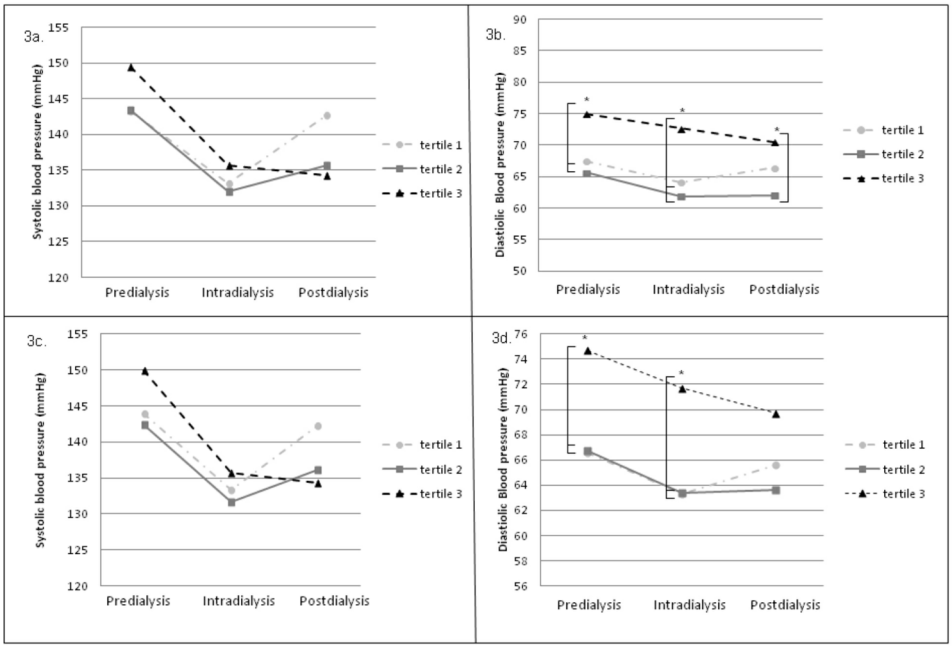
#P value denotes differences between the tertiles with ANOVA. Differences between the groups were analysed with a post-hoc Tukey Honest test.

Table 5.
Differences in blood pressures within tertiles of %IDWG.

	Tertile 1 IDWG <2.00% (N=46)	Tertile 2 IDWG 2.00 – 2.97% (N=46)	Tertile 3 IDWG ≥2.97% (N=46)	P#	Tertiles	95% CI for differences between tertiles
SBP (mm/Hg) predialysis	143.9±21.3	142.4±25.2	149.9±25.5	0.294	1 – 2 3 – 2 3 – 1	[-10.38 – 13.42] [-4.44 – 19.36] [-5.96 – 17.84]
DBP (mm/Hg) predialysis	66.6±12.4	66.7±12.5	74.7±15.4	0.005*	1 – 2 3 – 2 3 – 1	[-6.76 – 6.58] [1.35 – 14.68]* [1.43 – 14.77]*
SBP (mm/Hg) intradialysis	133.3±20.9	131.7±24.7	135.7±25.6	0.732	1 – 2 3 – 2 3 – 1	[-10.32 – 13.48] [-8.09 – 16.13] [-9.67 – 14.55]
DBP (mm/Hg) intradialysis	63.3±12.4	63.4±13.8	71.7±15.7	0.008*	1 – 2 3 – 2 3 – 1	[-7.08 – 6.93] [1.17 – 15.42]* [1.25 – 15.50]*
SBP (mm/Hg) postdialysis	142.3±23.6	136.1±26.9	134.3±27.1	0.305	1 – 2 3 – 2 3 – 1	[-6.64 – 18.99] [-14.63 – 11.00] [-20.80 – 4.83]
DBP (mm/Hg) postdialysis	65.6±11.7	63.6±12.4	69.7±14.1	0.071	1 – 2 3 – 2 3 – 1	[-4.32 – 8.29] [-0.24 – 12.37] [-2.23 – 10.38]

Abbreviations: IDWG: interdialytic weight gain, CI: confidence interval; SBP: systolic blood pressure; DBP: diastolic blood pressure.
#P value denotes differences between the tertiles with ANOVA. Differences between the groups were analysed with a post-hoc Tukey Honest test.

Figure 3.
Differences in systolic (left panel) and diastolic (right panel) blood pressures between absolute IDWG (upper panel) and %IDWG tertiles (lower panel).



DISCUSSION

In this study, we found that a higher IDWG was notably evident for those of a younger age, greater height and weight, presence of residual diuresis, and lower postdialysis sodium levels. In a combined analysis of age and gender, younger men had the highest IDWG, and patients with a higher IDWG had significantly higher diastolic blood pressures. Although gender was not associated with IDWG in multivariate analysis, body height and weight were important determinants of IDWG. Our results indicate that dietary advice including fluid restriction should be individualized based on age, body height and weight, and residual diuresis.

Our finding that age is an important factor in IDWG is in accordance with previous studies[23-24]. Residual diuresis is an obvious determinant of IDWG and reveals that it is important to maintain residual diuresis.

SGA was significantly higher in the highest IDWG tertile, however, in multivariate analysis, SGA did not significantly contribute to IDWG. Other nutritional indicators such as serum albumin and nPCR also did not have significant associations with IDWG. In this study, in contrast with other studies, we did not find a strong association between IDWG and nutritional status[2-8-10-11]. PCR was higher in the highest IDWG tertile, but when PCR was normalised by weight (nPCR) there was no significant difference between IDWG tertiles. In multivariate analysis, nPCR was not significantly associated with IDWG. Taller and heavier dialysis patients generally consume more protein and, thus, have a higher PCR. A higher PCR may contribute to a higher IDWG. When in a steady state, PCR mirrors protein anabolism/protein intake. A higher protein intake could reflect a higher overall metabolic rate with more substantial amounts of proteins, carbohydrates, and fats used for energy production and the subsequent generation of carbon dioxide and water. The carbon hydrate is eliminated from the body by pulmonary ventilation whereas the water will result in higher IDWG. However, the contribution of this effect to the total IDWG has not yet been quantified. Additionally, it is conceivable that patients who consume more protein have a higher salt intake resulting in thirst. Thirst is prevalent in dialysis patients and is associated with higher IDWG and lower quality of life[25].

Salt intake is a major factor in IDWG[26]. Haemodialysis patients primarily have osmometric thirst of which salt intake is the primary cause[9-26], however, during haemodialysis, there may also be diffusive sodium transfer to the patient. Immediately following a dialysis session, patients may also experience volumetric thirst caused by hypovolemia as a result of the ultrafiltration of fluid[26]. Several studies found that diffusive sodium transfer to the patient during haemodialysis contributed to incomplete sodium removal which could be prevented by individualizing the dialysate sodium prescription[27-30]. Combined dietary and dialytic sodium restriction can possibly prevent volume overload in haemodialysis patients[28-31].

Remarkably, higher postdialysis sodium levels were associated with a lower IDWG. This contrasts with the general belief that higher postdialysis plasma sodium levels induce thirst and subsequent increased fluid intake. This can possibly be explained by the fact that patients with a high IDWG often begin haemodialysis with a low plasma sodium concentration resulting from dilution that does not rise to normal levels during treatment despite diffusive sodium transfer to the patient during haemodialysis. Our finding that postdialysis plasma sodium concentrations indeed differ between the IDWG tertiles may suggest that this could be the case (Supplementary file 1). Additionally, patients with a high IDWG often do not achieve their dry weight by the end of the dialysis session and may have a decreased postdialysis plasma sodium concentration as a result of dilution. There are only a minimal number of studies that have specifically studied the association between postdialysis plasma sodium levels and IDWG. To the best of our knowledge, there is only one study that found a trend towards higher postdialysis sodium levels with higher IDWG, but this was not statistically significant[32]. A few authors measured predialysis and postdialysis plasma sodium concentration and suggested that postdialysis sodium reflects the prescription of the dialysate sodium[33-34]. However, in neither of these studies was the relation between postdialysis plasma sodium levels and IDWG studied. All of our patients were dialyzed with a dialysate sodium concentration of 139 mmol/l. Thus, differences in sodium dialysate concentration cannot explain the association between the higher postdialysis sodium levels and lower IDWG. Notably, predialysis sodium in our study was not associated with higher IDWG, however, in other studies, a relationship between low predialysis plasma sodium and high IDWG was found[31-35].

In our study, patients with the highest IDWG had a significantly higher predialysis DBP. This observation is in accordance with previous studies[2-4]. Inrig et al. found that a higher %IDWG was associated with higher predialysis blood pressure[4]. Kuipers et al. found that predialysis blood pressure is highest during the first dialysis session of the week probably due to a more pronounced fluid overload[3]. Patients with the highest IDWG also had a significantly higher DBP during and after dialysis. These findings are in line with other studies and are a consequence of a higher IDWG[3-27-36].

According to the EBPG guidelines, diet restrictions for fluids do not need to be adjusted for weight, gender, body composition, or age. The guidelines for daily fluid intake vary from 500 to 1000 ml in addition to daily urine output, although 4.0-4.5% weight gain as a percentage of dry weight may be acceptable in patients with an optimal nutritional intake and salt restriction [9]. Our results show that various factors affect IDWG. Being both young and male is associated with a higher IDWG. Flythe et al. suggested a different approach to the fluid guidelines that focuses on the amount of time of the treatment that allow target levels of ultrafiltration to be achieved without exceeding ultrafiltration rates of 10 ml/hour/kg dry body weight while still respecting a minimum time to enable beneficial dialysis efficiency[37]. Besides fluid restriction, longer and/or more frequent dialysis sessions have been suggested to decrease the IDWG[37-38].

However, various studies indicated an increase in daily fluid intake after the transition from conventional to frequent nocturnal haemodialysis[39-41]. Munoz Mendoza et al. demonstrated that patients undergoing thrice-weekly in-center nocturnal haemodialysis with lower sodium concentrations in the dialysate experienced a lower IDWG and predialysis systolic blood pressure compared with treatment on dialysate sodium concentrations of the standard 140 mEq/L[38]. Modification of dialysate sodium concentrations should also be considered as a tool to lower the IDWG[38].

A limitation of our study is the relatively small number of patients. However, most of our results are in accordance with previous studies. The use of predialysis serum albumin concentration as a marker for nutritional status in studies on IDWG is limited by possible dilution as a result of fluid overload[42-43]]. Another limitation is that we did not include information on antihypertensive medication. The strong points are that we created comprehensive models of factors that may be associated with IDWG including nutritional parameters and that we also focus on the relation between IDWG and blood pressure.

Our overall conclusion is that the major associations of the IDWG and %IDWG in our cohort are age, body height and weight, diuresis, and postdialysis sodium. Being male and of a young age are major risk factors for a significantly higher IDWG. Our findings highlight the importance of a personalized advice on fluid and sodium restriction.

REFERENCES

1. Ifudu O, Uribarri J, Rajwani I, et al. Relation between interdialytic weight gain, body weight and nutrition in hemodialysis patients. *Am J Nephrol*. 2002;22(4):363-368.
2. Lopez-Gomez JM, Villaverde M, Jofre R, Rodriguez-Benitez P, Perez-Garcia R. Interdialytic weight gain as a marker of blood pressure, nutrition, and survival in hemo dialysis patients. *Kidney Int Suppl*. 2005;(93)(93):S63-8.
3. Kuipers J, Usvyat LA, Oosterhuis JK, et al. Variability of predialytic, intradialytic, and postdialytic blood pressures in the course of a week: A study of dutch and US maintenance hemodialysis patients. *Am J Kidney Dis*. 2013;62(4):779-788.
4. Inrig JK, Patel UD, Gillespie BS, et al. Relationship between interdialytic weight gain and blood pressure among prevalent hemodialysis patients. *Am J Kidney Dis*. 2007;50(1):108-18, 118.e1-4.
5. Foley RN, Herzog CA, Collins AJ, United States Renal Data System. Blood pressure and long-term mortality in united states hemodialysis patients: USRDS waves 3 and 4 study. *Kidney Int*. 2002;62(5):1784-1790.
6. Flythe JE, Curhan GC, Brunelli SM. Disentangling the ultrafiltration rate-mortality association: The respective roles of session length and weight gain. *Clin J Am Soc Nephrol*. 2013;8(7):1151-1161.
7. Sarkar SR, Kotanko P, Levin NW. Interdialytic weight gain: Implications in hemodialysis patients. *Semin Dial*. 2006;19(5):429-433.
8. Kalantar-Zadeh K, Regidor DL, Kovesdy CP, et al. Fluid retention is associated with cardiovascular mortality in patients undergoing long-term hemodialysis. *Circulation*. 2009;119(5):671-679.
9. Fouque D, Vennegoor M, ter Wee P, et al. EBPG guideline on nutrition. *Nephrol Dial Transplant*. 2007;22 Suppl 2:ii45-87.
10. Sherman RA, Cody RP, Rogers ME, Solanchick JC. Interdialytic weight gain and nutritional parameters in chronic hemodialysis patients. *Am J Kidney Dis*. 1995;25(4):579-583.
11. Testa A, Beaud JM. The other side of the coin: Interdialytic weight gain as an index of good nutrition. *Am J Kidney Dis*. 1998;31(5):830-834.
12. Araujo IC, Kamimura MA, Draibe SA, et al. Nutritional parameters and mortality in incident hemodialysis patients. *J Ren Nutr*. 2006;16(1):27-35.

13. Herselman M, Moosa MR, Kotze TJ, Kritzinger M, Wuister S, Mostert D. Protein-energy malnutrition as a risk factor for increased morbidity in long-term hemodialysis patients. *J Ren Nutr*. 2000;10(1):7-15.

14. Bossola M, Muscaritoli M, Tazza L, et al. Variables associated with reduced dietary intake in hemodialysis patients. *J Ren Nutr*. 2005;15(2):244-252.

15. Burrowes JD, Larive B, Chertow GM, et al. Self-reported appetite, hospitalization and death in haemodialysis patients: Findings from the hemodialysis (HEMO) study. *Nephrol Dial Transplant*. 2005;20(12):2765-2774.

16. Carrero JJ, Stenvinkel P, Cuppari L, et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: A consensus statement from the international society of renal nutrition and metabolism (ISRNM). *J Ren Nutr*. 2013;23(2):77-90.

17. Johansen KL, Kaysen GA, Young BS, Hung AM, da Silva M, Chertow GM. Longitudinal study of nutritional status, body composition, and physical function in hemodialysis patients. *Am J Clin Nutr*. 2003;77(4):842-846.

18. Usvyat LA, Barth C, Bayh I, et al. Interdialytic weight gain, systolic blood pressure, serum albumin, and C-reactive protein levels change in chronic dialysis patients prior to death. *Kidney Int*. 2013;84(1):149-157.

19. Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume kt/V: An analysis of error. *Journal of the American Society of Nephrology*. 1993;4(5):1205-1213.

20. Visser R, Dekker FW, Boeschoten EW, Stevens P, Krediet RT. Reliability of the 7-point subjective global assessment scale in assessing nutritional status of dialysis patients. *Adv Perit Dial*. 1999;15:222-225.

21. Schwarz G. Estimating the dimension of a model. *The annals of statistics*. 1978;6(2):461-464.

22. Bates D, Maechler M, Bolker B, Walker S. Lme4: Linear mixed-effects models using eigen and S4. R package version 1.1-7. *This is computer program (R package).The URL of the package is:* http://CRAN.R-project.org/package= *lme4*. 2014.

23. Yang SC, Chiang CK, Hsu SP, Hung KY. Relationship between interdialytic weight gain and nutritional markers in younger and older hemodialysis patients. *J Ren Nutr*. 2008;18(2):210-222.

24. Testa A, Plou A. Clinical determinants of interdialytic weight gain. *J Ren Nutr*. 2001;11(3):155-160.

25. Fan WF, Zhang Q, Luo LH, Niu JY, Gu Y. Study on the clinical significance and related factors of thirst and xerostomia in maintenance hemodialysis patients. *Kidney Blood Press Res*. 2013;37(4-5):464-474.

26. Lindley EJ. Reducing sodium intake in hemodialysis patients. *Semin Dial*. 2009;22(3):260-263.

27. Van der Sande FM, Kooman JP, Leunissen KM. Intradialytic hypotension--new concepts on an old problem. *Nephrol Dial Transplant*. 2000;15(11):1746-1748.

28. Kooman JP, van der Sande F, Leunissen K, Locatelli F. Sodium balance in hemodialysis therapy. *Semin Dial*. 2003;16(5):351-355.

29. Penne EL, Levin NW, Kotanko P. Improving volume status by comprehensive dietary and dialytic sodium management in chronic hemodialysis patients. *Blood Purif*. 2010;30(1):71-78.

30. Thijssen S, Raimann JG, Usvyat LA, Levin NW, Kotanko P. The evils of intradialytic sodium loading. *Contrib Nephrol*. 2011;171:84-91.

31. Hecking M, Karaboyas A, Saran R, et al. Dialysate sodium concentration and the association with interdialytic weight gain, hospitalization, and mortality. *Clin J Am Soc Nephrol*. 2012;7(1):92-100.

32. Abbas Ghulam G. Relationship of postdialysis serum sodium level and interdialytic weight gain in patients on maintenance hemodialysis. *Journal of the College of Physicians and Surgeons--Pakistan : JCPSP*. 2007-8;17(8):482-5.

33. Hecking M, Kainz A, Horl WH, Herkner H, Sunder-Plassmann G. Sodium setpoint and sodium gradient: Influence on plasma sodium change and weight gain. *Am J Nephrol*. 2011;33(1):39-48.

34. Thomson BK, Dixon SN, Huang SH, et al. Modifiable variables affecting interdialytic weight gain include dialysis time, frequency, and dialysate sodium. *Hemodial Int*. 2013;17(4):576-585.

35. Hecking M, Karaboyas A, Saran R, et al. Predialysis serum sodium level, dialysate sodium, and mortality in maintenance hemodialysis patients: The dialysis outcomes and practice patterns study (DOPPS). *Am J Kidney Dis*. 2012;59(2):238-248.

36. Ventura JE, Sposito M. Volume sensitivity of blood pressure in end-stage renal disease. *Nephrol Dial Transplant*. 1997;12(3):485-491.

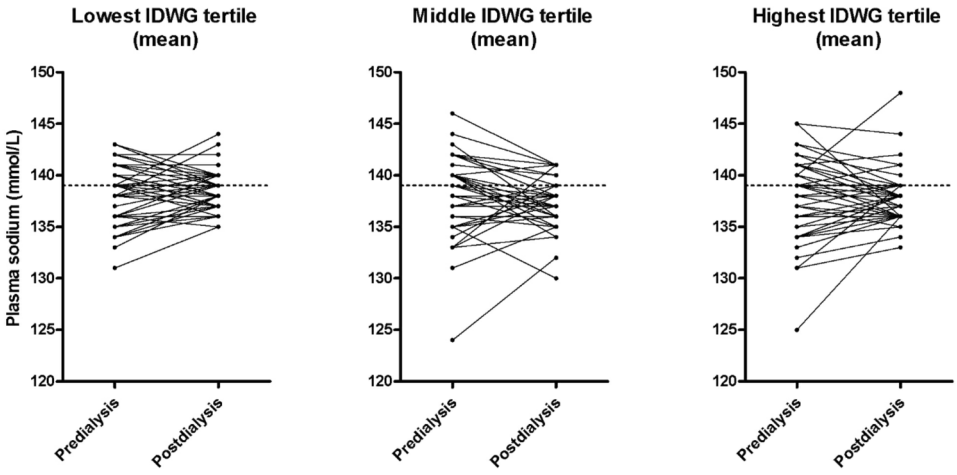
37. Flythe JE, Brunelli SM. The risks of high ultrafiltration rate in chronic hemodialysis: Implications for patient care. *Semin Dial*. 2011;24(3):259-265.

38. Munoz Mendoza J, Bayes LY, Sun S, Doss S, Schiller B. Effect of lowering dialysate sodium concentration on interdialytic weight gain and blood pressure in patients

undergoing thrice-weekly in-center nocturnal hemodialysis: A quality improvement study. *Am J Kidney Dis*. 2011;58(6):956-963.

39. Lacson Jr. E, Wang W, Lester K, Ofsthun N, Lazarus JM, Hakim RM. Outcomes associated with in-center nocturnal hemodialysis from a large multicenter program. *Clin J Am Soc Nephrol*. 2010;5(2):220-226.
40. Ipema KJ, van der Schans CP, Vonk N, et al. A difference between day and night: Protein intake improves after the transition from conventional to frequent nocturnal home hemodialysis. *J Ren Nutr*. 2012;22(3):365-372.
41. Demirci C, Ozkahya M, Demirci MS, et al. Effects of three times weekly eight-hour nocturnal hemodialysis on volume and nutritional status. *Am J Nephrol*. 2013;37(6):559-567.
42. Jones CH, Akbani H, Croft DC, Worth DP. The relationship between serum albumin and hydration status in hemodialysis patients. *J Ren Nutr*. 2002;12(4):209-212.
43. Antlanger M, Hecking M, Haidinger M, et al. Fluid overload in hemodialysis patients: A cross-sectional study to determine its association with cardiac biomarkers and nutritional status. *BMC Nephrol*. 2013;14:266-2369-14-266.

Supplementary file 1.
Course of pre- and postdialysis plasma sodium concentration per absolute IDWG tertile.



Chapter 4

Prevalence of dialysis hypotension - A three-month, prospective study of 3818 hemodialysis sessions in 124 hemodialysis patients

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ABSTRACT

Background: Intradialytic hypotension (IDH) is considered one of the most frequent complications of haemodialysis with an estimated prevalence of 20-50%, but studies investigating its exact prevalence are scarce. A complicating factor is that several definitions of IDH are used. The goal of this study was, to assess the prevalence of IDH, primarily in reference to the European Best Practice Guideline (EBPG) on haemodynamic instability: A decrease in systolic blood pressure (SBP) ≥20 mmHg or in mean arterial pressure (MAP) ≥10 mmHg associated with a clinical event and the need for nursing intervention.

Methods: During 3 months we prospectively collected haemodynamic data, clinical events, and nursing interventions of 3818 haemodialysis sessions from 124 prevalent patients who dialyzed with constant ultrafiltration rate and dialysate conductivity. Patients were considered as having frequent IDH if it occurred in >20% of dialysis sessions.

Results: Decreases in SBP ≥20 mmHg or MAP ≥10 mmHg occurred in 77.7%, clinical symptoms occurred in 21.4%, and nursing interventions were performed in 8.5% of dialysis sessions. Dialysis hypotension according to the full EBPG definition occurred in only 6.7% of dialysis sessions. Eight percent of patients had frequent IDH.

Conclusion: The prevalence of IDH according to the EBPG definition is low. The dominant determinant of the EBPG definition was nursing intervention since this was the component with the lowest prevalence. IDH seems to be less common than indicated in the literature but a proper comparison with previous studies is complicated by the lack of a uniform definition.

BACKGROUND

Intradialytic hypotension (IDH) is considered one of the most frequent complications of haemodialysis treatment and is associated with increased cardiovascular morbidity and mortality[1]. Various reviews report that up 30% of haemodialysis sessions are complicated by IDH[2-9]. However, studies on the prevalence of IDH are relatively scarce[10-13] and most of these studies were conducted more than 10 years ago[10-11-13]. Since then, dialysis techniques have improved and there is more awareness of strategies to prevent IDH, e.g. by lowering the dialysate temperature[14-15] and monitoring of relative blood volume changes[16]. At the same time, the average age of dialysis patients as well as the proportion of patients with significant co-morbidities such as diabetes mellitus and heart failure has increased[17-18]. It follows that the current prevalence of IDH is unknown.

A complicating factor in the analysis of IDH is that many different definitions of hypotension are used in the literature. These vary from liberal definitions that only require a minimum fall (e.g. ^{3}20 or ^{3}30 mmHg) in systolic blood pressure (SBP)[19-21] to strict definitions that require the combination of a clinical event and a nursing intervention in addition to a minimum fall in blood pressure[22-24]. The European Best Practice Guideline (EBPG) on haemodynamic instability defines IDH as a decrease in SBP ≥20 mmHg or a decrease in mean arterial pressure (MAP) by ≥10 mmHg associated with a clinical event and the need for a nursing intervention[22]. To the best of our knowledge, there are only two small studies that investigated the prevalence of IDH according to the EBPG definition[24-25].

The goal of this study was to assess the prevalence of IDH and to identify patient and treatment factors that are associated with its presence. For this purpose, we prospectively collected the haemodynamic data, clinical events and nursing interventions of 3818 dialysis sessions from 124 patients. We primarily used the EBPG definition[22] and studied in detail the prevalence of the separate items of this definition to get a better insight in their relative contributions to the definition. Additionally, we computed the prevalence of IDH using additional cut-off values for the required blood pressure drop (≥30 mmHg and ≥40 mmHg). These analyses facilitate the comparison of the prevalence of IDH in our population with previous studies that used other definitions.

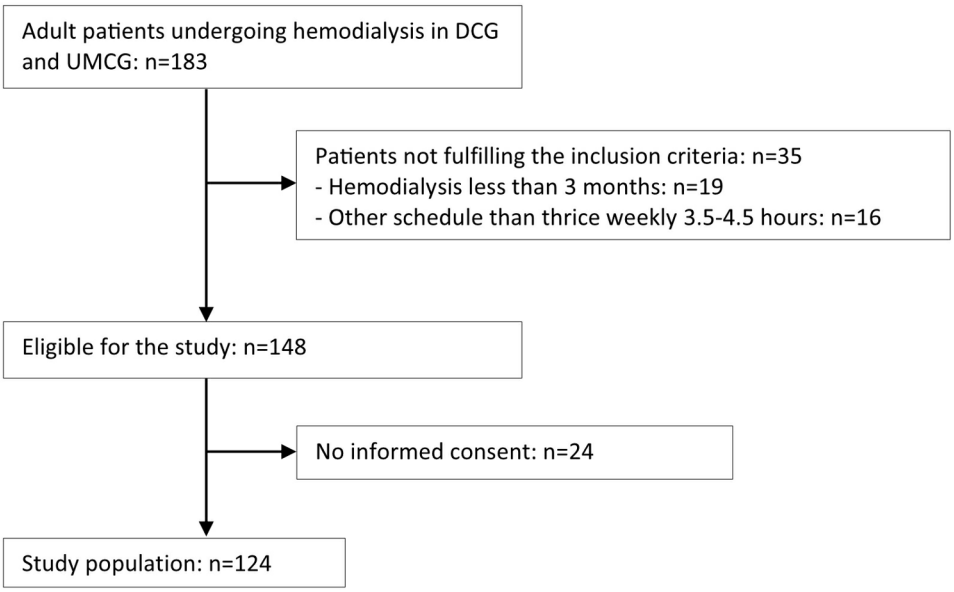
METHODS

Patients

This multicenter prospective observational study included adult (≥18 years) incenter haemodialysis patients from the Dialysis Center Groningen and the dialysis unit of the University Medical Center Groningen (figure 1). They were eligible for the study when they fulfilled the following criteria: maintenance bicarbonate haemodialysis for more than 3 months, three times a week 3.5 to 4.5 hours haemodialysis schedule.

This observational study was conducted without intervention or obtaining any patient material. The laboratory measurements described in this manuscript were performed as part of clinical routine. Therefore, according to Dutch legislation, an ethic statement for approval by the local Medical Ethical Committee (University Medical Center Groningen) was not necessary. All personal information was de-identified and analyzed anonymously. Patients gave oral informed consent.. The study was performed in accordance with the principles of the Declaration of Helsinki.

Figure 1.
The details of patient selection.



Study protocol

During 3 months (February, March and April) we prospectively collected the haemodynamic data of all the haemodialysis sessions from participating patients. At each session, patients were evaluated for pre- and postdialysis weight and pre-, intra-, and postdialysis blood pressures and heart rate, ultrafiltration volume, and the occurrence of clinical events possibly related to dialysis hypotension, and nursing interventions. Clinical events were defined as nausea, dizziness, light-headedness, fatigue occurring during haemodialysis, muscle cramps, loss of consciousness or any other additional complaint that was related to the dialysis procedure as judged by the patient and/or nurse (miscellaneous clinical events). Nursing interventions were defined as temporary interruption of ultrafiltration, Trendelenburg position, and administration of intravenous fluids. All data were registered on a run sheet and stored electronically.

Blood pressure and heart rate were measured with an automated oscillometric monitor at standardized intervals: before haemodialysis, at 10, 30, 60, 120, and 180 min intra-dialysis, and at the end of the dialysis session (240 min of dialysis). Haemodialysis sessions during hospitalization were excluded from the analysis. Prescriptions regarding dry weight and antihypertensive medication were made by the nephrologists during their weekly visit to the participating patients. Dry weight was evaluated clinically (peripheral edema, signs of pulmonary congestion, intra- and extra-dialytic blood pressure course, muscle cramps) and by the cardiopulmonary radiological aspect. Ultrafiltration rate was calculated by dividing ultrafiltration volume by dialysis session length.

Cardiovascular history was defined as any history of ischemic heart disease, congestive heart failure, stroke or peripheral vascular disease. Residual diuresis was defined as ≥200 ml/day. Equilibrated Kt/V was calculated from pre- and postdialysis plasma urea concentration according to the second-generation logarithmic Daugirdas equation[26].

Dialysis hypotension was primarily defined according to the EBPG definition[22] as a decrease in SBP ≥20 mmHg or a decrease in MAP by ≥10 mmHg associated with a clinical event and need for nursing interventions. Patients were considered to have frequent dialysis hypotension when they fulfilled the full EBPG definition of dialysis hypotension in ≥20% of dialysis sessions. In separate analyses, we additionally studied the prevalence of dialysis hypotension using different cut-off values (≥30 mmHg and ≥40 mmHg) as the required blood pressure drop.

Dialysis settings

All patients were dialysed with bicarbonate dialysis, thrice weekly for 3.5 to 4.5 hours with a low-flux polysulphone hollow-fiber dialyser, F8 or F10 (Fresenius Medical Care, Bad Homburg, Germany). Blood flow rates ranged between 250 and 350 ml/min. The dialysate flow rate was 500 or 700 ml/min. The blood flow and dialysate flow were kept constant throughout the study period in the individual patient. All patients were dialyzed with a constant dialysate conductivity of 13.9 mS/cm and a constant ultra-filtration rate. The dialysate temperature, 36.0 or 36.5 °C, was kept constant during the study period for the individual patient. The dialysate composition was as follows: sodium 139 mmol/l, potassium 1.0 or 2.0 mmol/l, calcium 1.5 mmol/l, magnesium 0,5 mmol/l, chloride 108 mmol/l, bicarbonate 34 mmol/l, acetate 3 mmol/l, glucose 1.0 g/l. Patients received a light meal and two cups of coffee or tea during haemodialysis as usual.

Statistical analysis

Continuous variables with normal distributions are reported as mean ± SD, skewed data as median (interquartile range), and categorical data by number (percentage). Normality was tested with the Shapiro Wilkinson test. Comparisons of variables with a normal distribution were made with the T-test and comparisons of variables with a skewed distribution were performed with the Mann Whitney U test.

For the analysis of the determinants of dialysis hypotension a multivariate repeated generalized (logistic) linear mixed model was estimated[27] followed by a model building strategy based upon the Bayesian Information Criterion (BIC model)[28]. The following parameters were included: age, sex, body weight, body height, Body Mass Index (BMI), dialysis vintage, residual kidney function, diabetic status, Kt/V, haemoglobin, plasma albumin concentration, haemodialysis access (central venous catheter versus fistula), ultrafiltration volume, ultrafiltration rate, bloodflow, predialysis SBP, predialysis diastolic blood pressure (DBP), predialysis heartrate, comorbid conditions of ischemic heart disease and congestive heart failure and use of cardiovascular medication. Each parameter was used as covariate in an repeated logistic regressions analysis, taking the patient as random effect.

Analyses were performed with SPSS version 20.0, GraphPad Prism version 5.0 and statistical programming language R (R Development Core Team (2011). Two tailed P-values <0.05 were considered statistically significant.

RESULTS

Patients

One hundred twenty-four patients were included in this study. Patient characteristics are shown in Table 1. Mean (±SD) haemoglobin and albumin levels were 6.9±0.8 mmol/l and 39.2±3.2 g/l, respectively. eKt/V was 1.32±0.36 per session. Haemodialysis access was an arterio-venous fistula or polytetrafluoroethylene (PTFE) graft in 77% of patients and a tunneled central venous catheter in 23% of patients. Cardiovascular medication was used by 67% of the patients.

In total 3818 haemodialysis sessions were analyzed. The average number of dialysis sessions per patient was 32 (range 9-36).

Weight, ultrafiltration volume, blood pressure, and heart rate

The average pre- and postdialysis body weight was 74.7±15.8 kg and 72.8±15.8 kg, respectively. The average ultrafiltration volume and ultrafiltration rate in all 3818 dialysis sessions was 2386±834 ml and 8.5±3.3 ml/kg/hour, respectively.

Average courses of blood pressure and heart rate of the 3818 dialysis sessions are shown in Figure 2. The lowest blood pressure was documented at the end of the dialysis session. Blood pressure decreased from 146±27 / 72±15 mmHg predialysis to 120±27 / 63±15 mmHg at the end of the dialysis session. The average MAP decreased from 97±16 mmHg predialysis to 82±17 mmHg postdialysis. Heart rate rose from 75±12 mmHg predialysis to 77±16 beats/min at the end of the dialysis sessions. The average change in SBP, DBP and MAP from predialysis to the end of the dialysis sessions was -23±26, -9±14, and -14±17 mmHg, respectively. The average change in heart rate from pre to postdialysis sessions was +1.6±12.9 beats/min (Figure 2).

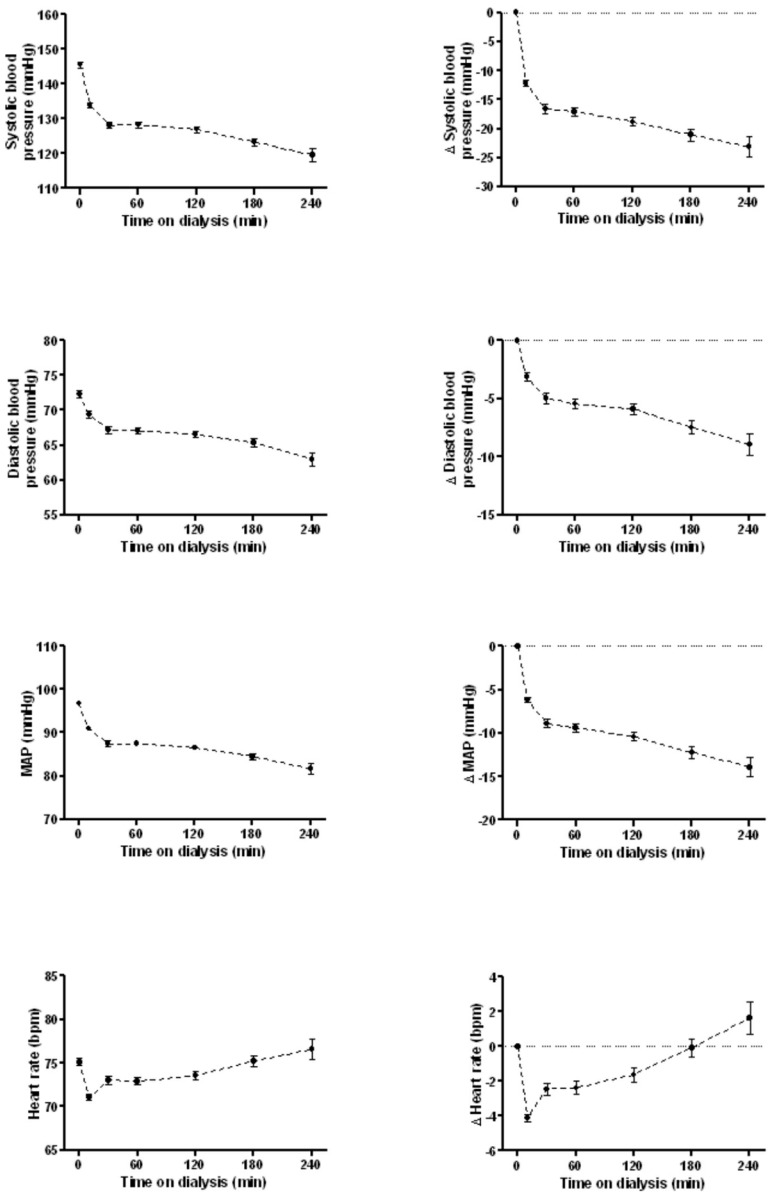
Table 1.
Patient characteristics.

Characteristic	n=124
Age, year	64.1 ± 15.7
Dialysis vintage, months	32.0 ± 30.7
Males	69 (56)
Diabetics	31 (27)
Body mass index (kg/m²)	25.3 ± 4.9
Number of patients with residual renal function	26 (21)
Cardiovascular history	39 (31)
Acute myocardial infarction	8 (6.5)
Congestive heartfailure	9 (7.3)
Peripheral vascular disease	25 (20.2)
Cerebral vascular disease	14 (11.3)
Primary renal disease	
Hypertension	32 (26)
Diabetes	19 (15)
Glomerulonefritis	17 (14)
Obstructive uropathy	17 (14)
ADPKD	10 (8)
IgA nephropathy	6 (5)
Alports' disease	2 (2)
Other diagnoses	11 (9)
Unknown	10 (8)
Cardiovascular medication	
Beta-blocker	72 (58)
CCB	31 (25)
ACE-I/ ARB	24 (19)

Note: categorical variables are presented as number (percentage); continuous variables are presented as mean ± standard deviation.
Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; CCB: calcium channel blocker; ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Figure 2.

Average courses of systolic blood pressure, diastolic blood pressure, mean arterial pressure, and heart rate. Each line represents the mean value of the 3818 haemodialysis sessions. The error bars represent the 95% confidence interval.



Prevalence of hypotension, clinical events and nursing interventions

As much as 63.8% of dialysis sessions were complicated by a decrease in SPB of ≥20 mmHg (Table 2). A decrease in MAP ≥10 mmHg occurred in 71.2% of dialysis sessions. A decrease in SBP of ≥20 mmHg or MAP≥10 was present in 77.7% of dialysis sessions.

A total of 21.4% of dialysis sessions was complicated by a clinical event. The most frequent clinical event was muscle cramp, occurring in 8.8% of dialysis sessions (Table 2). Nursing interventions were carried out in 8.5% of dialysis sessions. The most frequent nursing intervention was stop of ultrafiltration, which was applied in 7.0% of dialysis sessions.

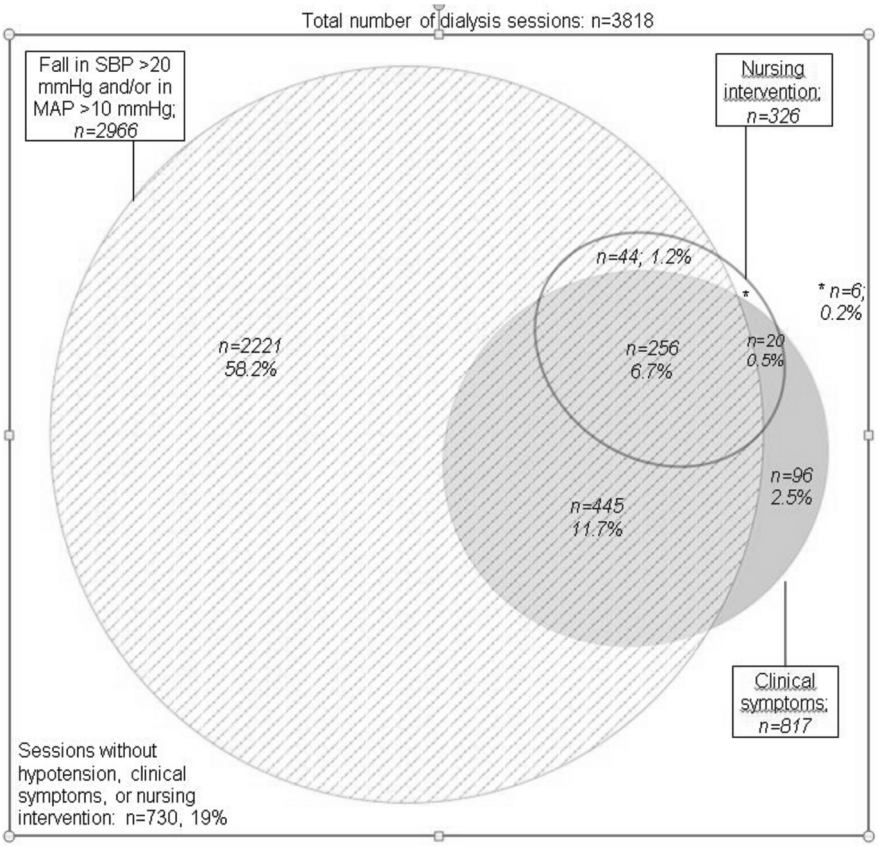
Table 2.
Prevalence of blood pressure drop, clinical events, and nursing interventions in all 3818 haemodialysis sessions.

	Nr of dialysis sessions (%)
Blood pressure drop	
Decrease in SBP ≥20 mmHg	2434 (63.8)
Decrease in MAP of ≥10 mmHg	2719 (71.2)
Decrease in SBP ≥20 mmHg or in MAP ≥10 mmHg	2966 (77.7)
Clinical events	
Any clinical event	817 (21.4)
Cramps	337 (8.8)
Dizziness	187 (4.9)
Nausea	101 (2.6)
Vomiting	18 (0.5)
Fatigue	131 (3.4)
Loss of consciousness	20 (0.5)
Miscellaneous	233 (6.1)
Nursing interventions	
Any nursing intervention	326 (8.5)
Stop of ultrafiltration	267 (7.0)
Trendelenburg position	219 (5.7)
Administration of isotonic saline	132 (3.5)
Administration of colloid solution	47 (1.2)
BP drop in combination with a clinical event	
Decrease in SBP ≥20 mmHg	610 (16.0)
Decrease in MAP ≥10 mmHg	662 (17.3)
Decrease in SBP ≥20 mmHg or decrease in MAP ≥10 mmHg	701 (18.4)
BP drop in combination with a nursing intervention	
Decrease in SBP ≥20 mmHg	285 (7.5)
Decrease in MAP ≥10 mmHg	288 (7.5)
Decrease in SBP ≥20 mmHg or decrease in MAP ≥10 mmHg	300 (7.9)
BP drop in combination with a clinical event and nursing intervention	
Decrease in SBP ≥20 mmHg	242 (6.3)
Decrease in MAP ≥10 mmHg	247 (6.5)
Decrease in SBP ≥20 mmHg or in MAP ≥10 mmHg (full EBPG definition)	256 (6.7)

Note: values are given as number (percentage). Abbreviations: BP: blood pressure; SBP: systolic blood pressure. MAP: mean arterial blood pressure. The total number of patients with clinical events and nursing interventions is lower than the separate items since some patients had more than one clinical event and/or intervention.

Figure 3 shows the relations and overlap of the 3 components of the EBPG definition of IDH. Notably, in most (58.2%) dialysis sessions that fulfilled the hypotension component of the EBPG definition, there was no clinical event or intervention. In another 11.7% of dialysis sessions that fulfilled the hypotension component of the definition, a clinical event occurred but no nursing intervention was carried out. A combination of a decrease in SBP of ≥20 mmHg or MAP≥10 mmHg with a clinical event and nursing intervention (full EBPG definition) occurred in 6.7% of dialysis sessions. Of the dialysis sessions, 3.0% were complicated by a clinical event without fulfilling the hypotension component of the definition. In 0.5% of dialysis sessions, both a clinical event occurred and a nursing intervention was performed without fulfilling the hypotension component of the definition.

Figure 3.
Proportional Venn-diagram showing the relationship and overlap between the blood pressure drop (a decrease in systolic blood pressure SBP of ≥20mmHg or a decrease in MAP≥10 mmHg).



Prevalence of dialysis hypotension using alternative cut-off values for the fall in SBP

Supplementary file 1 shows the frequencies of the 3 components of the definition using different cut-off values for the reduction in SBP: a fall in SBP ≥30 mmHg (present in 43.5% of dialysis sessions) and a fall in SBP ≥40mmHg (present in 27.4% of dialysis sessions). A decrease in SBP ≥30mmHg in combination with a clinical event and a nursing intervention was present in 5.6% of the dialysis sessions. A decrease in SBP ≥40mmHg in combination with a clinical event and a nursing intervention was observed in 4.6% of the dialysis sessions. We also computed the prevalence of intradialytic hypotension according to nadir-based definitions (as recently described by Flythe et al)[29]. As shown in supplementary file 2 the prevalence of intradialytic hypotension according to the nadir of SBP <90 mmHg in combination with a fall in of ≥20 or ≥30 mmHg was 9.2% and 7.1%, respectively.

Prevalence of dialysis hypotension at patient level

Since the occurrence of dialysis hypotension may not be evenly distributed over patients, we also analyzed which proportion of patients fulfilled the separate items as well as the full EBPG definition. We specifically analyzed which proportion of patients fulfilled the EBPG criteria for IDH in 0 to 10%, in 10 to 20% or in >20% of dialysis sessions. We found that 89.9% of patients had a decrease in SBP of ≥20mmHg in more than 20% of dialysis sessions (Table 3). As much as 96.8% of patients had either a decrease in SBP of ≥20mmHg or a decrease in MAP≥10 in more than 20% of dialysis sessions.

Ten (8.1%) patients fulfilled the full EBPG definition of dialysis hypotension in more than 20% of dialysis sessions (Table 3).

Similar analyses were performed for alternative cut-offs for SBP showing that 74.2% of patients had a decrease in SBP ≥30 mmHg and 52.4% of patients had a decrease in SBP ≥40 mmHg in more than 20% of the dialysis sessions. A total of 6.5% of patients had a decrease in SBP ≥30 mmHg in combination with a clinical event and a nursing intervention in more that 20% of dialysis sessions; 5.6% of patients had a decrease in SBP ≥40 mmHg in combination with a clinical event and a nursing intervention in more than 20% of dialysis sessions.

Table 3.
Frequency of blood pressure drop, clinical events, and nursing interventions at patient level in 124 patients**.**

	Number of patients, n (%)		
	In <10% of dialysis sessions	In 10-20% of dialysis sessions	In ≥20% of dialysis sessions
Blood pressure drop			
Decrease in SBP ≥20 mmHg	3 (2.4)	10 (8.1)	111 (89.5)
Decrease in MAP ≥10 mmHg	0	5 (4.0)	119 (96.0)
Decrease in SBP ≥20 mmHg or in MAP ≥10 mmHg	0	4 (3.2)	120 (96.8)
Clinical event	45 (36.2)	31 (25.0)	48 (38.8)
Nursing intervention	93 (75.0)	16 (12.9)	15 (12.1)
Clinical event and nursing intervention	99 (79.8)	15 (12.1)	10 (8.1)
BP drop in combination with clinical event and nursing intervention			
Decrease in SBP ≥20 mmHg	101 (81.5)	13 (10.4)	10 (8.1)
Decrease in MAP ≥10 mmHg	102 (82.2)	12 (9.7)	10 (8.1)
Decrease in SBP ≥20 mmHg or decrease in MAP ≥10 mmHg (EBPG definition)	101 (81.5)	13 (10.4)	10 (8.1)

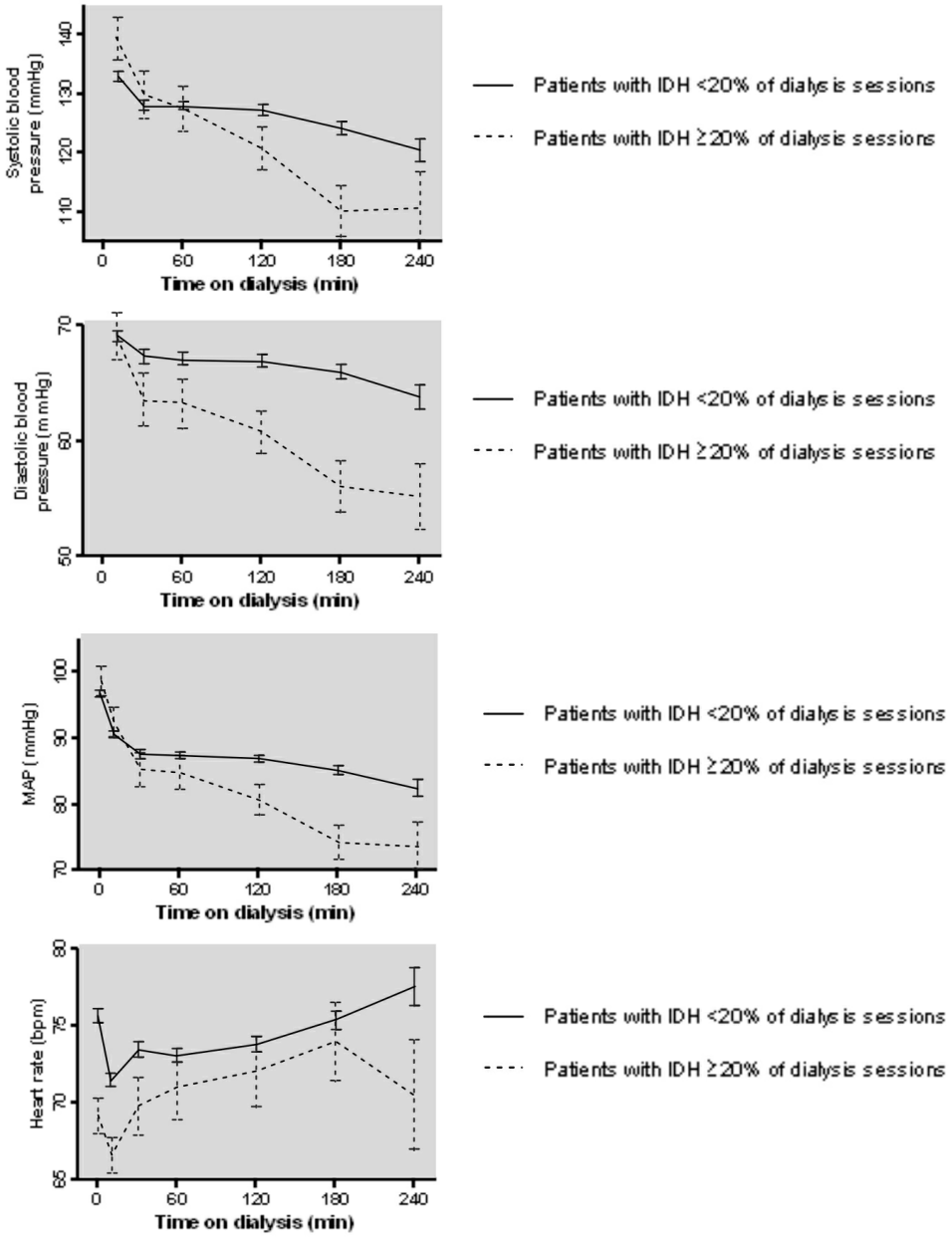
Note: values are given as number (percentage). Abbreviations: BP: blood pressure; SBP: systolic blood pressure; MAP: mean arterial blood pressure.

Intradialytic blood pressure and heart rate in patients with and without frequent dialysis hypotension

Patients who experienced frequent dialysis hypotension according to the full EBPG definition had significantly higher predialysis SBP (P=0.001) and a greater decline in SBP during dialysis in comparison with patients without frequent IDH (Figure 4). Predialysis heart rate was significantly lower in patients with frequent IDH (P=0.001) compared with patients without frequent IDH. The proportion of patients that used a beta-blocker did not differ between these 2 groups, 70% and 57% in patients with and without frequent IDH, respectively (Supplementary file 3).

Figure 4.

Average course of systolic blood pressure, diastolic blood pressure, mean arterial pressure, and heart rate for haemodialysis sessions of patients with (n= 10) and without (n=114) frequent dialysis hypotension according to the EBPG definition in ≥20% of haemodialysis sessions. The error bars represent the 95% confidence interval.



Variables associated with intradialytic hypotension according to the EBPG definition

In univariate analysis, the following parameters had a significant association with the occurrence of dialysis hypotension according to the EBPG guideline: female sex, lower body weight, lower body height, absence of residual kidney function, higher plasma albumin concentration, higher ultrafiltration volume, and higher dialysis vintage (Table 4).

The BIC model building strategy showed that the occurrence of dialysis hypotension according to the full EBPG definition was strongly associated with lower body height (p=0.0001) and a higher ultrafiltration volume (p=0.0004) (Supplementary file 4).

Table 4.

Variables that are significantly associated with the occurrence of dialysis hypotension according to the full EBPG definition in univariate analysis**.**

							Odds of dialysis hypotension		
	Estimate	SE	Z	P	Lower 95% CI	Upper 95% CI	Estimate	Lower 95% CI	Upper 95% CI
Sex (female vs male)	0.695	0.289	2.409	0.016	0.128	1.277	2.004	1.137	3.586
Body weight (kg)	-0.022	0.009	-2.338	0.019	-0.041	-0.004	0.979	0.960	0.996
Body height (m)	-0.048	0.015	-3.282	0.001	-0.077	-0.019	0.953	0.926	0.980
Residual renal function	-0.705	0.344	-2.025	0.043	-1.394	-0.025	0.498	0.248	0.975
Albumin (g/l)	0.108	0.048	2.232	0.026	0.014	0.207	1.114	1.014	1.229
Ultrafiltration volume (l)	0.231	0.079	2.907	0.004	0.075	0.386	1.259	1.077	1.471
Dialysis vintage (months)	0.009	0.004	2.081	0.037	0.0004	0.018	1.009	1.0004	1.018

Abbreviations: SE: standard error; Z: Z score; CI: confidence interval.

DISCUSSION

The main finding of this study is that the prevalence of dialysis hypotension when applying the EBPG definition was relatively low and occurred in only 6.7% of dialysis sessions. Frequent dialysis hypotension, tentatively defined as dialysis hypotension in more than 20% of dialysis sessions, was observed in 8.1% of patients.

In various reviews, it is stated that 20-50% of haemodialysis sessions are complicated by dialysis hypotension[2-7-9]. However, in the limited number of studies on this topic, the prevalence of dialysis hypotension was lower, ranging between 2% and 30% of dialysis sessions[12-13-25]. It should be noted that these studies used different definitions of dialysis hypotension, which complicates a proper comparison with our study. To the best of our knowledge, there are only 2 other studies that investigated the prevalence of dialysis hypotension as defined according to the definition in the EBPG guideline on haemodynamic stability. The prevalence of dialysis hypotension according to this definition in these studies was 5.0%[25] and 11.2%[24].

Our study shows that dialysis hypotension according to the EBPG definition is relatively rare (6.7% of sessions). Even if we use a more liberal definition, e.g., a fall in SBP >20 mmHg or a fall in MAP >10 mmHg in combination with a clinical event (thus without the need for nursing intervention), the prevalence of dialysis hypotension is 18.4% which is still lower compared with the prevalence of 20-50% stated in most reviews. It is unlikely that our study underestimated the true prevalence of dialysis hypotension since blood pressure was measured much more frequently than is usual in clinical practice, facilitating the finding of a minimum reduction in blood pressure. In addition, both patients and nurses were instructed to register any complaint or symptom that could be related to dialysis hypotension.

It is evident that the prevalence of dialysis hypotension is influenced by the dialysis settings. Shorter treatment times[7-30], higher ultrafiltration rates[31] and relatively high dialysate temperatures[14-15] are all risk factors for dialysis hypotension. Notably, in the present study dialysis duration was 3.5, to 4.5 hours, ultrafiltration rate was relatively low (8.5±3.3 ml/kg/hour) and dialysate temperature was set at 36.0 or 36.5 ˚C. These dialysis settings may have contributed to the low prevalence of dialysis hypotension in our study relative to other studies.

A fall in SBP ≥20 mmHg or a fall in MAP ≥10 mmHg occurred in more than three quarters of dialysis sessions. At patient level, as much as 96.8% of patients had a decrease in SBP ≥20mmHg or a decrease in MAP≥10 mmHg in more than 20% of dialysis sessions. It follows that a decrease in SBP ≥20 mmHg or a fall in MAP≥ 10 mmHg is so common that it is not specific for symptomatic dialysis hypotension. Notably, in most (58.2%) dialysis sessions that fulfilled the hypotension component of the EBPG definition, there was no clinical event or intervention. This raises the question whether a decrease in SBP ≥20 mmHg or a decrease in MAP≥10 mmHg discriminates between patients with and

without symptomatic dialysis hypotension. Various factors may affect predialysis blood pressure like stress due to transportation to the dialysis unit and anxiety for puncture of the fistula. When predialysis blood pressure is used as the reference point, part of the early intradialytic fall in blood pressure may be explained by the relief of stress/ anxiety, e.g. after successful puncture of the fistula, and not by dialysis-specific haemodynamic stress. Conversely, haemodialysis may exert haemodynamic stress, including cardiac stunning, even in the absence of a significant blood pressure drop[32]. Indeed, in this study, 3.0% of dialysis sessions were complicated by a clinical event without fulfilling the hypotension component of the definition. In our view, the starting point for a definition of symptomatic dialysis hypotension should be the occurrence of a clinical event and/or a nursing intervention instead of a minimum fall in SBP.

In a composited definition as the EBPG definition, the prevalence of dialysis hypotension can never be higher than the component with the lowest prevalence. The component with the lowest prevalence in this study was nursing intervention.

In multivariate analyses, the strongest determinants of dialysis hypotension defined by the full EBPG definition were lower body height and higher ultrafiltration volume. Where there is abundant literature linking dialysis hypotension to higher ultrafiltration volumes and ultrafiltration rate[9-17-33], the association between dialysis hypotension and lower body height has not been described before. This could be related to an unfavorable balance between ultrafiltration rate and refill rate in smaller patients.

A limitation of our study is that we did not use an objective method to assess dry weight, e.g. bioimpedance. Therefore, we cannot exclude that a proportion of patients were not at their true dry weight at the end of dialysis which may have affected the course of blood pressure as well as the frequency of clinical events and nursing interventions. Bias in blood pressure measurements could be introduced by underlying vascular disease. Finally, it should be noted that the EBPG definition, like any other definition using clinical symptoms or nursing interventions is subject to bias. The interpretation of patient complaints as part of the symptomatology of dialysis hypotension as well as the threshold to perform an intervention may differ between nurses (and between physicians). Strong points of our study are the relatively long study duration of 3 months and the frequent measurement of blood pressure (and active search for patient complaints at each dialysis session) which reduced the chance of underestimation of dialysis hypotension.

CONCLUSION

In conclusion, the prevalence of dialysis hypotension according to the EBPG definition is low. The dominant determinant of the EBPG definition was nursing intervention since this was the component with the lowest prevalence. Dialysis hypotension might be less common than indicated in the literature however a proper comparison with previous studies is complicated by the lack of a uniform definition.

REFERENCES

1. Stefánsson BV, Brunelli SM, Cabrera C, et al. Intradialytic hypotension and risk of cardiovascular disease. *Clin J Am Soc of Nephrol.* 2014-12-5;9(12):2124-32.
2. Davenport A. Can advances in hemodialysis machine technology prevent intradialytic hypotension? *Semin Dial*. 2009;22(3):231-236.
3. Dubin R, Owens C, Gasper W, Ganz P, Johansen K. Associations of endothelial dysfunction and arterial stiffness with intradialytic hypotension and hypertension. *Hemodial Int.* 2011;15(3):350-358.
4. Perazella MA. Pharmacologic options available to treat symptomatic intradialytic hypotension. *Am J Kidney Dis.* 2001;38(4 Suppl 4):S26-S36.
5. Passauer J, Büssemaker E, Gross P. Dialysis hypotension: Do we see light at the end of the tunnel? *Nephrol Dial Transplant.* 1998;13(12):3024-3029.
6. Daugirdas JT. Pathophysiology of dialysis hypotension: An update. *Am J Kidney Dis.* 2001;38(4, Supplement 4):S11-S17.
7. Daugirdas JT. Preventing and managing hypotension. *Semin Dial*. 1994;7(4):276-283.
8. Zucchelli P, Santoro A. Dialysis-induced hypotension: A fresh look at pathophysiology. *Blood Purif*. 1993;11(2):85-98.
9. Sands J, Usvyat LA, Sullivan T, et al. Intradialytic hypotension: Frequency, sources of variation and correlation with clinical outcome. *Hemodial Int.* 2014;18:415-422.
10. Tislér A, Akócsi K, Hárshegyi I, et al. Comparison of dialysis and clinical characteristics of patients with frequent and occasional hemodialysis-associated hypotension. *Kidney Blood Press Res*. 2002;25(2):97-102.
11. Converse RL, Jacobsen TN, Jost CM, et al. Paradoxical withdrawal of reflex vasoconstriction as a cause of hemodialysis-induced hypotension. *J Clin Invest*. 1992;90(5):1657-1665.
12. Hossli S. Clinical management of intradialytic hypotension: Survey results. *Nephrol Nurs J.* 2005;32(3):287-91.
13. Oliver MJ, Edwards LJ, Churchill DN. Impact of sodium and ultrafiltration profiling on hemodialysis-related symptoms. *J Am Soc Nephrol.* 2001;12(1):151-156.
14. Chesterton LJ, Selby NM, Burton JO, McIntyre CW. Cool dialysate reduces asymptomatic intradialytic hypotension and increases baroreflex variability. *Hemodial Int.* 2009;13(2):189-196.

15. Jefferies HJ, Burton JO, McIntyre CW. Individualised dialysate temperature improves intradialytic haemodynamics and abrogates haemodialysis-induced myocardial stunning, without compromising tolerability. *Blood Purif*. 2011;32(1):63-68.

16. Franssen CFM, Dasselaar J, Sytsma P, Burgerhof JGM, Jong de PE, Huisman RM. Automatic feedback control of relative blood volume changes during hemodialysis improves blood pressure stability during and after dialysis. *Hemodial Int.* 2005;9(4):383-392.

17. Davenport A, Cox C, Thuraisingham R. Blood pressure control and symptomatic intradialytic hypotension in diabetic haemodialysis patients: A cross-sectional survey. *Nephron.Clinical practice*. 2008;109(2):c65-c71.

18. Mc Causland FR, Brunelli SM, Waikar S. Dialysis dose and intradialytic hypotension: Results from the HEMO study. *Am J Nephrol*. 2013;38(5):388-396.

19. Zimmerman CY, Ladefoged A, Søren SN. Can haemodialysis-induced hypotension be predicted? *Nephron*. 2002;92(3):582-588.

20. Schreiber MJ. Setting the stage. *Am J Kidney Dis.* 2001;38(4, Supplement 4):S1-S10.

21. Shimizu K, Kurosawa T, Sanjo T. Effect of hyperosmolality on vasopressin secretion in intradialytic hypotension: A mechanistic study. *Am J Kidney Dis.* 2008;52(2):294-304.

22. Kooman J, Basci A, Pizzarelli F, et al. EBPG guideline on haemodynamic instability. *Nephrol Dial Transplant.* 2007;22 Suppl 2:ii22-ii44.

23. Prakash S, Garg AX, Heidenheim AP, House A. Midodrine appears to be safe and effective for dialysis-induced hypotension: A systematic review. *Nephrol Dial Transplant.* 2004;19(10):2553-2558.

24. Bossola M, Laudisio A, Antocicco M, et al. Intradialytic hypotension is associated with dialytic age in patients on chronic hemodialysis. *Ren Fail*. 2013;35(9):1260-1263.

25. Akhmouch I, Bahadi A, Zajjari Y, et al. Characteristics of intradialytic hypotension: Experience of agadir center-morocco. *Saudi J Kidney Dis Transpl*. 2010;21(4):756-761.

26. Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume kt/V: An analysis of error. *Journal of the American Society of Nephrology*. 1993;4(5):1205-1213.

27. Bates D, Maechler M, Bolker B, Walker S. Lme4: Linear mixed-effects models using eigen and S4. R package version 1.1-7. *This is computer program (R package).The URL of the package is:* http://CRAN.R-project.org/package= *lme4*. 2014.

28. Schwarz G. Estimating the dimension of a model. *Ann Stat.* 1978;6(2):461-464.

29. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol*. 2014.

30. Agarwal R. How can we prevent intradialytic hypotension? *Curr Opin Nephrol Hypertens*. 2012;21(6):593-599.

31. Flythe JE, Kimmel SE, Brunelli SM. Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. *Kidney Int*. 2011-1;79(2):250-7.

32. Assa S, Hummel YM, Voors A, et al. Hemodialysis-induced regional left ventricular systolic dysfunction: Prevalence, patient and dialysis treatment-related factors, and prognostic significance. *Clin J Am Soc Nephrol.* 2012-10;7(10):1615-23.

33. Flythe JE, Brunelli SM. Blood pressure variability among chronic dialysis patients: Recent advances in knowledge. *Curr Opin Nephrol Hypertens*. 2015-3;24(2):163-9.

Supplementary file 1.

Prevalence of a decrease in SBP ≥30 mmHg and decrease in SBP ≥40 mmHg, clinical events and nursing interventions in all 3818 haemodialysis sessions.

	Nr of dialysis sessions (%)
Blood pressure drop	
Decrease in SBP ≥30 mmHg	1662 (43.5)
Decrease in SBP ≥40 mmHg	1047 (27.4)
Blood pressure drop in combination with a clinical event	
Decrease in SBP ≥30 mmHg	483 (12.7)
Decrease in SBP ≥40 mmHg	361 (9.5)
Blood pressure drop in combination with a nursing intervention	
Decrease in SBP ≥30 mmHg	249 (6.5)
Decrease in SBP ≥40 mmHg	203 (5.3)
Blood pressure drop in combination with a clinical event and nursing intervention	
Decrease in SBP ≥30 mmHg	213(5.6)
Decrease in SBP ≥40 mmHg	175 (4.6)

Note: values are given as number (percentage). Abbreviations: SBP: systolic blood pressure.

Supplementary file 2.

Prevalence of nadir-based definitions of dialysis hypotension according to reference 29.

	Nr of dialysis sessions (%)
Nadir SBP	
Nadir90 mmHg	481 (12.6)
Nadir100 mmHg	918 (24.1)
Fall in SBP and nadir SBP	
Fall20 and nadir90	352 (9.2)
Fall30 and nadir90	271 (7.1)
Pre-dialysis SBP and nadir SBP	
<120 mmHg and nadir90	265 (6.9)
120-159 mmHg and nadir90	156 (4.1)
≥160 mmHg and nadir100	98 (2.6)

Note: values are given as number (percentage). Abbreviations: SBP: systolic blood pressure; Nadir90: minimum intradialytic SBP <90 mmHg; Nadir100: minimum intradialytic SBP <100 mmHg; Fall20: predialysis SBP-minimum intradialytic SBP ≥20 mmHg; Fall30: predialysis SBP-minimum intradialytic SBP ≥30 mmHg.

Supplementary file 3.

Comparison between patients with and those without frequent dialysis hypotension according to the EBPG definition.

	Patients with IDH in <20% of dialysis sessions N = 114	Patients with IDH in ≥20% of dialysis sessions N = 10	P-value
Male sex	68 (60)	1 (10)	0.003
Age	64.5 ± 15.9	65.3 ± 14.2	0.99
Dialysis vintage (months), median (IQR)	26 (6 - 46)	42.0 (18.3-55.3)	0.11
Dry body weight (kg) median (IQR)	73.5(62.4-81.5)	56.0(51.8 - 68.6)	0.008
Body Height (m)	1.71 ± 0.9	1.60 ± 0.8	0.002
BMI (kg/m²) median (IQR)	24.5 (21.7 – 27.9)	22.7 (21.7 – 27.5)	0.52
eKt/V	1.36 ± 0.27	1.45 ± 0.25	0.31
Ultrafiltration volume (L) median (IQR)	2.1 (1.4 – 2.5)	2.0 (1.5 – 2.9)	0.58
Ultrafiltration rate (ml/kg/h) median (IQR)	8.2 (6.5 -10.0)	9.2 (7.9 – 10.3)	0.18
Number of patient with residual renal function	34 (30)	0	0.059
Primary renal disease			
Hypertension	30 (26)	2 (100)	1
Diabetes	16 (13)	3 (30)	0.80
Cardiovascular comorbidity	56 (49)	6 (60)	0.51
Cardiovascular medication			
Beta-blocker	65 (57)	7 (70)	0.43
CCB	27 (24)	4 (40)	0.26
ACE-I/ARB	21 (18)	3 (30)	0.38

Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation.
Abbreviations: IDH: intra-dialytic hypotension; CV medication: calcium channel blocker; ACE-I: angiotensin converting enzyme inhibitor; angiotensin receptor blocker.

Supplementary file 4.

Multivariate linear regression analysis (BIC) with determinants of dialysis hypotension according to the full EBPG definition.

					95% CI	
	Estimate	**SE**	**Z**	**P**	**Lower**	**Upper**
Height (m)	-0.055	0.015	-3.816	0.0001	-0.846	-0.027
Ultrafiltration volume (l)	0.278	0.079	3.505	0.0004	0.122	0.433

Abbreviations: SE: standard error; CI: confidence interval.

Chapter 5

The prevalence of intra-dialytic hypotension in hemodialysis patients on conventional hemodialysis. A systematic review with meta-analysis

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ABSTRACT

Background: Intradialytic hypotension (IDH) is considered to be a frequent complication of haemodialysis (HD) and is associated with symptom burden, increased incidence of access failure, cardiovascular events and higher mortality. This systematic literature review aims to analyse studies that investigated the prevalence of IDH. A complicating factor herein is that many different definitions of IDH are used in literature.

Methods: A systematic literature search from databases, Medline, Cinahl, EMBASE and the Cochrane library to identify studies reporting on the actual prevalence of IDH was conducted. Studies were categorized by the type of definition used for the prevalence of IDH. A meta-analysis of the prevalence of IDH was performed.

Results: In a meta-analysis comprising 4 studies including 1694 patients and 4 studies including 13.189 patients, the prevalence of HD sessions complicated by IDH was 10.1% and 11.6% for the EBPG definition and the Nadir <90 definition, respectively. The proportion of patients with frequent IDH could not reliably be established because of the wide range in cut-off values that were used to identify patients with frequent IDH. There was a large variety in the prevalence of symptoms and interventions. Major risk factors associated with IDH across studies were diabetes, a higher interdialytic weight gain, female gender and lower body weight.

Conclusion: Our meta-analysis suggests that the prevalence of IDH is lower than 12% for both the EBPG and the Nadir <90 definition which is much lower than stated in most reviews.

INTRODUCTION

Intradialytic hypotension (IDH) is considered to be one of the most frequent complications of haemodialysis (HD). IDH is associated with a considerable symptom burden and an increased incidence of access failure, cardiovascular events and mortality [1-2-3-4-5-6]. The pathophysiology of intradialytic hypotension and methods to prevent this complication have been extensively investigated[1-5]. Over the years, dialysis techniques have improved and there is more attention for the prevention of dialysis hypotension, e.g. by lowering the dialysate temperature[7] and monitoring of relative blood volume changes[8]. At the same time, the average age of dialysis patients as well as the proportion of patients with significant co-morbidities such as diabetes mellitus and heart failure has increased[9-10]. Therefore, the exact prevalence of dialysis hypotension is unknown. The major aim of this systematic literature review is to present an overview of studies that investigated the prevalence of IDH. A complicating factor in the analysis of the prevalence of IDH is that many different definitions are used. In this review we categorized studies by the type of definition used. The second goal was to assess the frequency of patient symptoms and nursing interventions related to IDH. Finally, we aimed to assess patient and treatment factors associated with IDH.

MATERIALS AND METHODS

Study protocol and information sources

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews an Meta-Analyses (PRISMA) checklist[11]. The literature search included articles that were published between January 1st 1980 and January 1st, 2019, from databases of Medline, Cinahl, EMBASE and The Cochrane Library.

Eligibility criteria

Studies were eligible for inclusion if the following criteria were met: (1) HD treated adults (aged ≥18 years) with chronic kidney disease; (2) outcome of interest was the actually studied prevalence of IDH in HD patients (3) full-length articles without language restriction, published between January 1st, 1980 and January 1st, 2019. Data was required to be obtained by original research and not from reviews. The selection procedure included cohort studies, observational studies and controlled clinical trials. Articles were excluded (based upon methodology) when the focus was on the comparison between patients with and those without hypotension since this design precluded the unbiased assessment of the prevalence of IDH.

Search strategy

Different combinations of terms and search strings were used in order to identify eligible articles. The search strategy for Medline is detailed in Supplementary file 1. The same strategy was followed in all electronic databases searched.

Study selection and data collection

Two reviewers (LV, JK) separately screened the titles and abstracts of studies that were identified through electronic searching to select studies that were potentially eligible for inclusion. Additional studies were identified through checking relevant references of the included studies. After screening, the reviewers discussed any difference in study selection. Studies were found eligible for inclusion if outcomes were available for IDH prevalence.

Risk of bias and quality assessment

All full-text versions of potentially relevant studies were independently screened by two reviewers (LV, JK) to identify whether studies were eligible for inclusion. Study quality was assessed using the Newcastle-Ottawa Scale for cohort studies[12]. The scale consists three quality criteria: selection, comparability, and outcome. The maximal score is 9 points (4 for selection, 2 for comparability, and 3 for outcome). Study quality was defined as poor when the score was 1-3, fair when the score was 4-6, and good when the score was 7-9 points.

Data items

Data for study design, participant details, exclusion/ inclusion criteria, interventions and any comparators and outcomes were collected. The following variables were selected and included as outcome variables: Type of IDH definition that was used, the prevalence of IDH, SBP and/or diastolic blood pressure (DBP) and/or mean arterial pressure (MAP), prevalence of a decrease in SBP, DBP or MAP, prevalence and type of symptoms, prevalence and type of interventions.

Statistical analysis

Characteristics of the HD patients were reported as mean ± SD, mean ± standard error of the mean (SEM), range or median with interquartile range.

For a proper comparison, studies were categorized into 5 types according to the definition or description of IDH: 1. a decrease in SBP of ≥20 mmHg; 2. an intradialytic decrease in SBP of ≥20 mmHg in combination with clinical events and interventions according to the European Best Practice Guideline on hemodynamic instability (EBPG) [13]; 3. an intradialytic nadir SBP below 90 mmHg (Nadir <90); 4. studies with multiple cut-off values; 5. studies in which there was no detailed information on the definition of IDH.

The frequency of IDH was reported as the percentage of HD sessions that fulfilled the study's criteria for IDH of the total number of HD sessions. These data were either directly available or could be calculated from the information in the manuscript.
The proportion of patients with frequent IDH was reported as the percentage of patients that met the criteria for frequent IDH as defined by the authors.

To assess the pooled estimate of the prevalence of IDH, meta-analyses were conducted when in three or more articles, the same definition of the prevalence of IDH was used. The weights of the meta-analyses were based on the inverse variance method; the heterogeneity parameter (Tau^2) for effect size was based on restricted maximum-likelihood. The random effects model was selected for the mean difference because of expected differences in the number of patients and study duration between studies. Forest plots were constructed to summarize the outcome of the meta-analyses. An influence analysis was a component of each meta-analysis to check whether the conclusion critically depended upon the result of a single study. A test for funnel plot asymmetry based on the linear regression was added to indicate any risk of bias. The meta-analyses were performed using statistical programming language R (R Core Team, 2018). P-values <0.05 were considered statistically significant.

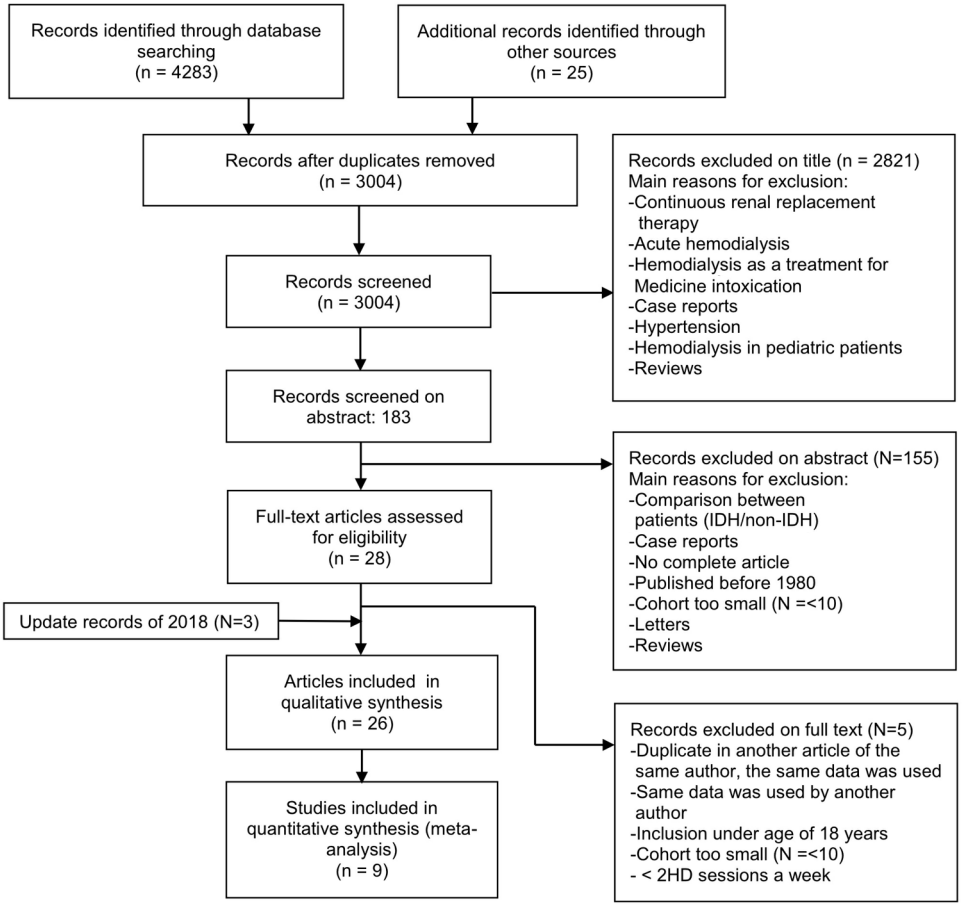
RESULTS

Search results

Figure 1 shows the flow diagram of the selection of articles. A total of 4283 articles were identified, 2124 in Pubmed and 2159 in Embase and 25 from other sources, such as searching citations and examinations of reference lists from relevant studies. After screening, a total of 1279 duplicates were eliminated. 3004 articles were screened on title and abstract, resulting in 31 full text articles that were assessed for eligibility. From these, 5 articles were excluded for the following reasons: the number of HD sessions was equal to or less than 2 per week [14-15], small number of patients [16], use of a database that was also used for another article included in this review [17-18]. Finally, 26 articles were included for this systematic review.

Figure 1.

Selection of articles for the systematic review on the prevalence of intradialytic hypotension.



Characteristics of the studies

Table 1 summarizes patient characteristics and study quality of the 26 articles. The number of patients included varied between 28 to 112,013 patients. The mean age of patients ranged from 48.0 to 66.6 years and most studies included adult patients (>18 years) or age was not specified; Degoulet et al[19] and Awan et al[20] included patients with a minimum age of 15 years and 10 years, respectively. The shortest dialysis vintage at the time that patients were included varied markedly between studies: 1 month[21], 2 months[22-23], 3 months[5-6-9-20-24-25-26-27-28-29], 6 months[30] and 12 months[24]. In nine studies the dialysis vintage was not specified (Table 1). Degoulet et al included only patients who were treated for more than 50 consecutive HD sessions during the follow up period[19].

The majority of studies were based on a thrice weekly dialysis schedule with a duration of HD sessions between 3 and 5 h. In 4 studies, the dialysis schedule nor the duration of the HD session was specified (Table 1). In 2 studies, the schedule was 2 HD sessions per week[20-31] and 2 other studies used a dialysis schedule of twice or thrice weekly with a minimum duration of 3 hours per HD session[24-32]. In 4 studies, the dialysis duration was not specified[21-22-27-29] One study described a retrospective survey with 369 patients on 2 HD sessions per week and a group of 741 patients on 3 HD sessions per week[19].

Exclusion criteria were not specified in 13 studies (Supplementary file 2).Two studies excluded patients because of incomplete or unavailable BP data[22-33] and one study specified that patients with acute renal failure were not included[31]. Three studies excluded patients with comorbidities[5-29-34] or diabetes[35] (Supplementary file 2).
Three types of study design were used among the included studies: cross-sectional study, prospective cohort study and retrospective study. There were no randomized controlled trials among the studies. In the majority of studies, the research questions comprised the frequency of IDH and to identify patient or treatment factors associated with IDH or to assess the relationship between IDH and mortality (Supplementary file 2)[5-22-29-36-37]. A number of studies compared specific patient or treatment factors in order to establish which factor was associated with IDH, e.g. interdialytic weight gain (IDWG)[21], antihypertensive medication[30], combined sodium and UF profiling[38], diabetes[9], dialysate temperature[35], and type of dialyzer used[39]. Detailed information on study design, primary research question and use of CV medication is described in Supplementary file 2.

The score on the Newcastle Ottawa quality scale for cohort studies ranged from 3 to 8, one study was evaluated as having poor quality (score 3)[20], 20 were assessed as having fair quality (score 4 en 5, 6) and 2 studies as having good quality (score 8)[5-39] (Table 1).

Table 1.

Summary of study characteristics.

Author	Duration studies (days)	Nr of patients	Men (n (%)	Mean age (years)	Diabetes (%)	HD vintage (months)	Nr of HD sessions per week	Duration of session (h)	Study quality
Agrawal, 2012	183	28	19 (68.0%)	48.8 (range 25-71)	17.9		2	4	6
Akhmouch, 2010	548	54	33 (61.1%)	54.1 (range 21-80)	31.5	59.8 (range 5-240)	2,5	3.5	5
Al-Hilali, 2004		40	15 (37.5%)	48.6±14.9	45	34.5±2.7			5
Awan, 2011	91	100	57 (57.0%)	51±16	51		2		3
Bossola, 2013	30	68	43 (63.2%)	61±16		92±71	3	4	6
Caplin, 2011		508	272 (53.6%)	64 (IQR 60-74.5)	36.3	37 (range 18-64)	3	4	5
Cho, 2017	7	191	49 (25.7%)	60±12	53.9		3	4	6
Chou, 2017	91	11.2013	63.847 (57.0%)	63±15	58		3		6
Collins, 1993	183	40	16 (40.0%)	52.5(NS)	425		3	3.3	8
Davenport, 2008	7	2193	1326 (60.5%)	61.2 (IQR 46.9-72.3)	32		3	4	6
Degoulet, 1981	365	1110		49±15.2			3	4.6	5
Flythe, 2014 (HEMO)	183	1409	625 (44.4%)	59.4±13.4	44.8		3	3.5	8
Flythe, 2014 (LDO)	30	10392	5819 (56.0 %)	62.7±14.4	60		3	3.5	8
Kuipers, 2016	91	124	69 (50.6%)	64,1±15.7	27	32±30.7	3	4	5

Lai, 2012	335	255	129 (50.6%)	62.5 (range 16.0-93)	45.5		3		6
Levin, 2018	91	54	29 (54.0%)	67.0±10.0	56				5
Meredith, 2015	30	77	55 (71.0%)	65 (IQR 51-75)	40.3	26 (IQR 11-49)			5
Ogochukwu, 2017	1460	404	225 (55.7%)	48±17					4
Orofino, 1990	365	60	39 (65.0%)	51 (range 15-72)	0	41,7 (range 8-96)	3	3.5	5
Rocha, 2015	214	43	25 (58.1%)	66.6±13.2	27.9	86 (range 2-388)	3	3.5	5
Sands, 2014	579	1137	608 (53.5%)	61.9±15.8	56.2	54±50.3		3.6	5
Sangala, 2017	83	432		65.9 NS	31	36.8 NS	3		6
Stefánsson, 2014	91	39.497	17.335 (43.9%)	61.8±15.2	68.2	3 NS			6
Steinwandel, 2018	91	64	45 (70.3%)	63.0±15.8	28.1		3	4	6
Straver, 1999	1	68	38 (55.9%)	56 (SEM 3.2)	8.8	49 (SEM 8.8)	2.5	3.5	5
Takeda, 2006	91	111	63 (64.9%)	60.5±11.6	37.8	64±6.1	3	4	5
Yu, 2018	91	293	180 (61.4%)	55.7±14.1	45	106.4± 54.1	3		5

Definitions of IDH

Of the included studies, 2 studies (including 1 study applying multiple definitions) had a decrease in SBP of ≥20 mmHg as main component in the definition. Ten other studies, (including 2 studies applying multiple definitions[5-40]), used a decrease in SBP of ≥20 mmHg in combination with clinical events and interventions as definition of IDH. This definition is equivalent to the definition used in the EBPG guideline[13] and in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guideline[41]. In 6 studies, IDH was defined as Nadir <90 mmHg including the study that used multiple definitions for 2 different cohorts[5]. Five studies used complicated definitions with multiple cut-off values and another 5 studies lacked detailed information on the definition of IDH or described IDH non-specifically as a sudden decrease in blood pressure (Supplementary file 2).

Prevalence of IDH on session level

Of the studies that measured the prevalence on session level, the percentage of HD sessions that was complicated by IDH ranged between 4.0 and 30.7% (Supplementary file 3). Of the studies that used the EBPG or a similar definition to identify IDH, there were 5 studies that measured the prevalence of IDH on session level. The prevalence of IDH in these studies ranged between 5.0% in a study with 54 patients and a total of 10,494 HD sessions during an observation period of 18 months[24] and 30.7% in a study with 43 patients with 18 HD sessions per patient over a 1.5 month period[23] (Supplementary file 3).

Of the 6 studies that used the Nadir <90 definition, 5 studies reported the prevalence of IDH on session level. In these studies, the prevalence of IDH ranged between 4.0% in a study with 112,013 patients with a total number of 3,472,403 HD sessions during an observation period of 91 days[22] and 17.2% in a study with 1,137 patients with a total number of 44,801 HD sessions during an observation period of 579 days[37] (Supplementary file 3).

Three of the 5 studies that used IDH definitions with multiple cut-off values reported an IDH prevalence of 4.5%[31] and 5.4%[20] and 23.3%[28] at session level, but did not specify the used definitions (Supplementary file 3).

Of the 5 studies that did not provide detailed information of the definition used, 2 studies reported an IDH prevalence of 4.8%[27] and 5.5%[9] on session level (Supplementary file 3).

Meta-analysis of the prevalence of IDH on session level

The 5 studies that measured the prevalence of IDH on session level using the EBPG guideline or similar definitions, were included in a meta-analysis comprising a total of 1,694 patients and 30.004 HD sessions. In a random effects model analysis, 10.1% (95% CI 6.1; 16.5) of IDH sessions were complicated by IDH (figure 2A). Homogeneity of effects was rejected in this analysis by a P value of 0.01 (Figure 2A). Influence analysis indicated no bias (Supplementary file 4A). The Linear regression test of the funnel plot did not indicate significant evidence for asymmetry (t = 0.54, p-value = 0.6).

Of the 5 studies that reported the prevalence of IDH on session level using Nadir SBP <90 mmHg as definition 4 were included in a meta-analysis comprising a total of 13.189 patients and 203.768 HD sessions. In a random effects model analysis, 11.6% (95% CI 8.4; 15.7) of HD sessions was complicated by IDH (figure 2B). Homogeneity of effects was rejected in this analysis by a P-value <0.01 (Figure 2B). Influence analysis indicated no evidence for bias (Supplementary file 4B).
The study of Chou et al. was excluded from the primary meta-analysis because of the deviating inclusion criteria (they enrolled incident HD patients and evaluated the prevalence of intradialytic hypotension within the first 91 days of HD) in combination with a large number of patients. If the study of Chou et al. was included in meta-analysis the random effect model analysis revealed that 9.7% (95% CI 5.2 -17.5) of HD sessions was complicated by IDH.

Figure 2A.
Prevalence of intradialytic hypotension defined according to the EBPG definition on session level with a meta-analysis.

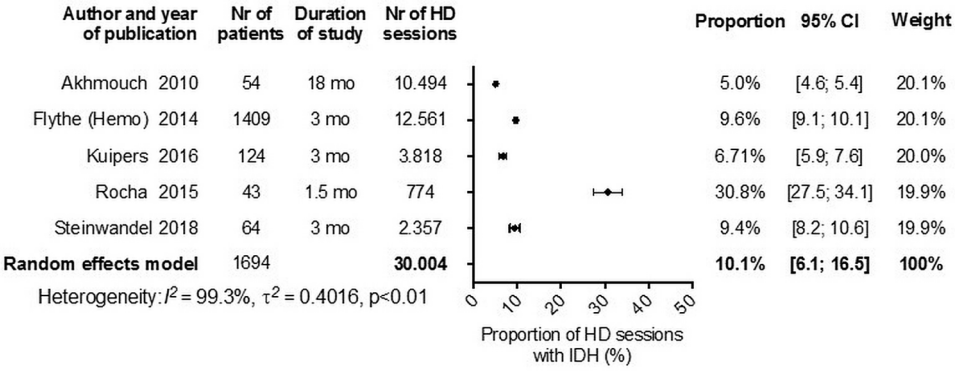
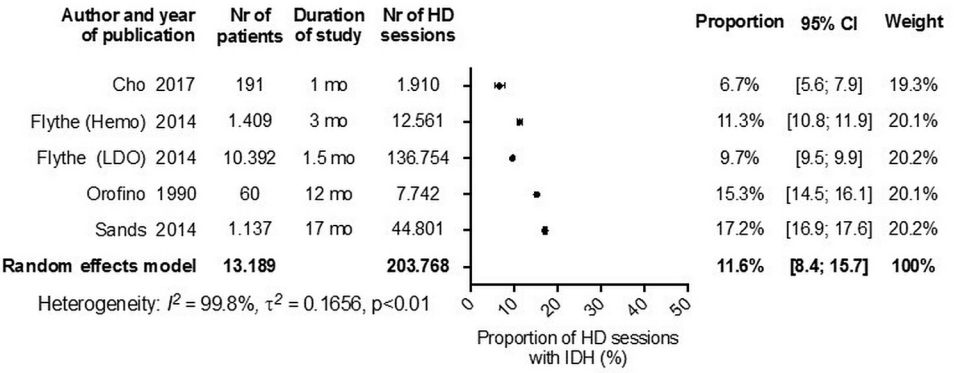


Figure 2B.
Prevalence of intradialytic hypotension defined according to the SBP nadir <90 mmHg definition on session level with meta-analysis.



Proportion of patients with frequent IDH

Seven studies provided information on the proportion of patients with frequent IDH defined according to the EBPG definition. In these studies, the proportion of patients with frequent IDH ranged from 5.6 to 76.7% (figure 3A).

Six studies give information on the proportion of patients with frequent IDH defined as the Nadir <90 definition. In these 6 studies the proportion of patients with frequent IDH ranged from 10.1% to 75.1% (figure 3B).

Of the 5 studies that used definitions with multiple cut-off values, two reported a proportion of patients with frequent IDH was 57%[39] and 26%[28]. In the 5 studies that did not provide detailed information on the IDH definition, the proportion of patients with frequent IDH ranged between 4.8%[27] and 76.4%[6], (Supplementary file 3). A meta-analysis of proportions on patient level was not possible given the large difference in cut-off values between studies.

Figure 3A.

Proportion of patients with frequent IDH as defined according to the EBPG definition.

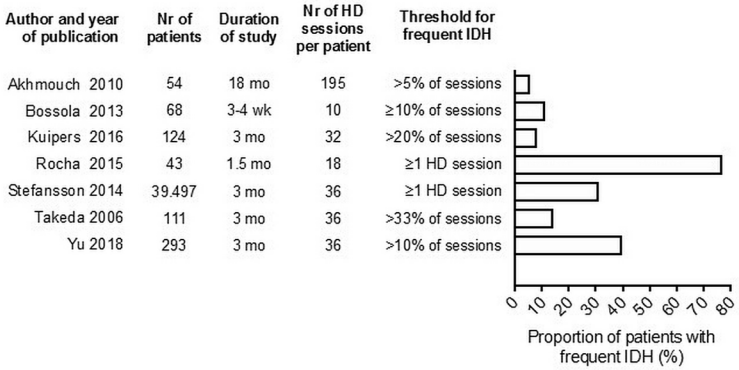
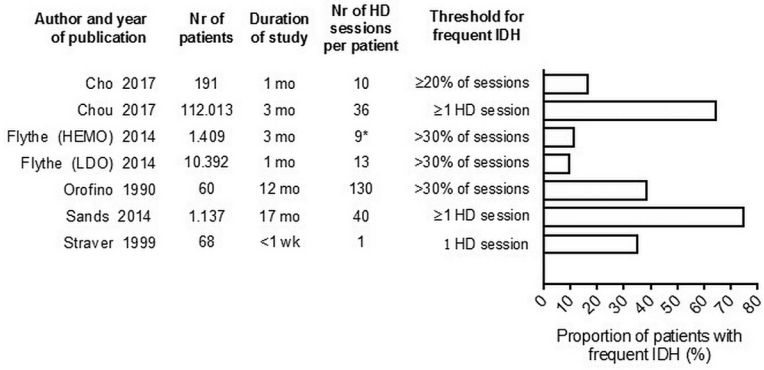


Figure 3B.

Proportion of patients with frequent IDH as defined according to the SBP nadir <90 mmHg definition.



*Only data of one treatment a month were used

Symptoms of IDH

Symptoms of IDH and/or the need for nursing interventions were described in 8 studies using various definitions and methodology (Supplementary file 5).

The most common symptoms were cramps, nausea, vomiting and dizziness. Caplin et al reported that cramps occurred in 74.3% of HD sessions[6] whereas Agrawal et al described cramps in 0.8% of HD sessions[30] (Supplementary file 5).

Interventions

Interventions were described in 3 studies. Kuipers et al reported interventions in 8.5% of HD sessions. Ogochukwu observed interventions in 28.5% of HD sessions, Collins reported interventions occurring in 29.2% of HD sessions, defined as saline administration during episodes of symptomatic hypotension or cramping[37] (Supplementary file 5).

Hemodynamic data

Hemodynamic data were available in 20 studies (Supplementary file 6). Pre-HD SBP was mostly described and ranged from 128 to 156 mmHg. Post-HD SBP ranged from 106 to 144 mmHg. Pre-HD DBP ranged from 67 to 84 mmHg. Post HD DPB ranged from 59 to 74 mmHg. IDWG varied from 2.2 to 4.5 L. Total UF per HD session ranged from 1.7 to 2.9 L (Supplementary file 6).

Patient and treatment factors associated with IDH

Fourteen studies described specific patient or treatment factors that were related to IDH. The most commonly reported patient-related factors were the presence of diabetes[9,19,23,24,29,30,36,37] and a higher IDWG[20,21,26,30,34,36,37]. Both factors together were mentioned in 3 studies[30,36,37].

Being female was mentioned as a risk factor for IDH in 5 studies[19,20,26,29,35,37,40]. In 1 study female gender was identified as a risk factor in combination with the factors IDWG and UF rate[20]. In 2 other studies, female gender was found to be a risk factor in combination with lower body weight[26,35], one of these studies also found small height as a risk factor[26].

Low predialysis SBP was reported as a risk factor for IDH in 4 studies[27,29,35,37], whereas another study identified a high SBP as a risk factor for IDH[26].

In 2 studies, dialysate temperature was identified as a risk factor for IDH. A higher temperature (37°C versus 35°C) was associated with a higher rate of symptomatic IDH in one of these studies[45].

DISCUSSION / CONCLUSION

The major conclusion of this review is that, as seen in our meta-analysis, the prevalence of IDH according to both the EBPG (10.1%) and the Nadir <90 mmHg definition (11.6%) was much lower than the 20 to 30% prevalence that is stated in most reviews[37-42-43-44-45-46-47-48]. The proportion of patients with frequent IDH varied between studies, in part depending on the threshold that is used to identify patients with frequent IDH. Major risk factors associated with IDH across studies were diabetes, a higher interdialytic weight gain, female gender and lower body weight.

Interestingly, the studies within the EBPG definition showed a rather uniform pattern with a prevalence of IDH below 12% with only one exception: Rocha et al reported that as much as 30.7% of HD sessions was complicated by IDH[23]. These authors included multiple episodes of IDH during a single HD session whereas in most studies HD sessions with IDH were considered as one event. For the Nadir <90 mmHg definition there was more variation between studies with the prevalence ranging between 4,0% and 17.2% of HD sessions.

If a liberal definition of IDH is used such as a fall in SBP >20 mmHg the prevalence will be higher than when stricter definitions are used, such as the EBPG definition. However, even within a homogenous category of, for instance the EBPG definition, it remains difficult to compare studies for several reasons. First, studies differed markedly with regard to the number of patients included, the observation period and whether IDH was measured on session level or on patient level. Second, the prevalence of symptoms may differ depending on how these data was collected with 'actively' using questionnaires at each dialysis session, yielding a higher prevalence than 'passively' waiting for the patient to report symptoms. Finally, an intervention is, like a symptom, not a hard end point but is subject to bias with variation in the threshold to start an intervention between healthcare professionals. Notably, most of the studies lacked a detailed description of the interventions that were used to treat IDH; only one study[26] described specific interventions other than the administration of fluid.

Despite the differences between the studies there was a similarity in the factors that were associated with IDH across studies. Diabetes is an obvious risk factor for IDH, explained by a higher prevalence of cardiovascular complications and diabetic complications such as autonomous neuropathy[9]. Higher IDWG is also a well-known risk factor for the occurrence of IDH[49-50-51]. Rocha found a significant association between lower dry weight and recurrent IDH episodes[23]. A higher refill rate from the interstitial tissues in a more fluid overloaded state can be seen as the cause of the higher BP during the first HD session of the week[52].

Female gender was reported as a risk factor for IDH in 7 studies[19-20-26-29-35-37-40]. Notably, 2 studies reported female gender in combination with a lower body weight as a risk factor for IDH[26-35]. This can be explained by the fact that females in general have a lower body weight than men and, consequently have a higher UF rate (ml/h/kg bodyweight) during HD for a similar IDWG.

Although we did a broad search of the available literature and included the studies that actually investigated the prevalence of IDH, we cannot exclude the possibility of

publication bias. However, the funnel plot did not indicate significant evidence for publication bias. The literature search showed that the EBPG and the nadir <90 mmHg definition are most frequently used. In our opinion it is justified to perform a meta-analysis for studies using these definitions despite the differences in the number of patients investigated and the number HD treatments between studies. A limitation of this analysis is the significant heterogeneity across studies. However, the random effects model and the influence analysis by leaving one study out, showed that the results of the prevalence of IDH were robust. Although these results show a lower than expected pooled estimates, the content evaluation makes the results appear reasonable given the current state of literature in the field of intradialytic hypotension in hemodialysis patient. Presently, there is no general consensus regarding the best evidence-based indicators of IDH. Surprisingly, in none of the articles it was stated what the underlying motivation was for the use of that specific definition. Depending on the purpose of the study, the appropriate definition may differ as also stated by Assismon[53]. In our opinion, the definition of IDH should be refined based on the purpose for which the definition is used. Thus, when the goal of the study is to examine the relation between IDH and outcome, a nadir definition may be appropriate whereas when the purpose of the study is to investigate the relation between IDH and patient reported outcome measurements or quality of life a definition of IDH that incorporates intradialytic (and preferably also post-dialytic) symptoms may be more relevant. Further research is needed to understand the underlying mechanisms of IDH and its symptoms in order to provide the patient with the optimal dialysis treatment. This is relevant not only for preventing morbidity and decreasing mortality, but also to support patients in their wellbeing and to improve quality of life.

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REFERENCES

1. Tisler A, Akocsi K, Borbas B, et al. The effect of frequent or occasional dialysis-associated hypotension on survival of patients on maintenance haemodialysis. *Nephrol Dial Transplant*. 2003;18(12):2601-2605.
2. Shoji T, Tsubakihara Y, Fujii M, Imai E. Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. *Kidney Int*. 2004;66(3):1212-1220.
3. Chang TI, Paik J, Greene T, et al. Intradialytic hypotension and vascular access thrombosis. *J Am Soc Nephrol*. 2011;22(8):1526-1533.
4. McIntyre CW. Haemodialysis-induced myocardial stunning in chronic kidney disease - a new aspect of cardiovascular disease. *Blood Purif*. 2010;29(2):105-110.
5. Flythe JE, Xue H, Lynch KE, et al. Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol*. 2014.
6. Caplin B, Kumar S, Davenport A. Patients' perspective of haemodialysis-associated symptoms. *Nephrol Dial Transplant*. 2011;26(8):2656-2663.
7. Jefferies HJ, Burton JO, McIntyre CW. Individualised dialysate temperature improves intradialytic haemodynamics and abrogates haemodialysis-induced myocardial stunning, without compromising tolerability. *Blood Purif*. 2011;32(1):63-68.
8. Franssen CFM, Dasselaar J, Sytsma P, et al.. Automatic feedback control of relative blood volume changes during hemodialysis improves blood pressure stability during and after dialysis. *Hemodial Int.* 2005;9(4):383-392.
9. Davenport A, Cox C, Thuraisingham R. Blood pressure control and symptomatic intradialytic hypotension in diabetic haemodialysis patients: A cross-sectional survey. *Nephron.Clinical practice*. 2008;109(2):c65-c71.
10. Mc Causland FR, Brunelli SM, Waikar S. Dialysis dose and intradialytic hypotension: Results from the HEMO study. *Am J Nephrol*. 2013;38(5):388-396.
11. Liberati A. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *PLoS Medicine*. 2009-7-21;6(7).
12. Wells G. The newcastle-ottawa scale (NOS) for assessing the quality of nonrand-omised studies in meta-analysis. *http://www,ohri.ca/programs/clinical_epidemiology.oxford.htm*. 2004.
13. Kooman J, Basci A, Pizzarelli F, et al. EBPG guideline on haemodynamic instability. *Nephrol Dial Transplant.* 2007;22 Suppl 2:ii22-ii44.
14. Shaikh RA, Solangi S, Rathi SK, et al.. Frequency of acute complications during haemodialysis. *J Liaquat Univ Med Health Sci*. 2013;12(2):94-97.
15. Amira CO, Braimoh RW, Bello BT. Pattern of intradialytic complications at the lagos university teaching hospital. *Afr J Med Med Sci*. 2012;41(4):411-416.
16. Ghaffar U. A quality improvement project: Strategies to reduce intradialytic hypotension in hemodialysis patients. *Nephrology news issues*. 2015-5;29(5).
17. Mc Causland FR, Brunelli SM, Waikar SS. Dialysis dose and intradialytic hypotension: Results from the HEMO study. *Am J Nephrol*. 2013;38(5):388-396.

18. Rocha A, Sousa C, Teles P, et al. Effect of dialysis day on intradialytic hypotension risk. *Kidney Blood Press Res*. 2016;41(2):168-174.
19. Degoulet P, Reach I, Di Giulio S, et al. Epidemiology of dialysis induced hypotension. *Proc Eur Dial Transplant Assoc*. 1981;18:133-138.
20. Awan AUR, Shafi T, Ahmed AM, et al. Frequency of intradialytic hypotension among patients on maintenance heamodialysis. *Pak J Med Health Sci*. 2011;5(3):471-475.
21. Lai CT, Wu CJ, Chen HH, et al. Absolute interdialytic weight gain is more important than percent weight gain for intradialytic hypotension in heavy patients. *Nephrology (Carlton)*. 2012;17(3):230-236.
22. Chou JA. Intradialytic hypotension, blood pressure changes and mortality risk in incident hemodialysis patients. *Nephrology Dialysis Transplantation*. 2018-1-01;33(1):149-159.
23. Rocha A, Sousa C, Teles P, et al.. Frequency of intradialytic hypotensive episodes: Old problem, new insights. *J Am Soc Hypertens*. 2015;9(10):763-768.
24. Akhmouch I, Bahadi A, Zajjari Y, et al. Characteristics of intradialytic hypotension: Experience of agadir center-morocco. *Saudi J Kidney Dis Transpl*. 2010;21(4):756-761.
25. Cho AJ. The relationship between intradialytic hypotension and vascular calcification in hemodialysis patients. *PLoS ONE*. 2017;12(10).
26. Kuipers J, Oosterhuis JK, Krijnen WP, et al. Prevalence of intradialytic hypotension, clinical symptoms and nursing interventions - a three-months, prospective study of 3818 haemodialysis sessions. *BMC Nephrol*. 2016;17(1):21.
27. Sangala N. Intra-dialytic hypotension: Identifying patients most at risk. *Journal of Renal Care*. 2017-6;43(2):92-97.
28. Levin NW. Hemodynamic response to fluid removal during hemodialysis: Categorization of causes of intradialytic hypotension. *Nephrology Dialysis Transplantation*. 2018-9-01;33(9):1643-1649.
29. Yu J. Intradialytic hypotension as an independent risk factor for long-term mortality in maintaining hemodialysis patients: A 5-year follow-up cohort study. *Blood Purif*. 2018;45(4):320-326.
30. Takeda A, Toda T, Fujii T, et al. Can predialysis hypertension prevent intradialytic hypotension in hemodialysis patients? *Nephron Clin Pract*. 2006;103(4):c137-43.
31. Agrawal RK, Khakurel S, Hada R, et al. Acute intradialytic complications in end stage renal disease on maintenance hemodialysis. *JNMA J Nepal Med Assoc*. 2012;52(187):118-121.
32. Straver B, Roggekamp MC, de Vries PM, et al. Systemic vascular resistance in intradialytic hypotension determined by means of impedance cardiography. *Blood Purif*. 1998;16(5):281-289.
33. Okoye OC. Prevalence and risk factors of intra-dialytic hypotension: A 5 year retrospective report from a single nigerian centre. *Pan African Medical Journal, The*. 2017;28.
34. Bossola M, Laudisio A, Antocicco M, et al. Intradialytic hypotension is associated with dialytic age in patients on chronic hemodialysis. *Ren Fail*. 2013;35(9):1260-1263.

35. Orofino L, Marcen R, Quereda C, et al. Epidemiology of symptomatic hypotension in hemodialysis: Is cool dialysate beneficial for all patients? *Am J Nephrol*. 1990;10(3):177-180.
36. Stefansson BV, Brunelli SM, Cabrera C, et al. Intradialytic hypotension and risk of cardiovascular disease. *Clin J Am Soc Nephrol*. 2014;9(12):2124-2132.
37. Sands JJ, Usvyat LA, Sullivan T, et al. Intradialytic hypotension: Frequency, sources of variation and correlation with clinical outcome. *Hemodial Int*. 2014;18(2):415-422.
38. Al-Hilali N, Al-Humoud HM, Ninan VT, et al. Profiled hemodialysis reduces intradialytic symptoms. *Transplant Proc*. 2004;36(6):1827-1828.
39. Collins DM, Lambert MB, Tannenbaum JS, et al.. Tolerance of hemodialysis: A randomized prospective trial of high-flux versus conventional high-efficiency hemodialysis. *J Am Soc Nephrol*. 1993;4(2):148-154.
40. Steinwandel U. Measuring the prevalence of intradialytic hypotension in a satellite dialysis clinic: Are we too complacent? *J Clin Nurs*. 2018-4;27(7-8):1561.
41. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *American Journal of Kidney Diseases*. 2005-4;45(4):1-153.
42. Davenport A. Can advances in hemodialysis machine technology prevent intradialytic hypotension? *Semin Dial*. 2009;22(3):231-236.
43. Perazella MA. Pharmacologic options available to treat symptomatic intradialytic hypotension. *Am J Kidney Dis.* 2001;38(4 Suppl 4):S26-S36.
44. Dubin R, Owens C, Gasper W, et al. Associations of endothelial dysfunction and arterial stiffness with intradialytic hypotension and hypertension. *Hemodial Int.* 2011;15(3):350-358.
45. Daugirdas JT. Pathophysiology of dialysis hypotension: An update. *Am J Kidney Dis.* 2001;38(4, Supplement 4):S11-S17.
46. Passauer J, Büssemaker E, Gross P. Dialysis hypotension: Do we see light at the end of the tunnel? *Nephrol Dial Transplant.* 1998;13(12):3024-3029.
47. Daugirdas JT. Preventing and managing hypotension. *Semin Dial*. 1994;7(4):276-283.
48. Zucchelli P, Santoro A. Dialysis-induced hypotension: A fresh look at pathophysiology. *Blood Purif*. 1993;11(2):85-98.
49. Hall JE, Guyton AC, Brands MW. Pressure-volume regulation in hypertension. *Kidney International Supplement*. 1996(55).
50. Koomans HA, Braam B, Geers AB, et al. The importance of plasma protein for blood volume and blood pressure homeostasis. *Kidney Int*. 1986;30(5):730-735.
51. Ventura JE, Sposito M. Volume sensitivity of blood pressure in end-stage renal disease. *Nephrol Dial Transplant*. 1997;12(3):485-491.
52. Koomans HA, Geers AB, Mees EJD. Plasma volume recovery after ultrafiltration in patients with chronic renal failure. *Kidney Int*. 1984;26(6):848-854.
53. Assimon MM, Flythe JE. Intradialytic blood pressure abnormalities: The highs, the lows and all that lies between. *Am J Nephrol*. 2015;42(5):337-350.

Supplementary file 1.

Search strategy for intradialytic hypotension.

To locate hemodialysis	
1.	**Renal Dialysis (Mesh)**
2.	**Hemodialysis (Mesh)**
3.	**Hemodialysis (tw)**
4.	**Haemodialysis (tw)**
5.	**Or 1-4**
To locate hypotension	
1.	**Hypotension (Mesh)**
2.	**Low blood pressure (tw)**
3.	**Intradialytic hypotension (tw)**
4.	**Or 1-3**

Abbreviations: Mesh: medical subject heading, tw: text words.

Supplementary File 2.
haracteristics of the inluded studies.

Author	Patients characteristics	In/ exclusion criteria	Dialysis regimen	Primary research question	Study details and design	Study quality
Agrawal, 2012	**N**: 28 **Age:** 48.8 yrs (range 25-71) **Gender:** male 19 pts (68.0%) **Time on HD:** NS **CV medication:** 96.4% of pts used anti-hypertensive drugs **Kt/V:** 75.0% of pts <1.2 **DM:** 5 pts (17.9%)	**Inclusion:** pts with end stage renal disease undergoing maintenance HD **Exclusion:** pts with acute chronic renal failure	**Sessions per week:** 2 (5 of 28 pts required additional emergency HD sessions) **Duration:** 4 hrs **Blood flow:** NS **Dialysate flow:** NS **Dialyzer type:** NS **Bicarbonate HD:** Y **D-temp:** NS	What is the frequency of acute intradialytic complications in chronic HD pts?	**Type:** Cross-sectional **Duration**: 6 mhts, 1455 HD sessions **Method:** pts symptoms, nurses records and physician's interventions were registered to analyze possible complications **Details:** NS	6
Akhmouch, 2010	**N**: 54 **Age:** 54.1 (range 21-80) yrs **Gender:** male 33 pts (61.1%) **Time on HD:** 59.8 mths (range 5-240**)** **CV medication:** 44.6% of pts in IDH group **Kt/V:** NS **DM:** 17 pts (31.5%)	**Inclusion:** >3 mhts on HD treatment **Age** >18 yrs **Dx hrs** >3 hrs **Exclusion:** NS	**Sessions per week:** mean of 194 (48-290) over a period of 18 mhts: 2 to 3 sessions a week **Duration:** 3-4 hrs **Blood flow:** NS **Dialysate flow:** NS **Dialyzer type:** NS **Bicarbonate HD:** NS **D-temp:** NS	What is the frequency of IDH and which risk factors may precipitate IDH?	**Type:** Retrospective, **Duration**: 18 mhts **Method:** comparison of characteristics of pts with and without IDH **Details:** pts were screened for demographic characteristics, clinical data, laboratory data, left ventricular hypertrophy, systolic and diastolic function	5
Al-Hilali, 2004	**N**: 40 **Age:** 48.6±14.9 yrs **Gender:** male 15 pts (37.5%) **Time on HD** 34.5±2.7 mhts **CV medication:** NS **Kt/V:** NS **DM:** 18 pts **(**45.0%)	**Inclusion:** pts were recruited between September-December 2002. 29 pts with IDH were approached to participate in the study with profiled HD **Exclusion:** NS	**Sessions a week:** NS **Duration in hrs:** NS **Blood flow:** NS **Dialysate flow:** NS **Dialyzer type:** NS **Bicarbonate HD:** NS **D-temp:** NS	To determine the efficacy of combined sodium and UF-profiled HD in comparison with standard HD to reduce IDH symptoms	**Type:** Prospective study. **Duration:** at 2, 4 and 6 weeks after inclusion a questionnaire was completed by the pts **Method:** NS **Details:** NS	5
Awan, 2011	**N**: 100 **Age**: 51±16 yrs **Gender:** male 57 pts (57.0%) **Time on HD:** NS **CV medication:** in pts with IDH: 23.3%; pts without IDH: 31.8% **Kt/V:** NS **DM:** 51 pts (51.0%)	**Inclusion:** all adult pts on maintenance HD were included **Exclusion:** Age<10 yrs; <3 mths on HD; Pts who developed vomiting, diarrhea or bleeding episodes before the HD session	**Sessions a week:** 1907 HD sessions in 3 mths in 100 pts: maximum of 2 HD sessions per week per pt. **Duration:** NS **Blood flow:** NS **Dialysate flow:** NS **Dialyzer type:** in 76.5% of HD sessions reuse dialyzers were used **Bicarbonate HD**: Y **D-temp:** 37°C	To find the exact frequency and factors related to IDH, and to be able to reduce the frequency of IDH by modifying risk factors and dialysis prescription, to improve the quality of life	**Type:** Cross-sectional study **Duration:** 3 mhts **Method:** a total of 1907 HD sessions were categorized into 2 groups, with and without IDH **Details:** Frequency of IDH was calculated and are given as percentage. Various risk factors were compared between patients with and without IDH	3

Bossola, 2013	**N**: 68 **Age:** 61±16 yrs **Gender:** male 43 pts (63.2%) **Time on HD:** 92±71 mhts **CV medication:** antihypertension drug use in 50.0% of pts **Kt/V:** NS **DM:** NS	**Inclusion:**>12 mths of HD treatment **Exclusion:** advanced heart failure, dementia, history of alcohol/ substance abuse, previous diagnosis of psychiatric disorder, clinically instable, requiring hospital admission	**Sessions a week:** 3 **Duration in hrs:** 4 **Blood flow:** 250-300 ml/min **Dialysate flow:** 500ml/min **Dialyzer type:** high permeability membrane (not reused) **Bicarbonate HD:** Y **D-temp:** NS	Evaluating the association between IDH and time on HD	**Type:** Cross-sectional study **Duration**: 3 to 4 weeks **Method:** for each pt, the nr of IDH episodes during 10 consecutive HD sessions were recorded **Details:** Multivariate logistic regression was used to estimate the association of IDH with covariates	6
Caplin, 2011	**N**: 508 **Age:** 64 (IQR 60-74.5) yrs **Gender:** male 272 pts (53.6%) **Time on HD:** 37 mhts (range 18-64) **CV medication:** NS **Kt/V:** 1.65 (1.44-1.86) per HD session. **DM:** 184 pts (36.3%)	**Inclusion:** Adult HD pts >3 mths of HD treatment **Exclusion:** home HD pts because of the small nr of pts	**Sessions a week:** 3 **Duration:** 4 hrs (range 2.5-5.25) **Blood flow:** 800 ml/min (79%) 500 ml/min (21%) **Dialysate flow:** NS **Dialyzer type:** polysulphone dialyzer (Fresenius) **Bicarbonate HD:** Y **D-temp:** 35 C° (49%); in the remaining HD sessions a higher D-temp was used	To establish the burden and duration of HD-associated symptoms. An attempt to characterize pts and HD-related factors that are associated with these outcomes	**Type:** observational study with a one-time questionnaire **Duration**: NS **Method:** Pts were asked to complete a visual analogue score of both a range and frequency of symptoms experienced during HD, and the time taken to recover from an HD session **Details:** multicenter trial in 6 different care settings	5
Cho, 2017	**N:** 191 **Age**: 60 ±12 yrs **Gender:** male 49 pts (25.7%) **Time on HD:** NS **CV medication:** NS **Kt/V:** NS **DM**: 103 pts (53.9%)	**Inclusion:** >3 mhts in HD and written informed consent **Exclusion:** NS	**Sessions a week:** 3 **Duration:** 4 hrs **Blood flow:** NS **Dialysate flow:** NS **Dialyzer type:** NS **Bicarbonate HD:** NS **D-temp**: NS	To determine the relationship between IDH and abdominal aortic calcification evaluated by plain abdomen radiography	**Type:** prospective observational study **Duration:** data collection per pt during one week **Method:** mean pre-HD SBP and DBP and UF volume were calculated as the average of 10 values at the time of IDH assessment **Details:** NS	6
Chou, 2017	**N:** 11.2013 **Age**: 63 ±15 yrs **Gender:** male 63847 pts (57.0%) **Time on HD:** NS **CV medication:** NS **Kt/V:** NS **DM**: 64967 pts (58.0%)	**Inclusion:** thrice weekly HD; availability of all BP during the first 91 days of HD treatment; time on HD >60 days **Exclusion:** No intradialytic BP`s available	**Sessions a week:** 3 **Duration:** NS **Blood flow:** NS **Dialysate flow:** NS **Dialyzer type:** NS **Bicarbonate HD:** NS **D-temp**: NS	To evaluate a comprehensive set of HD-related BP variables including nadir intradialytic SBP, pre-HD SBP minus nadir intradialytic BP, and frequency of IDH and their relationship to mortality	**Type:** prospective observational study **Duration:** 91 days of collecting of intradialytic hemodynamic data; patients were followed for 5 years of all-cause mortality **Method:** during the first 91 days of HD treatment, comprising a mean (±SD) of 31±8 HD sessions per patient, pre- and intradialytic data were collected. BP data were averaged over this period **Details:** US based large dialysis organization (LDO)	**6**

Author	Patients characteristics	In/ exclusion criteria	Dialysis regimen	Primary research question	Study details and design	Study quality
Collins, 1993	**N:** 40 **Age**: 52.5 yrs **Gender:** male 16 pts (40.0%) **Time on HD:** NS **CV medication:** NS **Kt/V:** NS **DM**: 17 pts (42.5%)	**Inclusion:** Informed consent **Exclusion:** NS	**Sessions a week:** 3 **Duration:** 3.3 hrs **Blood flow:** 300-400 ml/min **Dialysate flow:** 500 ml/min **Dialyzer type:** NS **Bicarbonate HD:** Y **D-temp**: NS	To examine whether pts dialyzed with one of the most compatible synthetic membranes (PAN or AN69) had a lower incidence of IDH and acute HD-related symptoms when compared to pts dialyzed with cuprophane membrane	**Type:** randomized prospective cross-over study **Duration:** 6 mhts **Method**: cross-over: 3 mhts of HD with cuprophane and 3mhts of HD with AN69 **Details:** NS	8
Davenport, 2008	**N**: 2193 **Age:** 61.2 (IQR 46.9-72.3) yrs **Gender:** male 1326 pts (60.5%) **Time on HD:** NS **CV medication:** 70% of pts **Kt/V:** NS **DM:** 658 pts (32.0%)	**Inclusion:** adult HD pts dialyzing thrice weekly; >90 days of HD treatment **Exclusion:** NS	**Sessions a week:** 3 **Duration:** median 4 hrs **Blood flow:** 250-300 ml/min **Dialysate flow:** 500 ml/min **Dialyzer type:** single use, polysulfon, 2 centers used modified cellulose acetate dialyzers **Bicarbonate HD:** Y **D-temp:** NS 50 pts were treated with post-dilution HDF	To audit BP control in a cohort of adult HD pts and to assess whether BP control was different in pts with DM compared to non-DM pts. Episodes of IDH were also recorded	**Type:** prospective study **Duration**: 7 day period, a total of 6579 HD sessions **Method:** data obtained from 13 main hospital and 30 satellite units in the region of London, UK **Details:** Multivariate logistic regression was used to estimate the association of IDH with covariates	**6**
Degoulet, 1981	**N**: 1110 **Age:** 49.0±15.2 yrs **Gender:** NS **Time on HD:** NS **CV medication:** NS **Kt/V:** NS **DM:** NS	**Inclusion:** age ≥15 yrs; >50 consecutive HD sessions during follow-up period, no other mode of treatment during this period **Exclusion:** NS	**Sessions a week:** Thrice weekly HD: N: 741, 4.6±0.8 hrs Twice weekly HD: N: 369, 6.5±1.6 hrs **Blood flow:** NS **Dialysate flow:** NS **Dialyzer type:** coil type and hollow fiber **Bicarbonate HD:** Y **D-temp:** NS	To investigate the epidemiological influence of commonly accepted symptomatic hypotension	**Type:** a survey based on data records for a large population of pts **Duration**: 12 mhts **Method:** between January 1st, 1979 and December 31th, 1979 a total of 29 clinical and biological parameters were studied. **Details:** data obtained from 32 French dialysis centers; per pt the prevalence of IDH was calculated by the proportion of HD sessions of total HD sessions during which IDH was recorded at least once	5
Flythe, 2014	**HEMO cohort:** **N**: 1409 **Age:** 59.4 ± 13.4 yrs **Gender:** male 625 pts (44.4%) **Time on HD:** NS **CV Medication:** NS **Kt/V:** NS **DM:** 631 pts (44.8%)	**Inclusion:** adult subjects (18-80 yrs) receiving thrice weekly in-center HD for >3 mths **Exclusion:** baseline serum albumin <2.6 g/dl, residual urea clearance ≥1.5 ml/min /35liters of urea distribution volume, inability to consistently achieve an equilibrated Kt/V of >1.3 or	**HEMO cohort:** **Sessions a week:** 3 **Duration:** 212±23 min **Blood flow:** NS **Dialysate flow:** NS **Dialyzer type:** NS **Bicarbonate HD:** NS **D-temp:** NS	To examine the association of commonly used IDH definitions and mortality. IDH definitions were selected a priori by literature review. A secondary analysis	**Type:** a secondary analysis of the HEMO study and a replication study (LDO) **Duration**: approx. 6 mhts, 12,561 treatments (8.9±1.6 per pt): only data of one treatment per month was used in HEMO study **Method: s**tudy data were derived from the HEMO study **LDO:**	8

	LDO cohort: **N**: 10392 **Age:** 62.7 ± 14.4 yrs **Gender:** male 5819 pts (56.0 %) **Time on HD:** NS **CV medication:** NS **Kt/V:** NS **DM:** 6237 pts (60.0%)	presence of end- stage comorbid conditions other than kidney failure	**LDO-cohort** **Sessions a week**: 3 **Duration:** 216±28.6 min **Blood flow:** NS **Dialysate flow:** NS **Dialyzer type:** NS **Bicarbonate HD:** NS **D-temp:** NS	of the HEMO study was done to test mortality associations across a range of IDH definitions and a replication study was performed to confirm results using data from a nationally representative cohort of pts from a single large dialysis organization	**Type:** a replication study **Duration**: 136,754 treatments during a baseline period of 30 days (13.3±1.3 per pt) session to session HD data were available **Method:** Study data were obtained from the electronic record of LDO	
Kuipers, 2016	**N**: 124 **Age:** 64.1±15.7 yrs **Gender:** male 69 pts (56.0%) **Time on HD:** 32.0±30.7 mhts; **CV medication:** 67.0 % of pts **Kt/V:**.1.32±0.36 per session **DM:** 31pts (27.0%)	**Inclusion:** Age **>**18 yrs and >3mths of HD treatment **Exclusion:** HD sessions during hospitalization	**Sessions a week**: 3 (mean 32 per patient) **Duration:** 3.5-4.5 hrs **Blood flow:** 250-350 ml/min **Dialysate flow:** 500-700 ml/min **Dialyzer type:** low-flux polysulphon hollow fiber (Fresenius) **Bicarbonate HD:** Y **D-temp:** 36.0-36.5 °C	To assess the prevalence of IDH and identify pts treatment factors associated with IDH	**Type:** Multicenter, prospective, observational study **Duration:** 3 mhts **Method:** prospective collection of hemodynamic data of 3818 HD sessions **Details:** clinical events and interventions were recorded in addition to detailed hemodynamic data	5
Lai, 2012	**N:** 255 **Age**: 62.5 yrs (range 16.0-93) **Gender:** Male 129 pts (50.6%) **Time on HD:** NS **CV medication:** NS **Kt/V:** 1.4 (SEM 0.02) **DM**: 116 pts (45.5%)	**Inclusion:** pts with at least one year follow up of HD treatment **Exclusion:** data acquired during the first 4 weeks of HD treatment	**Sessions a week:** 3 **Duration:** NS **Blood flow:** NS **Dialysate flow:** NS **Dialyzer type:** NS **Bicarbonate HD**: NS **D-temp:** NS	To evaluate the difference between IDWG and %IDWG in new HD pts	**Type:** Retrospective, single-center cohort study **Duration:** 1 year **Method:** the first 4 weeks after initiating HD was defined as pre-study. Data were collected for the 11 mths following the pre-study period **Details:** the arrhythmic means of BP, absolute IDWG and %IDWG were recorded during 12 consecutive HD sessions	6
Levin, 2018	**N**: 54 **Age:** 67.0±10.0 yrs **Gender:** male 29 pts (54.0%) **Time on HD:** NS **CV medication:** NS **Kt/V:**.NS **DM:** 30pts (56.0%)	**Inclusion:** >3 mhts in HD and written informed consent **Exclusion:** NS	**Sessions a week:** NS **Duration:** NS **Blood flow:** NS **Dialysate flow:** NS **Dialyzer type:** NS **Bicarbonate HD**: NS **D-temp:** NS	To report the hemodynamic changes during HD, focusing on those responsible for IDH episodes	**Type:** Multicenter, prospective, study **Duration:** A total of 263 sessions were evaluated, an average of 4.9±2.3 HD sessions per patient **Method:** all hemodynamic measurements were made using a regional impedance cardiography device **Details:** measurements were made at baseline, at the middle, just before end and 10 minutes after the end of treatment	5

Author	Patients characteristics	In/ exclusion criteria	Dialysis regimen	Primary research question	Study details and design	Study quality
Meredith, 2015	**N**: 77 **Age:** 65 yrs (IQR 51-75) **Gender:** male 55 pts(71.0%) **Time on HD:** 26 mths (IQR 11-49) **CV medication:** 70% **Kt/V:** NS **DM:** 31 pts (40.3%)	**Inclusion:** all adult HD pts within a single outpatient dialysis unit **Exclusion:** NS	**Sessions a week:** NS **Duration:** NS **Blood flow:** NS **Dialysate flow:** NS **Dialyzer type:** high-flux **Bicarbonate HD:** Y **D-temp:** 36.5-37.0 °C; HD prescription and medication were not changed for the purpose of this study	Exploring the propensity of pts to report symptoms; outlining the association between symptoms and BP; establishing the frequency of asymptomatic IDH	**Type:** Prospective observational study **Duration:** each patient was studied for a mean of 5.9 sessions (range 1-19) over 12 mths **Method:** A total of 456 HD sessions; participants completed a questionnaire after HD concerning HD symptoms. For comparison, nursing documentation was also collected **Details:**. NS	5
Ogochukwu, 2017	**N:** 404 **Age**: 48 ±17 yrs **Gender:** male 225 pts (55.7%) **Time on HD:** NS **CV medication:** NS **Kt/V:** NS **DM**: NS	**Inclusion:** adult HD pts with acute or chronic kidney disease **Exclusion:** Pts with incomplete or incorrect data	**Sessions a week:** NS **Duration:** NS **Blood flow:** NS **Dialysate flow:** NS **Dialyzer type:** NS **Bicarbonate HD:** NS **D-temp**: NS	To determine the prevalence and risk factors of IDH	**Type:** retrospective cross- sectional study **Duration:** 4 years (January 2012-January 2016) **Method**: records were obtained from individual case folders **Details:** NS	4
Orofino, 1990	**N**: 60 **Age:** 51 yrs (range 15-72) **Gender:** male 39 pts (65.0%) **Time on HD:** 41.7 mhts (range 8-96) **CV medication:** NS **Kt/V:** NS **DM:** all non-diabetic	**Inclusion:** NS **Exclusion:** pts with DM	**Sessions a week:** 3 **Duration:** 3-4 hrs **Blood flow:** NS **Dialysate flow:** 400 ml/min **Dialyzer type:** cuprophane hollow-fiber **Acetate dx** **D-temp:** 35 or 37 °C, see study details	To assess the characteristics of pts most affected by IDH and to assess the potential benefits of reducing dialysate temperature	**Type:** Prospective, single-blind **Duration:** 12 mhts **Method:** 3723 HD sessions with D-temp of 37.0 °C for 6 mhts, 4019 HD sessions with D-temp of 35.0 °C for 6 mhts **Details:** BP was measured at least hourly; all symptoms were spontaneously referred by pts and written down by the nurse in charge	5
Rocha, 2015/2016	**N:** 43 **Age:** 66.6±13.2 yrs **Gender:** Male 25 pts (58.1%) **Time on HD:** 86 mhts (range 2-388) **CV medication:** 28 pts (65.1%) **Kt/V:** NS **DM:** 12 pts (27.9%)	**Inclusion:** Age >18 yrs; medically stable; 3 HD sessions a week for 4 hrs; >2 mths of HD treatment **Exclusion:** NS	**Sessions a week:** 3 **Duration in hrs:** 3-4 **Blood flow:** 300-450 ml/min **Dialysate flow:** 500-700 ml/min **Dialyzer type:** synthetic hollow- fiber (Nipro) **Bicarbonate HD:** Y **D-temp:** 35.5-36.0 **°C**	To evaluate the frequency of symptomatic IDH and to uncover the variables associated with those episodes. To evaluate the influence of variations in fluid status over the week on BP	**Type:** Retrospective cross-sectional study **Duration:** 6 weeks (18 HD sessions per pt) **Method:** data were recorded on a session to session basis **Details:** Data were recorded on a session tot session basis	5
Sands, 2014	**N:** 1137 **Age:** 61.9±15.8 yrs **Gender:** Male 608 pts (53.5%) **Time on HD:** 4.5±4.3 yrs **CV medication:** NS **Kt/V:** 1.58±0.29 **DM:** 639 pts **(**56.2%)	**Inclusion:** all HD treatments with available data were included for data analysis **Exclusion:** NS	**Sessions a week:** NS **Duration:** 3.6 ±0.5 hrs **Blood flow:** 428 ±46.8ml/min **Dialysate flow:** 680 ±68.9 ml/min **Dialyzer type:** **Bicarbonate HD:** 35.4 ±1.1 mmol/l **D-temp:** 36.5 ±0.39 °C	To determine the variability of IDH in individual pts and pts and treatment factors associated with IDH; the impact of IDH on pts outcomes and mortality	**Type:** Prospective evaluation of the epidemiology of IDH in 13 out-patient HD facilities **Duration:** 17 mths (between March 2011 and July 2012) **Method:** BP captured by direct machine download, measured every 30 min **Details:** 44,801 HD sessions in 1137 pts	5

Sangala, 2017	**N**: 432 **Age:** 65.9±NS yrs **Gender:** NS **Time on HD:** 36.8 ± NS mths **CV medication:** 255 pts (59%) **Kt/V:** NS **DM:** 134 pts (31.0%)	**Inclusion:** HD pts dialyzing thrice weekly; >3mths of HD treatment and had received 7 consecutive weeks of HD treatment at their usual center without any intercurrent illness requiring hospitalization **Exclusion:** NS	**Sessions a week:** 3 **Duration:** NS **Blood flow:** NS **Dialysate flow:** NS **Dialyzer type:** coil type and hollow fiber **Bicarbonate HD:** Y **D-temp:** NS	An observational analysis of our prevalent dialysis population with an aim to establish the rate of IDH and identify the characteristic of patients most at risk	**Type:** a retrospective observational analysis **Duration**: 7 weeks (21 consecutive HD sessions per pt); a total of 9,072 HD sessions **Method:** Data were extracted from an online database including pt characteristics and detailed information of the HD sessions **Details:** delta SBP is calculated as: (pre SBP - post SBP)/pre-SBPx100	6
Stefánsson, 2014	**N:** 39497 **Age**: 61.8± 15.2 yrs **Gender:** male 17335 pts (43.9%) **Time on HD:** approximately 3 mhts **CV medication:** NS **Kt/V:** NS **DM:** 26937 pts (68.2%)	**Inclusion:** Pts who began in-center HD between January 1st, 2007 and December 31th, 2008 **Exclusion:** pts without Medicare insurance, data were retrieved from Medicare claim files	**Sessions a week:** NS **Duration:** NS **Blood flow:** NS **Dialysate flow:** NS **Dialyzer type:** NS **Bicarbonate HD:** NS **D-temp**: NS	To measure the frequency of IDH according to IDWG and the association between IDH and CV events or mortality	**Type:** Retrospective study **Duration:** during 90 days, hemodynamic data and IDWG was recorded **Method:** data were obtained from a large dialysis organization's centralized warehouse and the US Renal Data System **Details:** after the 90 days of collecting data pts were followed for outcome of CV events up to a period of 30 mhts	6
Steinwandel, 2018	**N:** 64 **Age**: 63.0± 15.8 yrs **Gender:** Male: 45 pts (70.3%) **Time on HD:** NS **CV medication:** NS **Kt/V:** NS **DM:** 18 pts (28.1%)	**Inclusion:** NS **Exclusion:** NS	**Sessions a week:** 3 **Duration:** 3-5hrs **Blood flow:** NS **Dialysate flow:** NS **Dialyzer type:** NS **Bicarbonate HD:** NS **D-temp:** NS	To measure the prevalence of symptomatic IDH and asymptomatic IDH or post dialysis overhydration	**Type:** Retrospective observational study **Duration:** 3 mths (2.357 HD sessions) **Method:** renal nurses created a progress report after each HD session **Details:** the report contains information about transcribed pre- and post HD weight, UF and BP recordings	6
Straver, 1999	**N:** 68 **Age**: 56 yrs (SEM 3.2) **Gender:** Male: 38 pts (55.9%) **Time on HD:** 49 mhts (SEM 8.8) **CV medication:** No difference in the distribution of CV medication between groups **Kt/V:** NS **DM**: 6 pts (8.8%)	**Inclusion:** NS **Exclusion:** NS	**Sessions a week:** 2-3 **Duration:** 9-15 hrs/week **Blood flow:** 180-300 ml/min **Dialysate flow:** 500 ml/min **Dialyzer type:** polysulfon membranes **Bicarbonate HD:** Y **D-temp:** NS	To investigate hemodynamic interactions during a single HD session between the group that fulfilled the IDH definition and the hemodynamically stable group, in order to specify which mechanisms underlie the occurrence of symptomatic hypotensive episodes during HD	**Type:** Prospective study **Duration:** a single HD session **Method:** examine the difference between the group which fulfilled the IDH definition and the stable group variations in BV, stroke volume, CO, and systemic vascular resistance utilizing bioelectrical impedance cardiography (every hour or when symptoms of hypotension occurred) and monitoring of blood volume with Crit-line	5

Author	Patients characteristics	In/ exclusion criteria	Dialysis regimen	Primary research question	Study details and design	Study quality
Takeda, 2006	**N:** 111 **Age**: 60.5±11.6 yrs **Gender:** male 63 pts (64.9%) **Time on HD:** 5.3 ±5.1 yrs **CV medication:** 80.1% of pts **Kt/V:** 1.34 ±0.24 **DM**: 42 pts (37.8%)	**Inclusion:** Age >20 yrs; >6 mhts of HD treatment **Exclusion:** NS	**Sessions a week:** 3 **Duration:** 4 hrs **Blood flow:** NS **Dialysate flow:** NS **Dialyzer type:** NS **Bicarbonate HD:** Y **D-temp:** 35.0-36.5°C	To investigate the relationship between pre-HD BP and IDH and to study in an intervention trial the effect of additional antihypertensive medication on IDH	**Type:** cross-sectional **Duration:** 3 mhts **Method:** the data of the frequency of IDH and pre- HD BP was averaged over 3 mths **Details:** echocardiography was performed with the pt at dry weight within 24 hrs after a HD session	5
Yu, 2018	**N:** 293 **Age**: 55.7± 14.1 yrs **Gender:** male 180 pts (61.4%) **Time on HD:** 106.4± 54.1 mths **CV medication:** NS **Kt/V:** NS **DM**: 45 pts (15.4%)	**Inclusion:** Age >18 yrs; >3 mhts of HD treatment **Exclusion:** patients with acute heart failure and cardiac dysfunction	**Sessions a week:** 3 **Duration:** NS **Blood flow:** 200-280 ml/min **Dialysate flow:** 500 ml/min **Dialyzer type:** low flux, synthetic membranes; polyflux 14L **Bicarbonate HD:** Y **D-temp:** NS	To assess risk factors of IDH and the association of prognosis and IDH among HD patients. Primary endpoint was all-cause mortality	**Type:** single centre prospective cohort study **Duration:** 3 mhts **Method:** BP was estimated by averaging all the BP monitored during during HD over a 3 mths period **Details**: BP was measured every hour during HD	5

Abbreviations: Bicarbonate HD: hemodialysis with bicarbonate-containing dialysate; BP: blood pressure; CV: cardiovascular; DM: diabetes mellitus; D-temp: dialysate temperature; DBP: diastolic blood pressure; EBPG: European Best Practice Guideline on hemodynamic instability; HD: hemodialysis; Hrs.: hours; IDH: intradialytic hypotension; IDWG: interdialytic weight gain; KDOQI Kidney Disease Outcomes Quality Initiative; Mth: month; Mths: months; Nr: number; Nrs: numbers; NS: Not Specified; Pt: patient; Pts: patients; SBP: systolic blood pressure; UF: ultrafiltration volume; Y: yes; Yrs.: years.

Supplementary file 3.
IDH Details of studies.

Articles in which IDH is defined as a decrease in SBP 20mmHg

Author	Definition of IDH	Frequency of HD sessions with IDH	Frequency of HD sessions with symptoms and interventions	Important outcomes	Conclusion of authors	Comments
Lai, 2012	A decline in SBP >20mmHg from baseline requiring a saline infusion; results are expressed as the nr of IDH episodes per month	Pts in the highest %IDWG tertile had significantly more often IDH (3.58 times/mth versus 0.97 times/mth in the lowest tertile = 29.8%), had a higher pre-dialysis blood pressure, were younger and had lower dry weight compared with the other 2 tertiles	NS	A higher IDWG is associated with a higher incidence of IDH	Both absolute IDWG and %IDWG are significantly associated with higher predialysis BP and a higher incidence of IDH events; Absolute IDWG, rather than % IDWG is an independent risk factor for IDH in heavy HD pts	This article focusses mainly on IDWG and %IDWG parameters
Steinwandel, 2018	Symptomatic IDH: KDOQI: a fall in SBP ≥20 mmHg associated with symptoms; Asymptomatic IDH: a fall in SBP ≥20 mmHg with no further clinical symptoms	A total 309 (13.1%) A symptomatic IDH occurred in 88 (3.7%) treatments	Symptomatic IDH occurred in 221 (9.4%) HD sessions Symptoms and interventions NS	Females had almost twice the risk of an IDH event; patients with ≥4.5 hrs of HD treatment had more than 3 times the risk of an IDH event	The high occurrence of IDH related events demonstrates that UF treatment goals are sometimes overestimated; renal nurses need more objective parameters to measure to evaluate the intravascular volume status.	

Articles in which IDH is defined as the EBPG definition, a decrease in SBP of 20 mmHg with clinical events and interventions

Author	Definition of IDH	Freq. of HD sessions with IDH	Frequency of HD sessions with symptoms and interventions	Important outcomes	Conclusion of authors	Comments
Akhmouch, 2010	EBPG definition; defined as IDH if >10 episodes of IDH occurred during the study period	18 pts met the criteria of frequent IDH occurring >500 times in 18 mhts, with an average of 9.7 IDH episodes per pt per 18 mhts (range 0-54, 5.6%); IDH occurred in 5% of all HD sessions	NS	The presence of diabetes and the duration of HD <2 yrs significantly correlated with IDH	IDH is a common complication of HD. Factors predisposing to IDH are diabetes; recent entry in HD, LVH, alteration of cardiac diastolic function, and. excessive IDWG/high UF	
Bossola, 2013	EBPG definition	Presence of IDH in 11of 68 pts (11.2%); mean nr of IDH events was 0.8±0.2 per 10 consecutive HD sessions (8%)	NS	Time on HD is associated with an increased probability of IDH. IDWG was significantly correlated with time on HD; The %IDWG correlated with IDH. IDH was not correlated with age or comorbidities	Time on HD is associated with an increased probability of IDH	
Flythe, 2014	Nadir90: Minimum intradialytic SBP >90 mmHg; Fall30nadir90: Pre-HD SBP minus minimum intradialytic SBP ≥30 mmHg and minimum intradialytic SBP >90 mmHg; KDOQI: a fall in SBP ≥20 mmHg or MAP ≥10 mm Hg associated with symptoms; HEMO: Fall in SBP resulting in intervention of UF reduction,	**HEMO cohort:** Nadir90: 11.3%, in 11.9%of pts; Fall30nadir90: 9.3%; KDOQI definition: 9.6%; HEMO: 19.1% **LDO Cohort** Nadir90: 9.7%, in10.1% of pts; Fall30nadir90: 7.5%; KDOQI and HEMO definitions of IDH could not be assessed because of the lack of symptom and	NS	An absolute intra-dialytic nadir SBP <90mmHg was most potently associated with mortality. IDH defined by SPB fall with symptoms and interventions was not significantly associated with mortality	Additional studies are needed to confirm findings, and prospective studies using consistent IDH definitions are needed to effectively evaluate IDH treatment and preventive strategies	The main study question was the association between mortality and IDH. Absolute BP data are not mentioned, only the degree of decrease Not all definitions described in the study are shown. The definitions most commonly used in studies included in this review are used

	blood flow reduction, or saline administration; Pts fulfilled the definiton if the nr of HD sessions meeting the specified IDH definition occurred in at least 30% of HD sessions	intervention data in this cohort				
Kuipers, 2016	EBPG guideline; Additional analyses were performed using SBP drop ≥30 mmHg and SBP drop ≥40 mmHg; Comparison of patients with and those without IDH in >20% of HD sessions according to the EBPG definition	Full EBPG definition: 6.7% of HD sessions Ten pts (8.1%) fulfilled the EBPG definition in >20% of HD sessions; Decrease in SBP ≥20 mmHg: 63.8%; Decrease in MAP ≥10 mmHg: 71.2%; Decrease in SBP ≥30 mmHg: 43.5%; Decrease in SBP ≥40 mmHg: 27.4%	The following symptoms occurred in 817 HD sessions (21.1%): Cramps: 337 (8.8%); Dizziness: 187 (4.9%); Nausea:101 (2.6%); Vomiting: 18 (0.5%); fatigue: 131 (3.4%); loss of consciousness: 20 (0.5%); miscellaneous: 233 (6.1%); Interventions occurred in 326 HD sessions (8.5%)	Pts with IDH had significant higher pre-HD SPB and a greater decline in SPB; pre-HD heart rate was significantly lower in patients with IDH; variables associated with IDH: female sex, lower body weight, smaller height, absence of residual renal function, higher UF, lower plasma albumin	Prevalence of dialysis hypotension according to the full EBPG definition is low. The dominant determinant of the full EBPG definition was nursing intervention	
Ogochukwu, 2017	SBP drop >20 mmHg anytime during a HD sessions associated with clinical features and nursing intervention	IDH occurred in 8.6% of HD sessions; 45.7% of pts experienced a drop of >20mmHg	8.6% had symptoms and 28.5% of patients required nursing interventions	There was no statistical difference between male and female patients; risk of IDH was increased in pts with obstructive nephropathy and in acute pts with sepsis; IDH was less common amongst pts with pre HD systolic hypotension	IDH was common among the pts studied; The absence of a reliable tool for assessing dry weight may contribute to the high rate of IDH	Not all information available; no IDWG because of missing/incomplete pts records; no treatment protocol mentioned; Inclusion of patients who were dialyzed because of acute renal failure and many patients did not undergo HD beyond 1-3 mths
Rocha, 2015/2016	EBPG definition	30.7% of all HD treatments, and 93% of all pts; 76.7% of pts had ≤7 episodes of IDH during the studied 18 HD sessions with the highest prevalence on the first day of the week (38.4%)	NS	Pts with frequent IDH had a lower dry weight; a higher phosphorus level; and a greater prevalence of diabetes and hypertension The risk of IDH was not related with UF or IDWG	Dry weight, hypertension, and phosphorus are modifiable risk factors to possibly reduce the rate of IDH episodes Decreased risk of hypotensive events in a thrice weekly HD regimen from the first to the second and third HD of the week;	Additional information is added of another article from the same author, in which the same data was used for comparison of the first, second and third HD session of the week

Stefánsson, 2014	KDOQI, ≥20 mmHg fall in SBP from pre-dialysis to nadir intradialytic levels plus ≥2 responsive measures (interventions); Pts having at least 1 HD session with IDH within the study period of 90 days	31.1% of pts experienced IDH at least once; frequency (in % of HD treatments): in >0 to ≤5% of HD sessions: 6096 pts (15.4%); in >5 to ≤10% of HD sessions: 3789 pts (9.6%); in >10% of HD sessions: 2400 pts (6.1%)	NS	Pts with IDH were younger, less frequently of female sex, less frequently white; pts with IDH had more frequently diabetes and greater IDWG	A greater IDWG was associated with a greater risk of IDH. IDH was potently associated with CV morbidity and mortality	HD treatment details are not specified.
Steinwandel, 2018	Symptomatic IDH: KDOQI: a fall in SBP ≥20 mmHg associated with symptoms; Asymptomatic IDH: a fall in SBP ≥20 mmHg with no further clinical symptoms	A total 309 (13.1%) A symptomatic IDH occurred in 88 (3.7%) treatments	Symptomatic IDH occurred in 221 (9.4%) HD sessions Symptoms and interventions NS	Females had almost twice the risk of an IDH event; patients with ≥4.5 hrs of HD treatment had more than 3 times the risk of an IDH event	The high occurrence of IDH related events demonstrates that UF treatment goals are sometimes overestimated; renal nurses need more objective parameters to measure to evaluate the intravascular volume status.	
Takeda, 2006	A drop of ≥20 mmHg in SPB during HD to <100 mmHg, accompanied by typical symptoms and requiring a medical intervention; Hypotension-prone pts were defined as those in whom IDH occurred in at least one third of HD sessions	IDH occurred in 16 subjects defined as hypotension prone (14.4%) of participants	NS	Hypotension-prone pts more frequently had diabetes; had higher IDWG and higher serum cholesterol, and worse left ventricular function; there was no association between pre-HD SPB and IDH	Diabetes; excessive IDWG; worse left ventricular function were independent risk factors for IDH	Intervention trial for antihypertensive medication; Pts characteristics dived into 2 groups (hypotension-prone versus hypotension-resistant)
Yu, 2018	KDOQI: a fall in SBP ≥20 mmHg or MAP ≥10 mm Hg associated with clinical events and need for interventions; ; Hypotension-prone pts were defined as those who had ≥4 hypotensive events/3mths	IDH occurred in 117 patients (39.9%)	NS	Risk factors for IDH older age, high BMI, high UF rate, lower pre-HD BP, lower post-HD BP, longer time on HD, female gender, no residual function and DM	IDH is independent risk factor for long term mortality in HD patients	The main study question was the association between mortality and IDH. Exclusion of patients with acute heart failure and cardiac dysfunction

Articles in which IDH is defined as nadir SBP 90 mmHg

Author	Definition of IDH	Freq. of HD sessions with IDH	Freq. of HD sessions with symptoms and interventions	Important outcomes	Conclusion of authors	Comments
Cho, 2017	A nadir SBP <90 mmHg or requirement for bolus fluid administration; For IDH diagnosis >2 episode in 10 HD sessions was required	IDH occurred in 32 subjects (16.8%), IDH occurred in 6.7% of HD sessions	NS	Nr of hypotensive episodes was linearly associated with vascular calcification; IDH caused frequent ischemic episodes in the heart and arteries	Both IDH and abdominal aortic calcifications score were significant predictors for cardiovascular events	The focus of this study was on the relationship between IDH and aortic calcification
Chou, 2017	IDH was defined as nadir SBP <90 mmHg; The relative frequency of IDH was defined as the proportion of HD sessions in which the pts nadir intra-HD BP was <90 mmHg; The relative frequency of IDH was divided into six categories (in %): 0-5, >5-10, >10-20, >20-40, >40% of HD sessions	The average fall in SBP (difference between pre-HD and nadir SBP) was 30±13 mmHg; A total of 72, 983 patients (65%) had at least one IDH episode during the study period of 91 days; The average relative frequency of IDH was 4% of HD sessions	NS	There was a U-shaped association between nadir intradialytic SBP and all-cause mortality and a direct linear relationship between the frequency of IDH and mortality	Intradialytic BP behavior has prognostic impact	The focus of this study is on the association of intradialytic BP and all-cause mortality
Flythe, 2014	Nadir90: Minimum intradialytic SBP >90 mmHg; Fall30nadir90: Pre-HD SBP minus minimum intradialytic SBP ≥30 mmHg and minimum intradialytic SBP >90 mmHg; KDOQI: a fall in SBP ≥20 mmHg or MAP ≥10 mm Hg associated with symptoms; HEMO: Fall in SBP resulting in intervention of UF reduction, blood flow reduction, or saline administration; Pts fulfilled the definiton if the nr of HD sessions meeting the specified IDH definition occurred in at least 30% of HD sessions	**HEMO cohort:** Nadir90: 11.3%, in 11.9%of pts; Fall30nadir90: 9.3%; KDOQI definition: 9.6%; HEMO: 19.1% **LDO cohort:** Nadir90: 9.7%, in10.1% of pts; Fall30nadir90: 7.5%; KDOQI and HEMO definitions of IDH could not be assessed because of the lack of symptom and intervention data in this cohort	NS	An absolute intradialytic nadir SBP <90mmHg was most potently associated with mortality. IDH defined by SPB fall with symptoms and interventions was not significantly associated with mortality	Additional studies are needed to confirm findings, and prospective studies using consistent IDH definitions are needed to effectively evaluate IDH treatment and preventive strategies	The main study question was the association between mortality and IDH. Absolute BP data are not mentioned, only the degree of decrease Not all definitions described in the study are shown. The definitions most commonly used in studies included in this review are used

Orofino, 1990	Fall of SBP to ≤90 mmHg or decrease in SBP of at least 25% in pts with a baseline SBP of 90-100 mmHg	15.3% of HD sessions were complicated by IDH; D-temp 37°C group: 44.2% of pts with >30% IDH; D-temp 35 °C group: 34.1% of pts had IDH in >30% of HD sessions	Symptoms occurred in 15% of HD sessions; cramps in 9.6%, vomiting in 1.8%, headache in 1.1%, other symptoms in 1.6%	IDH occurred more frequently in females, in pts aged >55 yrs, pts with body surface area <1.6m², pts with CV disease and in patients with SBP <135 mmHg at the start of HD	HD with low D-temp is not the panacea for IDH, but a simple and economic procedure, particularly beneficial to pts with many symptoms	Comparison between pt groups with high and low D-temp, pts with DM were not included; Use of acetate dialysis
Sands, 2014	An intradialytic decrease in SBP >30 mmHg to a level <90 mmHg; Multiple episodes of IDH during the same HD treatment were considered as one IDH episode and the HD session was considered to have had one IDH event (this event is not further described)	IDH occurred in 17.2% of all HD sessions; 75.1 % of pts had one or more episodes of IDH; 25.1% had no IDH episodes; in 58.8% of pts IDH occurred in 1-35% of HD sessions; in 16.2% of pts IDH occurred in >35% of HD sessions	NS	Increased risk of IDH was associated with age, female sex, diabetes, time on HD, high BMI, high UF, lower pre-HD SPB, higher D-temp and a greater difference between prescribed and achieved post HD weight; risk of IDH was lower on the first dialysis day of the week	IDH is common and highly variable between pts and facilities; mortality rate, hospital admission and nr of hospital days were higher in pts with a higher frequency of IDH	
Straver, 1999	A decrease in supine SBP of ≥30 mmHg or an absolute SBP of <90 mmHg	In 24 of 68 pts (35.3%) a symptomatic hypotensive episode occurred requiring interruption of UF and infusion of isotonic saline	NS	Failure to increase the vascular systemic resistance is the most prominent cause of IDH; the UF- induced decrease in blood volume lowers BP, but the degree of hypo-volemia seems not to play a key role in the origin of acute IDH	IDH seems the consequence of an inadequate compensatory response to UF-induced blood volume reduction, resulting in a fall in systemic vascular resistance	

Articles in which IDH is defined using multiple cut off values

Author	Definition of IDH	Freq. of HD sessions with IDH	Freq. of HD sessions with symptoms and interventions	Important outcomes	Conclusion of authors	Comments
Agrawal, 2012	Any recorded intra-dialytic SBP that was >20 mmHg below baseline BP; during HD session <90/60 mmHg with or without symptoms	IDH occurred in 66 (4.5%) of HD sessions; it affected around 45% of pts	12 HD sessions with muscle cramps (0.8%), 20 with nausea/ vomiting (1.2%), 13 with chills and rigors (0.8%) Interventions: NS	Low incidence of complications during HD, possibly due to small sample size	Complications do occur, but are not very common and not severe of nature. HD is a safe and tolerable procedure in pts	Pts in this study had 2 HD sessions a week and, consequently, a relatively high UF-rate; not all complications are relevant for IDH (ascites, anemia, blood transfusion)
Awan, 2011	A decrease in SBP of ≥20 mmHg, associated with symptoms; if pre-HD SBP was <100 mmHg: a fall of ≥10 mmHg of SBP with symptoms; If pre-HD SBP was >100mHg: a fall of ≥30 mmHg of SBP with symptoms	103 HD sessions, (5.4%) were complicated by IDH	NS	Females developed IDH more frequently than men. IDWG and UF rate were significantly higher in the IDH group	Females developed IDH more frequently than men	Inclusion from age 10; No details on the HD prescription; max 2 HD sessions a week
Collins, 1993	SBP ≤100mmHg, or a reduction in SBP by 40% of the pre-dialysis value; if a pt was hypotensive at ≥4 BP determinations during a single HD session only a maximum of 4 episodes of hypotension were recorded.	Nr of events per pt: 41±3; if we assume that every patient underwent 72 HD sessions during the study period, the average percentage of pts with IDH was 57%	Saline administration in 21 HD sessions (29.2 %); vomiting in 10 HD sessions (13.9 %); cramping in 9 HD sessions (12.5 %); headache in 54 HD sessions (75.0 %)	Mean pre-HD BP and IDWG were not significant different between membrane types; There was no significant difference in IDH and events between the two groups	The use of synthetic non cellulosic membranes does not provide any advantage over the use of cuprophane dialyzers in reducing acute complications of HD	The main focus of this article is the comparison of 2 different dialyzer membranes
Levin, 2018	A decrease in SBP of ≥20 mmHg or a MAP reduction ≥10 mmHg and intradialytic nadir SBP to < 100 mmHg or MAP < 70 mmHg Pts with at least one IDH episode in 30% of HD sessions were defined as having IDH	IDH occurred in 23.2% of all HD sessions; 26% of pts had one or more episodes of IDH	NS	Hemodynamic variables did not significantly differ between the IDH and the non-IDH patients	The similarity in pretreatment hemodynamics in the IDH and non-IDH group increases the value of intradialytic characterization of IDH mechanism for appropriate interventions	The primary objective of this article was to report changes of cardiac output, peripheral resistance and cardiac power during incidents of IDH
Meredith, 2015	The HD sessions were divided in 3 categories according to the post-dialysis symptom questionnaire: asymptomatic group, symptomatic group and an intervention group; commonly cited descriptors of IDH were defined: 1.The nadir record value 2.Baseline BP minus nadir BP 3. Baseline BP minus nadir BP in %	A nadir SBP <100 mmHg is the threshold with greatest discrimination between the asymptomatic and the intervention group (35 vs 64% respectively	HD sessions with: nausea 22.1% (not related to BP definition); dizziness 12.3% (associated with nadir BP); cramp 7.5%	The SPB appears to be most strongly associated with dizziness and cramps; the odds of an intervention increased significantly for every 10 mmHg increment in nadir SBP; it is probable that the results underestimate the true incidence of asymptomatic IDH	The authors suggest that a reduction in SBP >20% from baseline to <100 mmHg is used to define those at risk for IDH regardless of symptoms	No details on HD prescription; baseline BP was measured immediately following bleed-out into extracorporeal circuit; no absolute nrs; complex definitions of IDH; Not all definitions described in the study are shown

Articles in which there is no detailed information on the type of definition that was used for IDH:

Author	Definition of IDH	Freq. of HD sessions with IDH	Frequency of HD sessions with symptoms and interventions	Important outcomes	Conclusion of authors	Comments
Al-Hilali, 2004	A decrease in BP necessitating IV administration of 200ml saline	In 29 (72.5%) pts hypotension was reported before the start of profiled HD	Occurrence of symptoms before start of profiled HD: Dizziness: 22 pts (55%); muscle cramps: 9 pts (22.5%); Headache: 15 pts (37.5%)	The symptoms of IDH significantly improved after 2, 4 and 6 weeks of profiled HD	Dialysate sodium and UF profiling are effective techniques to reduce the adverse effects of HD	Treatment details are not described; Hypotension definition is not specified as a minimum fall in mmHg; only the nrs from before start of profiled HD are of interest for this review
Caplin, 2011	No definition mentioned	Presence of IDH in 76.4% of pts	Occurrence of symptoms: fatigue 411pts (81%); cramps 377 pts (74.3%); dizziness 320 pts (63%); headache 272 pts (53.6%) pruritus 265 pts (52.2%); backache 259 pts (51%); nausea 175 pts (34.5%) dyspnea 165 pts (32.5%); palpitations 136 pts (26.8%); chest pain 126 pts (24.8%); vomiting 117 pts (23.1%)	Fewest symptoms were reported from pts dialyzing in centers with most frequent medical contact; significant difference between centers suggesting that there may be modifiable factors. Symptom burden was associated with delayed recovery	Many pts report symptoms during HD and it takes time to recover; Symptom burden was worse in women, South-Asian people and pts with longer duration of HD	No IDH definition mentioned; the study aimed to investigate the symptoms of HD and not the frequency of IDH; Information on BP is lacking; use of a very high blood flow (800 ml/min)
Davenport, 2008	A sudden decrease in BP that required intravenous fluid replacement	IDH occurred in5.5% of HD sessions; in 16.6% of pts;14.9% of pts in non-DM group (229 HD sessions) and in 20.3% of pts in DM group (134 HD sessions). BP and IDWG were higher in DM pts	NS	IDH occurred more frequently in pts with DM than in non-DM pts; pts with DM were more frequent from ethnic minorities and were prescribed CV medication more often; the average SBP was higher in pts with DM and these pts tended to be heavier and had a higher absolute IDWG;	To reduce the risk of CV and cerebrovascular disease in HD pts with DM, a greater emphasis has to be placed on both BP control and reducing IDWG	Comparison of pts with DM and non-DM pts

Degoulet, 1981	For each individual pt the percentage of HD sessions during which IDH occurred was recorded	Overall prevalence (the mean of the individual prevalence of IDH was 20.7% for patients on twice weekly and thrice weekly combined; 115 pts (10.4%) had IDH in ≥50%of HD sessions	NS	pts with DM had a higher prevalence of IDH than non-DM pts; IDH was higher in females (25.7%) than in males (16.5%); IDH was lower in pts on a thrice weekly schedule compared with pts on a twice weekly schedule	An increase in the number of weekly HD sessions from 2 to 3 seemed to facilitate BP control and to reduce IDH prevalence and could probably reduce CV morbidity	Minimal age of 15 yrs; IDH definition is not specified; older study, only the information of the thrice weekly pts can be used
Sangala, 2017	An acute symptomatic fall in BP during dialysis requiring immediate intervention to prevent syncope	IDH occurred in 438 (4.8%) of HD sessions; 38% of pat experienced at least 1 episode of symptomatic IDH	NS	Symptomatic pts had significantly lower pre-HD SBP and a significantly higher delta SBP; pts using either a single or no anti-hypertensive drug had a significantly lower pre-HD SBP and significantly higher delta SBP than those on ≥two anti- hypertensive drugs	Pre-HD SBP and delta SBP can be used to accurately identify pts most at risk of IDH independently of traditional risk factors such as age and comorbidities	

Abbreviations: Bicarbonate HD: hemodialysis with bicarbonate-containing dialysate; BP: blood pressure; CV: cardiovascular; DM: diabetes mellitus; D-temp: dialysate temperature; DBP: diastolic blood pressure; EBPG: European Best Practice Guideline on hemodynamic instability; HD: hemodialysis; Hrs: hours; IDH: intradialytic hypotension; IDWG: interdialytic weight gain; KDOQI Kidney Disease Outcomes Quality Initiative; Mth: month; Mths: months; Nr: number; Nrs: numbers; NS: not specified; Pt: patient; Pts: patients; SBP: systolic blood pressure; UF: ultrafiltration volume; Y: yes; Yrs.: years.

Supplementary table 4A.
Influence analysis of prevalence of intradialytic hypotension defined according to the EBPG definition on session level (random effects model).

	Proportion	95% confidence interval
Omitting Akhmouch, 2010	12.0	6.9-20.2
Omitting Flythe Hemocohort, 2014	10.3	4.7-21.2
Omitting Kuipers, 2016	11.2	6.0-20.0
Omitting Rocha, 2015	7.4	5.2-10.4
Omitting Steinwandel, 2018	10.3	0.06-0.19
Pooled estimate (without omitting studies)	0.10	5.5-18.6

Supplementary table 4B.
Influence analysis of prevalence of intradialytic hypotension defined according to the SPB nadir <90 mmHg definition on session level (random effects model).

	Proportion	95% confidence interval
Omitting Cho, 2017	0.12	0.12-0.12
Omitting Flythe Hemocohort, 2014	0.12	0.12-0.12
Omitting Flythe/ LDO, 2014	0.16	0.16-0.16
Omitting Orofino, 1990	0.13	0.12-0.12
Omitting Sands, 2014	0.10	0.10-0.10
Pooled estimate (without omitting studies)	0.12	0.12-0.12

Supplementary file 5.

Reported symptoms and interventions.

Author	Questionnaire yes/no	Cramps	Nausea	Vomiting	Dizziness	Headache	Total symptoms	Interventions
Orofino, 1990	no	9.6		1.8		1.1	15	
Collins, 1993	no	12.5		13.9		75		29.2
Al Hilali, 2004	yes	22.5			55	37.5		
Caplin, 2011	yes	74.3	34.5	23.1	63	53.6		
Agrawal, 2012	no	0.8	1.2					
Meredith, 2015	yes	7.5	22.1		12.3			
Kuipers, 2016	yes	8.8	2.6	0.5	4.9		21.1	8.5
Ogochuckwu, 2017	no						8.6	28.5

Values are given as percentages.

Supplementary file 6.
Hemodynamic data.

Author	Dry weight (kg)	IDWG (l)	UF (l)	UF rate (ml/h/kg)	Pre-dialysis SBP (mmHg)	Post-dialysis SBP (mmHg)	Pre-dialysis DBP (mmHg)	Post-dialysis DBP (mmHG)
Agrawal, 2012		4,5						
Akhmouch, 2010	63.8	2.7±1.0	1.9	498 ml/h	134	122	67	63
Awan, 2011		2.2±0.8	1.7±8.2	807±501 ml/h		117±30*		62±16*
Bossola, 2013		3.9%**			128±14			
Caplin, 2011	70.8±16.7		1.8 (1.2-2.4)					
Cho, 2017			2.80±0.9		149±27		76±13	
Chou, 2017	82±23		2.0±0.9		147±19	144±18		
Collins, 1993		3.0±0.2			155±4		84±2	
Davenport, 2008	71.7±17.1	2.3±1.2			148±24	135±25	78±13	72±13
Kuipers, 2016	73.5±16.3		2.4±8.3	8.5±3.3 ml/kg/h	146±27.0	120±27	72±15	63
Lai, 2012	57.3 (SEM 1.8)				145 (SEM 2.5)		78 (SEM 1.5)	
Levin, 2018	74.0±17.0			662 ml/h (601-72395%CI)	139 (133-144 95%CI)			
Meredith, 2015			2.3±0.13		140±3	106±3*	80±2	59±2*
Sands, 2014					145±20			
Sangala, 2017			1.7	5.95 ml/kg/h	143			
Stefánsson, 2014		4.3±2.3			149	141	78	74
Straver, 1999	65.9 (SEM 2.8)		2.9 (SEM 0.2)					
Takeda, 2006					156±16		83±9	
Yu, 2018	58.9±10.9			9.1±4.4	136±17	116±38	83±11	73±23

Abbreviations: IDWG: interdialytic weight gain; UF: ultrafiltration volume; SBP: systolic blood pressure; DBP: diastolic blood pressure; SEM: standard error of the mean.
Note: Flythe et al provided information on hemodynamic data per tertiles and did not report mean (or median) values.
*lowest blood pressure.
**expressed as percentage of dry weight.

Chapter 6

Association between Quality of Life and various aspects of intradialytic hypotension including patient-reported intradialytic symptom score

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ABSTRACT

Background: There is increasing awareness that, besides patient survival, Quality of Life (QOL) is a relevant outcome factor for patients who have a chronic disease. In haemodialysis (HD) patients, intradialytic hypotension (IDH) is considered one of the most frequent complications, and this is often accompanied by symptoms. Several studies have investigated QOL in dialysis patients, however, research on the association between intradialytic symptoms and QOL is minimal. The goal of this study was to determine whether the occurrence of IDH has an influence on the perception of QOL.

Methods: During three months, haemodynamic data, clinical events, and interventions of 2623 HD-sessions from 82 patients were prospectively collected. The patients filled out a patient-reported intradialytic symptom score (PRISS) after each HD session. IDH was defined according to the EBPG as a decrease in SBP ≥20 mmHg or in MAP ≥10 mmHg associated with a clinical event and need for nursing interventions. Patient's self-assessment of QOL was evaluated by the 36-Item Short-Form Health Survey. **Results:** There were no significant associations between the mental summary score or the physical summary score and the proportion of dialysis sessions that fulfilled the full EBPG definition. A lower PRISS was significantly associated with the proportion of dialysis sessions that fulfilled the full EBPG definition (R= -0.35, P=0.0011), the proportion of dialysis sessions with a clinical event (R= -0.64, P=0.001), and the proportion of dialysis sessions with nursing interventions (R= -0.41, P=0.0001). The physical component summary and mental component summary were significantly negatively associated with the variable diabetes and positively with PRISS (P=0.003 and P=0.005, respectively). UF volume was significantly negatively associated with mental health (P=0.02) and general health (P=0.01).

Conclusion: Our findings suggest that the EBPG definition of IDH does not capture aspects of intradialytic symptomatology that are relevant for the patient's QOL. In contrast, we found a significant association between QOL and a simple patient-reported intra-dialytic symptom score, implying that how patients experience HD treatment influences their QOL.

BACKGROUND

In the past ten to 15 years, there has been an increasing awareness that patient survival is not necessarily the main relevant outcome factor for patients with a chronic disease. Patient reported outcomes and Quality of Life (QOL) receive, with good reason, increasing attention in research regarding patients with chronic diseases, such as patients with end stage renal disease who depend on dialysis[1-2]. To assess QOL, the RAND SF-36 (SF-36) has been proven to be beneficial for comparing general and specific populations, estimating the relative burden of different diseases, assessing the health benefits produced by a wide range of different treatments, and screening individual patients[3].

Intradialytic hypotension (IDH) is a serious and frequent complication of haemodialysis (HD) treatment[4-5]. It is often accompanied by symptoms such as nausea, dizziness, light-headedness, fatigue, and muscle cramps which affect the daily lives of HD patients[6] and, consequently, likely influence QOL. Pathophysiology of intradialytic hypotension and the methods to avoid this complication have been extensively investigated[7-8]. Also, the association between IDH and mortality has been studied by several groups[7-8], Flythe *et.al.* showed that an absolute nadir systolic blood pressure (SBP) <90 mmHg was most potently associated with mortality[8]. In contrast, research on the association between intradialytic symptoms and QOL is minimal. Caplin *et.al.* studied the burden and duration of HD-associated symptoms with a survey but did not study the association between symptoms and QOL[6].

To support patients in effectively improving QOL, more knowledge is needed on the association between QOL and HD treatment-related factors like IDH. Furthermore, there is a need to identify aspects of IDH that have a (strong) effect on QOL. The goal of this study, therefore, was to determine whether the occurrence of IDH has an influence on the perception of QOL in HD patients. We studied this in a well-characterized patient group of 82 patients on maintenance HD over a period of three months comprising a total of 2623 HD-sessions. The focus of the study was on the association of QOL with the full definition of IDH according to the European Best Practice Guideline (EBPG) on haemodynamic instability as well as with its three components, i.e., a decrease in SBP of >20 mmHg, the occurrence of clinical events, and nursing interventions[9]. To gain better insight into how the patients experienced the overall HD treatment, we additionally employed a simple patient-reported intradialytic symptom score (PRISS) that was filled out by the patients after each dialysis session.

SUBJECTS AND METHODS

Patients

This is a post-hoc analysis of a previous study on the prevalence of dialysis hypotension[10]. This multicenter prospective observational study included adult (≥18 years) patients from the Dialysis Center Groningen and the dialysis unit of the University Medical Center Groningen. Patients were eligible for the study when they satisfied the following criteria: maintenance bicarbonate HD for more than three months, three times per week, 3 ½ -4 ½ hours HD schedule. The study was performed in accordance with the principles of the Declaration of Helsinki.

Study protocol

The design an methods of this study haven been previously reported[10]. In brief we prospectively collected the haemodynamic data of all of the HD sessions from participating patients during the three months of February, March, and April. At each session, patients were evaluated for hemodynamic parameters and the occurrence of clinical events possibly related to dialysis hypotension, and nursing interventions. All data were registered on a run sheet and stored electronically. The patients were asked to fill out a simple questionnaire after each HD session, i.e., a patient-reported intradialytic symptom score (PRISS). Patients scored how they had experienced the HD session on a 5 point Likert scale ranging from 0 ('bad HD session') to 5 ('very good HD session')[11]. Patient's self-assessment of QOL was evaluated in the third month of the study by the 36-Item Short Form Health Survey (RAND SF-36) scoring system in the Dutch version[12]. The SF-36 consists of 36 questions in eight categories: physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, social role functioning, emotional role functioning, and mental health. Among the eight categories, the four physical elements compose the physical component summary, and the emotional, mental and social functioning elements create the mental component summary.

Haemodialysis sessions during hospitalization were excluded from the analysis. Ultrafiltration rate was calculated by dividing ultrafiltration volume by dialysis session length and postdialysis body weight.

Cardiovascular history was defined as any history of ischemic heart disease, congestive heart failure, stroke, or peripheral vascular disease. Residual diuresis was defined as ≥200 ml/24 h. Equilibrated Kt/V was calculated from pre- and postdialysis plasma urea concentration according to the second-generation logarithmic Daugirdas equation[13].

Dialysis hypotension was primarily defined according to the EBPG definition[9] as a decrease in SBP ≥20 mmHg or a decrease in MAP by ≥10 mmHg associated with a clinical event and need for nursing interventions. In additional analyses, we also used a decrease

in SBP ≥30 and ≥40 mmHg as a designated limit. Patients were considered to have frequent dialysis hypotension when they fulfilled the entire EBPG definition of dialysis hypotension in ≥10% of dialysis sessions. The cut-off of 10% was arbitrarily chosen based on previous studies in which the prevalence of IDH ranged from 5 to 50% depending on the definition that was used[8-10-14-16]. Within this 5 to 50 range, we chose a relatively low cut-off of 10% since we used a strict definition of IDH.

Statistical analysis

Continuous variables with normal distributions are reported as mean ± SD, skewed data as median (interquartile range), and categorical data by number (percentage). Normality was tested with the Shapiro Wilkinson test. Comparisons of variables with a normal distribution were made with a T-test, and comparisons of variables with a skewed distribution were performed with the Mann Whitney U test or for multiple groups with the Kruskal Wallis-test.

For the analysis of pre-, intra- and postdialysis haemodynamic parameters and PRISS, the data of all available HD sessions were averaged per patient. For the analysis of the components of QOL, a multivariate repeated generalized (logistic) linear mixed effects model was estimated followed by a model building strategy based on the Akaike Information Criterion (AIC model)[17-19]. Given the collection of possible models for the data, minimum AIC best selected the model by a maximum likelihood with a correction for overfitting. The following parameters were included in the model: age, gender, dialysis vintage, BMI, diabetic status, comorbid conditions of ischemic heart disease and congestive heart failure, pre-dialysis SBP, ultrafiltration volume, intradialytic clinical events, nursing interventions, PRISS and, alternately, a decrease in SBP of 20 mmHg, 30 mmHg, or 40 mmHg. Analyses were performed with SPSS version 20.0 (SPSS inc., IBM company, USA), GraphPad Prism version 5.0 and statistical programming language R version 3.4.0 (R Core Team, 2017).

RESULTS

Patients

Of the 124 patients that participated in the original study, 82 patients filled out a QOL questionnaire. Patients who did not do so were not familiar with the Dutch language (n=10), were mentally disabled (n=4), or could not fill out a questionnaire due to intercurrent illness (n=3). The reason for not filling out a questionnaire is unknown for 25 patients. There were no significant differences in characteristics between the patients who filled out the QOL questionnaire and those who did not.

The characteristics of the 82 patients are shown in Table 1. Mean (±SD) haemoglobin and albumin levels were 7.0±0.8 mmol/l and 39.6±3.1 g/l, respectively. eKt/V was

1.39±0.26 per session. Haemodialysis access was an arteriovenous fistula or polytetrafluoroethylene (PTFE) graft in 82% of patients and a central venous catheter in 18% of patients. Cardiovascular medication was being used by 67% of the patients.

A total of 2623 HD sessions were analyzed with an average number of dialysis sessions per patient of 33 (range 14-36).

Table 1.
Patient characteristics.

Characteristic	n=82
Age, year	64.1 ± 15.6
Dialysis vintage, months	32.0 ± 28.9
Males	41 (50%)
Diabetes	18 (22%)
Body mass index (kg/m²)	25.7 ± 5.0
Residual renal function	23 (28%)
Cardiovascular history	36 (44%)
Acute myocardial infarction	5 (6.1%)
Congestive heart failure	4 (4.9%)
Peripheral vascular disease	17 (20.7%)
Cerebral vascular disease	7 (8.5%)
Primary renal disease	
Hypertension	25 (31%)
Diabetes	11 (13%)
Glomerulonephritis	5 (6%)
Obstructive uropathy	14 (17%)
ADPKD	7 (9%)
IgA nephropathy	4 (5%)
Alports' disease	1 (1%)
Other diagnoses	5 (6%)
Unknown	10 (12%)
Cardiovascular medication	
Beta-blocker	48 (59%)
CCB	21 (26%)
ACE-I/ ARB	16 (20%)

Note: continuous variables are presented as mean ± standard deviation.
Abbreviations: ADPKD: autosomal dominant polycystic kidney disease; CCB: calcium channel blocker; ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Weight, ultrafiltration volume, blood pressure, and heart rate

The average pre- and postdialysis body weight was 75.8±15.4 kg and 73.9±15.4 kg, respectively. The average ultrafiltration volume and ultrafiltration rate in all 2623 dialysis sessions was 2457±828 ml and 8.3±3.1 ml/kg/hour, respectively.

Blood pressure decreased, on average, from 145±26 / 72±15 mmHg predialysis to 130±25 / 67±14 mmHg at the end of the HD session. The average MAP decreased from 96±16 mmHg predialysis to 88±17 mmHg postdialysis. Heart rate rose, on average, from 75±11 mmHg predialysis to 76±14 bpm at the end of the HD sessions. The combination of a decrease in SBP of ≥20 mmHg or MAP ≥10 mmHg with a clinical event and nursing intervention (full EBPG definition) occurred in 6.7% of the HD sessions.

Association of patient characteristics and intradialytic hypotension variables with QOL

For the QOL component physical functioning, younger patients had a significantly higher score (P=0.003), and patients with a longer dialysis vintage had a considerably lower score (P=0.002) (Supplementary file 1). Patients with diabetes scored notably higher on the QOL component pain (P=0.04) (Supplementary file 1).

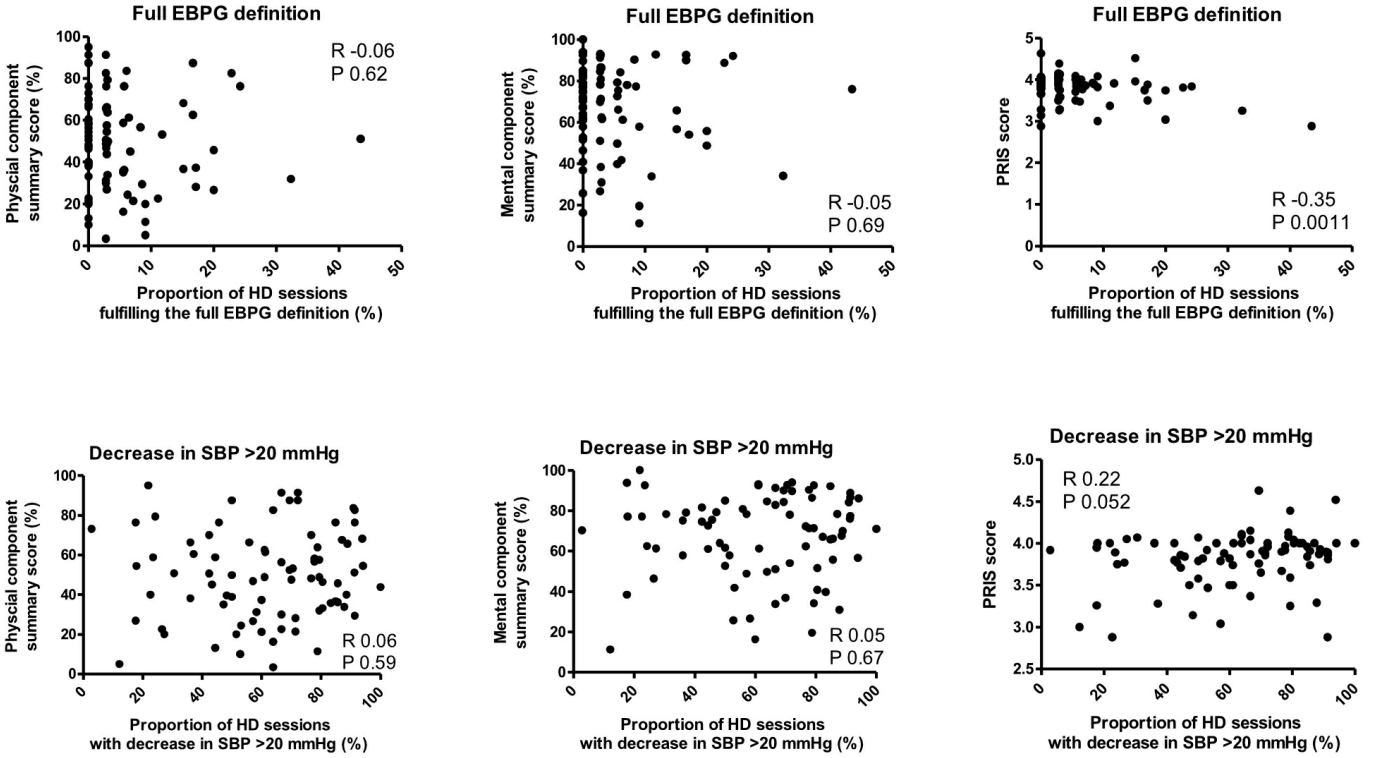
There were no significant associations between the mental summary score or the physical summary score and the proportion of dialysis sessions that fulfilled the full EBPG definition nor with the proportions of dialysis sessions that fulfilled one of the components of the EBPG definition (decrease in SBP of >20 mmHg, clinical event, nursing interventions) (Figure 1).

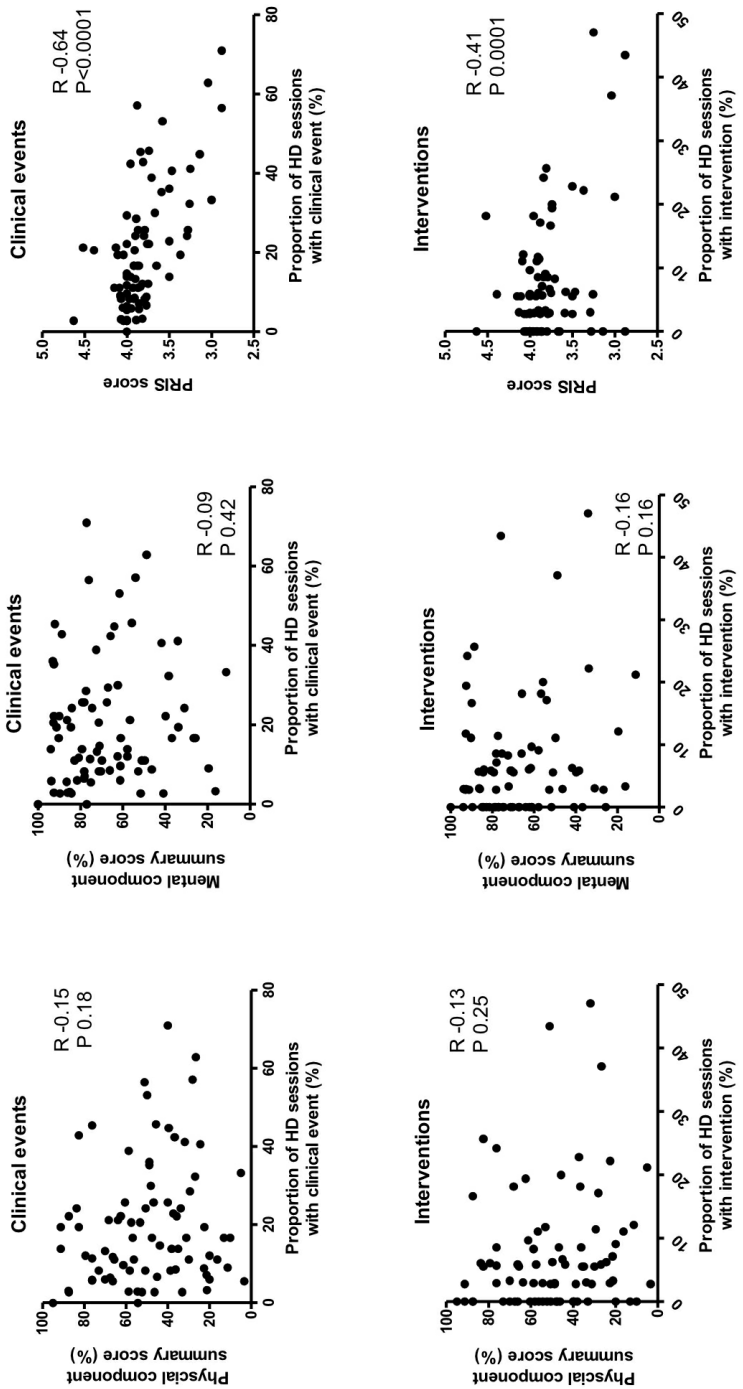
Intradialytic hypotension variables and PRISS

There was no significant association between the PRISS and the proportion of dialysis sessions in which a decrease in SBP of >20 mmHg occurred. A lower PRISS was significantly associated with the proportion of dialysis sessions that fulfilled the full EBPG definition (R= -0.35, P= 0.0011), the proportion of dialysis sessions with a clinical event (R= -0.64, P= 0.001), and the proportion of dialysis sessions with nursing interventions (R= -0.41, P= 0.0001) (Figure 1).

A lower PRISS score was significantly associated with a lower score for the QOL components general health (P=0.02), health change (P=0.03), and the physical summary score (P=0.02).

Figure 1.
Scatterplots with correlations between the full EBPG definition (upper panel) and the EGBG components decrease in SBP ≥20 mmHg (second panel), clinical events (third panel) and nursing interventions (lowest).




Clinical events
R -0.64
P<0.0001
PRIS score
Proportion of HD sessions with clinical event (%)
Interventions
R -0.41
P 0.0001
PRIS score
Proportion of HD sessions with intervention (%)
Clinical events
R -0.09
P 0.42
Mental component summary score (%)
Proportion of HD sessions with clinical event (%)
Interventions
R -0.16
P 0.16
Mental component summary score (%)
Proportion of HD sessions with intervention (%)
Clinical events
R -0.15
P 0.18
Physcial component summary score (%)
Proportion of HD sessions with clinical event (%)
Interventions
R -0.13
P 0.25
Physcial component summary score (%)
Proportion of HD sessions with intervention (%)

Multivariable analyses

In the multivariate linear regression model with optimizing AIC, the outcome variables of physical component summary and mental component summary were significantly negatively associated with the variable diabetes and positively with PRISS (P=0.003 and P=0.005, respectively) (Table 2). The response variable physical functioning was significantly negatively associated with age (P=0.00), dialysis vintage (P=0.04) and PRISS (P=0.004), and also negatively but not significantly with BMI (P=0.10). BMI was significantly negatively associated with the response variable social functioning (P= 0.05). The response variable emotional role functioning was negatively but not significantly associated with nursing interventions (P=0.08) and total UF volume (P=0.15) and significantly positively associated with clinical events (P=0.005) and with PRISS (P=0.01) (Supplementary file 2). UF volume was also negatively but not significantly associated with QOL components social functioning (P=0.16), physical role functioning (P=0.14), and emotional role functioning (P=0.15) and significantly negatively associated with mental health (P=0.02) and general health (P=0.01). These analyses included a decrease in SBP of ≥20 mmHg as a correcting explanatory variable. Analyses with pre-dialysis SBP, a decrease in SBP of ≥30 mmHg and ≥40 mmHg showed identical results.

Table 2.

Multivariate linear regression analysis with model building strategy Akaike Information Criterion (AIC); factors associated with Quality of life Summary scores.

		Gender	Age	Dialysis vintage	BMI	Diabetes	CV comorbidity	Decrease in SBP >20 mmHg (%)	Clinical events (%)	Interventions (%)	Total UF	PRISS	Adjusted R
Physical Component summary	Estimate					-12.00						23.02	
	95% CI					-23.69 to-0.31						7.89 to 38.14	
	SE					5.87						7.60	
	P					0.04*						0.003*	0.10
Mental component summary	Estimate					-9.36			0.30		0.01	27.91	
	95% CI					-20.88 to 2.16			-0.09 to 0.68		-0.01 to 0.00	8.80 to 47.03	
	SE					5.78			0.19		0.003	9.59	
	P					0.11			0.13		0.06	0.005*	0.10

Est= Estimate, SE= Standard Error, T= T-value, P= P-value, CI= Confidence Interval, U =Upper bound, L= Lower bound, * =significant, UF =Ultrafiltration volume, CV = Cardiovascular, R = the variance of the QOL variables explained by the explanatory variables (in %).

DISCUSSION

The main finding of this study is that there is no association between QOL and IDH as defined according to the EBPG guideline. This is factual for the standard EBPG definition as well as when a decrease in SBP of ≥30 or ≥40 mmHg is chosen as the blood pressure decline component instead of a decrease in SBP ≥20 mmHg or a decrease in MAP ≥10 mmHg. These findings suggest that the EBPG definition of IDH does not capture aspects of intradialytic symptomatology that are relevant for QOL. In contrast, we found a significant association between QOL and a simple patient-reported intradialytic symptom score, i.e., the PRISS, indicating that the way patients experience HD treatment indeed influences QOL.

The association between age and dialysis vintage with the physical functioning component of the QOL was expected and is explained by deteriorating physical function as patients become older and are on the HD treatment for a longer period of time[10-20]. BMI was significantly negatively associated with social functioning. Although HD patients with a higher BMI have been reported to have better survival, a higher BMI may be associated with a lower QOL in this population[21]. The association between diabetes and the QOL components, emotional functioning, and pain are also in accordance with previous studies and are explained by a higher prevalence of cardiovascular complication and diabetic complications such as neuropathy[22-23].

Our analyses show the association between QOL and UF-volume, clinical events, and nursing interventions which are parameters that are directly or indirectly related to fluid restriction. For some patients, this is very difficult to maintain, and this may cause stress and anxiety.

A complicating factor in the analysis of IDH is that many different definitions of hypotension are in use in the literature[10]. These vary from liberal definitions that only require a minimum decrease (e.g., 20 or 30 mmHg) in SBP[24-26] to strict definitions that require the combination of a clinical event and a nursing intervention in addition to a minimum fall in blood pressure[9-16-27]. In this study, there was no association encountered between a decrease in SBP of either ≥20, ≥30, or ≥40 mmHg and QOL. This finding suggests that a reduction in SBP does not have a major impact on QOL in HD patients. In our previous article we described that various factors such as stress due to transportation to the dialysis unit and anxiety for puncture of the fistula may affect pre-dialysis blood pressure. When predialysis blood pressure is used as the reference point, part of the early intradialytic fall in blood pressure may be explained by the relief of stress/ anxiety, e.g., after successful puncture of the fistula, and not by dialysis-specific haemodynamic stress[10].

Presently, there is no general consensus regarding the best evidence-based indicators of IDH. We agree with, e.g., Assismon et al, that the lack of such indicators has

hindered the data synthesis and the development of evidence-based guidelines for the prevention and treatment of IDH as well as prevented an accurate estimation of the population burden of IDH and patient risk assessment[28].

An absolute nadir intradialytic BP of SPB <90 mmHg was previously found to be associated with an increased mortality risk; however, intradialytic symptoms and interventions were not associated with this risk[8]. An important question is whether mortality can be lowered by preventing a decrease in SBP to <90 mmHg. This may depend on the type of preventive measures that are taken. Increasing dry weight or preventive intradialytic administration of saline carries the risk of chronic overhydration which has a strong negative impact on survival[29]

Further research is needed to understand the underlying mechanisms of the IDH related symptoms and to provide the patient with the optimal dialysis treatment[30-31]. The finding that the way patients experience HD treatment influences QOL may underscore the impact of dialysis on their personal life, not only for the patient but, most likely, also for their family members[32]. This information can be used by medical and nursing staff to provide a frame of reference to better understand the consequences on the daily life of patients. In addition to focusing on the medical condition and the blood pressure course during the HD treatment, more attention to the factors that influence QOL seems beneficial for patients.

It should be noted that the EBPG definition, like any other definition using clinical symptoms or nursing interventions, is subject to bias by the nurse and physician. This also applies for how patients interpreted their QOL and symptoms and rated the HD treatment in the PRISS. The PRISS is a 5-point Likert scale measuring a positive or negative response to a statement which was suitable for the question of how they had experienced the HD session. The validity of the Likert Scale attitude measurement can be compromised due to social desirability. The SF-36 does not include symptoms and problems that are specific to a particular condition, but SF-36 scales correlate substantially with most of the omitted general health concepts and with the frequency and severity of many specific symptoms[33]. Relative to other published measures, the mental health, role- emotional, and social functioning scale and the mental component summary have been shown to be the most valid mental health measures in the method of known groups-validity. The physical functioning, role- physical, and bodily pain scales and the physical component summary have shown to be the most valid physical health measures[33]. Future studies should preferably use the QDQOL, since this tool is supplemented with multi-item scales targeted at particular concerns of individuals with a kidney disease and on dialysis. The number of patients in our study is relatively low. However the long study duration of three months as well as the frequent measurement of blood pressure and the post-dialytic recording of the PRISS (and active search for patient complaints at each dialysis session) reduced the possibility of underestimation of dialysis hypotension. Another limitation of our study is that we did not take into

account seasonal variations in BP. Our study was performed in February through April and, therefore we do not have information on seasonal variations. We also acknowledge that the results in our Dutch cohort may not be representative for other populations that have a higher incidence of diabetes and overweight and higher ultrafiltration rates.

CONCLUSION

Our findings suggest that the EBPG definition of IDH does not capture aspects of intradialytic symptomatology that are relevant for the patient's QOL. In contrast, we found a significant association between QOL and a simple patient-reported intra-dialytic symptom score, i.e., the PRISS, indicating that how patients experience HD treatment influences their QOL. Further research is needed to confirm our findings and to refine the definition of IDH based on the purpose for which the definition is used. More attention to the impact of symptom burden of HD treatment is helpful for improving the QOL of HD patients.

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REFERENCES

1. Mingardi G, Cornalba L, Cortinovis E, Ruggiata R, Mosconi P, Apolone G. Health-related quality of life in dialysis patients. A report from an italian study using the SF-36 health survey. *Nephrology Dialysis Transplantation*. 1999;14(6):1503.
2. Merkus MP, Jager KJ, Dekker FW, Boeschoten EW, Stevens P, Krediet RT. Quality of life in patients on chronic dialysis: Self-assessment 3 months after the start of treatment. *American Journal of Kidney Diseases*. 1997;29(4):584-592. doi: https://doi.org/10.1016/S0272-6386(97)90342-5.
3. Ware JE Jr. SF-36 health survey update. *Spine*. 2000;25(24):3130-9.
4. Davenport A, Cox C, Thuraisingham R. Blood pressure control and symptomatic intradialytic hypotension in diabetic haemodialysis patients: A cross-sectional survey. *Nephron.Clinical practice*. 2008;109(2):c65-c71.
5. Sands J, Usvyat LA, Sullivan T, et al. Intradialytic hypotension: Frequency, sources of variation and correlation with clinical outcome. *Hemodial Int.* 2014;18:415-422.
6. Caplin B, Kumar S, Davenport A. Patients' perspective of haemodialysis-associated symptoms. *Nephrol Dial Transplant*. 2011;26(8):2656-2663.
7. Tisler A, Akocsi K, Borbas B, et al. The effect of frequent or occasional dialysis-associated hypotension on survival of patients on maintenance haemodialysis. *Nephrol Dial Transplant*. 2003;18(12):2601-2605.
8. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol*. 2014.
9. Kooman J, Basci A, Pizzarelli F, et al. EBPG guideline on haemodynamic instability. *Nephrol Dial Transplant.* 2007;22 Suppl 2:ii22-ii44.
10. Kuipers J, Oosterhuis JK, Krijnen WP, et al. Prevalence of intradialytic hypotension, clinical symptoms and nursing interventions - a three-months, prospective study of 3818 haemodialysis sessions. *BMC Nephrol*. 2016;17(1):21.
11. Likert R. *A Technique for the Measurement of Attitudes*. 1932:55.
12. Zee, KI. van der, Sanderman, R. Het meten van de algemene gezondheidstoestand met de RAND-36: Een handleiding. Updated 1993.
13. Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume kt/V: An analysis of error. *Journal of the American Society of Nephrology*. 1993;4(5):1205-1213.

14. Davenport A, Cox C, Thuraisingham R. Blood pressure control and symptomatic intradialytic hypotension in diabetic haemodialysis patients: A cross-sectional survey. *Nephron Clin Pract*. 2008;109(2):c65; c71.

15. Sands JJ, Usvyat LA, Sullivan T, et al. Intradialytic hypotension: Frequency, sources of variation and correlation with clinical outcome. *Hemodial Int*. 2014;18(2):415-422.

16. Bossola M, Laudisio A, Antocicco M, et al. Intradialytic hypotension is associated with dialytic age in patients on chronic hemodialysis. *Ren Fail*. 2013;35(9):1260-1263.

17. Akaike information criterion statistics. *Math Comput Simul*. 1987;29(5):452.

18. Akaike H. Information theory and an extension of maximum likelihood principle. *Proc.2nd Int.Symp.on Information Theory*. 1973:267-281.

19. Burnham KP, Anderson DR. *Model selection and multimodel inference: A practical information-theoretic approach.* Springer Science & Business Media; 2003.

20. Buemi M, Lacquaniti A, Bolignano D, et al. Dialysis and the elderly: An underestimated problem. *Kidney Blood Press Res*. 2008;31(5):330-336.

21. Kalantar-Zadeh K. Associations of body fat and its changes over time with quality of life and prospective mortality in hemodialysis patients. *Am J Clin Nutr*. 2006-2;83(2):202-10.

22. Freeman R. Chapter 6 - diabetic autonomic neuropathy. *Handbook of Clinical Neurology*.2014;126:63-79.doi:https://doi.org/10.1016/B978-0-444-53480-4.-00006-0.

23. Vinik AI, Nevoret ML, Casellini C, Parson H. Diabetic neuropathy. *Endocrinol Metab Clin North Am*. 2013;42(4):747-787.

24. Shimizu K, Kurosawa T, Sanjo T. Effect of hyperosmolality on vasopressin secretion in intradialytic hypotension: A mechanistic study. *Am J Kidney Dis.* 2008;52(2):294-304.

25. Zimmerman CY, Ladefoged A, Søren SN. Can haemodialysis-induced hypotension be predicted? *Nephron*. 2002;92(3):582-588.

26. Schreiber MJ. Setting the stage. *Am J Kidney Dis.* 2001;38(4, Supplement 4):S1-S10.

27. Prakash S, Garg AX, Heidenheim AP, House A. Midodrine appears to be safe and effective for dialysis-induced hypotension: A systematic review. *Nephrol Dial Transplant.* 2004;19(10):2553-2558.

28. Assimon MM. Definitions of intradialytic hypotension. *Semin Dial*. 2017 11;30(6):464-472.

29. Zoccali C. Chronic fluid overload and mortality in ESRD. *Journal of the American Society of Nephrology*. 2017-8;28(8):2491-2497.

30. Bossola M. Health-related quality of life of patients on chronic dialysis: The need for a focused effort. *Semin Dial*. 2017-9;30(5):413-416.

31. Flythe JE. Symptom prioritization among adults receiving in-center hemodialysis: A mixed methods study. *Clinical Journal of the American Society of Nephrology*. 2018-3-20.

32. White Y. The biopsychosocial impact of end-stage renal disease: The experience of dialysis patients and their partners. *J Adv Nurs*. 1999-12;30(6):1312-20.

33. Ware JE. Overview of the SF-36 health survey and the international quality of life assessment (IQOLA) project. *J Clin Epidemiol*. 1998-11;51(11):903-12.

Supplementary file 1.

Patient characteristics associated with Quality of life components.

	Gender		Age		Dialysis vintage			Diabetes		CV comorbidity	
	M	F	≤50	>50	≤12	>12-≤36	>36	Y	N	Y	N
N	41	41	16	66	20	37	25	18	64	36	46
Physical functioning	52.5 (31.3-75.0)	45 (25.0-75.0)	77.5 (52.5-85.0)	40.0 (25.0-65.0)	47.5 (27.5-75.0)	60.0 (36.3-83.8)	35.0 (17.5-50.0)	37.5 (23.8-76.3)	50 (30.0-75.0)	45.0 (31.3-68.8)	50.0 (25.0-80.0)
P	0.45		0.003*			0.02*		0.39		0.82	
Social functioning	75.0 (62.5-93.8)	75.0 (56.3-87.5)	68.8 (53.1-84.4)	87.5 (62.5-100)	68.8 (40.6-87.5)	87.5 (68.8-100)	75.0 (56.3-87.5)	75.0 (50.0-87.5)	75.0 (62.5-96.9)	87.5 (75.0-100)	75.0 (50.0-87.5)
P	0.71		0.12			0.07		0.46		0.02*	
Physical role functioning	25.0 (00.0-100)	00.0 (00.0-62.5)	00.0 (00.0-62.5)	25.0 (00.0-100)	25.0 (00.0-68.8)	25.0 (00.0-100)	00.0 (00.0-37.5)	00.0 (00.0-62.5)	25.0 (00.0-75.0)	25.0 (00.0-100)	00.0 (00.0-75.0)
P	0.07		0.32			0.22		0.52		0.25	
Emotional role functioning	100 (33.3-100)	100 (33.3-100)	100 (33.3-100)	100 (33.3-100)	100 (58.3-100)	100 (58.3-100)	33.3 (00.0-100)	66.7 (00.0-100)	100 (33.3-100)	100 (33.3-100)	100 (00.0-100)
P	0.78		0.64			0.01*		0.13		0.55	
Mental health	80.0 (60.0-96.0)	80.0 (64.0-88.0)	68.0 (52.0-88.0)	82.0 (64.0-92.0)	76.0 (52.0-88.0)	80.0 (64.0-95.0)	80.0 (64.0-92.0)	80.0 (54.0-90.0)	80.0 (64.0-92.0)	84.0 (66.0-96.0)	76.0 (64.0-88.0)
P	0.59		0.11			0.56		0.48		0.17	
Vitality	55.0 (40.0-70.0)	45.0 (30.0-63.8)	45.0 (31.3-58.8)	55.0 (35.0-70.0)	45.0 (35.0-60.0)	55.0 (37.5-70.0)	55.0 (30.0-70.0)	50.0 (27.5-75.0)	55.0 (35.0-70.0)	50.0 (40.0-70.0)	55.0 (32.5-70.0)
P	0.20		0.08			0.51		0.98		0.91	

Bodily Pain	87.8 (51.0-100)	67.3 (44.9-100)	67.3 (53.5-94.9)	87.8 (44.9-100)	67.3 (44.9-100)	89.8 (62.2-100)	67.3 (39.8-100)	44.9 (34.2-100)	83.7 (55.1-100)	83.7 (44.9-100)	78.6 (44.9-100)
P	0.37		0.59			0.14		0.04*		0.66	
General Health	45 (25.0-56.3)	42.5 (25.0-58.8)	37.5 (16.3-50.0)	45.0 (28.8-60.0)	40.0 (25.0-60.0)	45.0 (35.0-62.5)	42.5 (18.8-55.0)	42.5 (20.0-55.0)	45.0 (25.0-60.0)	40.0 (25.0-56.3)	45.0 (25.0-58.8)
P	0.75		0.13			0.39		0.63		0.52	
Health change	50 (50.0-75.0)	50 (25.0-62.5)	50.0 (25.0-75.0)	50.0 (25.0-75.0)	50.0 (31.3-75.0)	50.0 (25.0-75.0)	50.0 (25.0-50.0)	75.0 (43.8-81.3)	50.0 (25.0-75.0)	50.0 (25.0-75.0)	50.0 (43.8-75.0)
P	0.09		0.30			0.25		0.12		0.68	
Physical Component Summary	51.8 (36.8-69.4)	46.3 (27.4-63.4)	50.9 (35.2-58.4)	48.1 (29.6-66.9)	51.2 (25.8-65.6)	56.5 (37.0-74.7)	39.9 (28.1-50.6)	34.9 (23.6-60.0)	50.6 (36.2-66.3)	47.8 (34.1-65.6)	49.9 (31.5-67.2)
P	0.22		0.82			0.03*		0.12		0.89	
Mental Component Summary	72.3 (52.8-86.1)	68 (54.5-80.4)	70.9 (46.8-76.8)	72.3 (54.1-86.4)	71.3 (51.0-77.0)	78.3 (61.1-87.6)	67.5 (39.8-79.1)	65.8 (45.7-81.4)	72.5 (57.6-84.4)	76.4 (56.9-87.1)	67.0 (52.2-81.1)
P	0.58		0.22			0.16		0.46		0.20	

Continue variables are presented as Median (IQR), abbreviations: *= signifcant, CV = Cardiovascular.

Supplementary file 2.

Multivariate lineair regression analysis with model building strategy Akaike Information Criterion (AIC); factors associated with Quality of life components.

		Gender	Age	Dialysis vintage	BMI	Diabetes	CV comorbidity	Decrease in SBP >20 mmHg (%)	Clinical events (%)	Interventions (%)	Total UF	PRISS	Adjusted R
Physical functioning	Estimate		-0.80	-0.21	-0.93							26.08	
	95% CI		-1.16 to -0.45	-0.41 to 0.01	-2.04 to 0.18							8.28 to 43.87	
	SE		0.18	0.09	0.56							8.93	
	P		0.00**	0.04*	0.10							0.004*	0.28
Social functioning	Estimate				-1.11		8.91				-0.005	15.58	
	95% CI				-2.21 to -0.01		1.88 to 19.70				-0.01 to 0.002	-1.43 to 32.59	
	SE				0.55		5.42				0.003	8.54	
	P				0.05*		0.10				0.17	0.07	0.085
Physical role functioning	Estimate	-16.94						0.28			-0.01		
	95% CI	-35.76 to 1.87						-0.12 to 0.69			-0.02 to 0.003		
	SE	9.44						0.20			0.01		
	P	0.08						0.17			0.14		0.030
Emotional role functioning	Estimate			-0.24		-22.51			1.18	-0.99	-0.01	49.41	
	95% CI			-0.56 to 0.08		-44.72 to -0.31			0.37 to 1.99	-2.09 to 0.11	-0.02 to 0.003	12.14 to 86.67	
	SE			0.16		11.13			0.41	0.55	0.01	18.68	
	P			0.14		0.05*			0.005*	0.08	0.15	0.01*	0.16
Mental health	Estimate										-0.01		
	95% CI										0.012 to-0.001		
	SE										0.003		
	P										0.02*		0.053
Vitality	Estimate		0.25									13.57	
	95% CI		-0.06 to 0.55									-1.04 to 28.18	
	SE		0.15									7.34	
	P		0.11									0.07	0.075
Bodily Pain	Estimate					-20.78						27.13	
	95% CI					-35.68 to -5.88						7.86 to 46.41	
	SE					7.49						9.68	
	P					0.007*						0.006*	0.12
General Health	Estimate								0.27		-0.01	30.13	
	95% CI								0.10 to 0.65		-0.01 to-0.002	12.28 to 47.99	
	SE								0.19		0.003	8.95	
	P								0.15		0.01*	0.001*	0.17
Health change	Estimate											34.55	
	95% CI											16.88 to 52.23	
	SE											8.88	
	P											0.00*	0.15

Es t= Estimate, SE= Standard Error, P= P-value, CI= Confidence Interval, U =Upper bound, L= Lower bound, * =significant, UF = Ultrafiltration volume, CV = Cardiovascular, R =the variance of the QOL variables explained by the explanatory variables (in %).

Chapter 7

Summary and General discussion

Summary

The central theme of this thesis is intradialytic hypotension (IDH). Despite technological advances in hemodialysis treatment, IDH remains an important complication of the dialysis treatment and is associated with increased cardiovascular morbidity and mortality[1]. The haemodialysis schedule and treatment itself has a great impact on the daily lives of patients. Dialysis seriously impairs the quality of life due to a high symptom burden. Furthermore, most patients have a fluid restriction and a strict diet with low sodium and potassium. The treatment duration is generally thrice weekly for 4 hours and causes large changes in the composition of the blood over a short period of time. The removal of the excess fluid can lead to intradialytic hypotension, which is often symptomatic and persists for some time after completion of the treatment[2-3]. Over the years, dialysis techniques have improved and there is more awareness of strategies to prevent IDH[4-5] but studies on the prevalence of IDH are scarce with as complicating factor that a wide variation in definitions to identify IDH are used, depending on the goal of the study. Therefore, it is not clear what the exact impact is on patients.

Patients on a trice weekly haemodialysis schedule have higher pre-dialysis weights and higher ultrafiltration rates at the first dialysis session compared with the second and third dialysis session of the week. In **chapter 2** we studied whether these variations in excess weight and ultrafiltration rate are associated with a consistent difference in pre-, intra- and post-dialysis blood pressure behaviour between the first and the subsequent dialysis sessions of the week. The pre-dialysis systolic and diastolic BPs were significantly higher at the first compared with the two other dialysis sessions of the week, probably due to more pronounced fluid overload. A second, unexpected finding was that intra- and post-dialytic BPs were also significantly higher at the first session compared with the other dialysis sessions of the week despite higher ultrafiltration rates. Interestingly, identical results were found in a second cohort of 789 patients from six Unites States dialysis centers.

In **chapter 3** we aimed to identify the major determinants of a high interdialytic weight gain (IDWG) and its association with nutritional parameters. We collected data during one week for IDWG and hemodynamic parameters in 138 prevalent adult haemodialysis patients on a thrice-weekly haemodialysis schedule. We found that a higher IDWG was associated with a younger age, male gender, a greater height and weight, presence of residual diuresis, and lower post-dialysis sodium levels. Being both young and male was associated with a higher IDWG. Patients with a higher IDWG had significantly higher diastolic blood pressures, which is in line with our previous study, described in chapter 2 that more pronounced fluid overload at the first sessions of the week is associated with higher pre-dialysis BPs. Remarkably, higher postdialysis sodium levels were associated with a lower IDWG. This contrasts with the general belief that higher postdialysis plasma sodium levels induce thirst and subsequent increase fluid

intake. Our study suggests that this could be explained by the fact that patients with a high IDWG often begin haemodialysis with a low plasma sodium concentration resulting from dilution that does not rise to normal levels during treatment despite diffusive sodium transfer to the patient during haemodialysis. Our results indicate that dietary advice including fluid restriction should be individualized based on age, body height and weight, and residual diuresis.

In **chapter 4** we aimed to assess the prevalence of IDH in our patient population and to identify patient and treatment factors that are associated with its presence. The main finding of this study was that dialysis hypotension as defined according to the European Best Practice Guideline (EBPG) on haemodynamic instability (a decrease in SBP ≥20 mmHg or a decrease in mean arterial pressure (MAP) by ≥10 mmHg in combination with a clinical event and the need for a nursing intervention) occurred in only 6.7% of dialysis sessions. This contrasts with the estimate that is stated in most reviews that IDH occurs up to 30%. Frequent dialysis hypotension on patient level, defined as dialysis hypotension (EBPG) in >20% of dialysis sessions, was observed in 8.1% of patients. Even if we used a more liberal definition, e.g., a fall in SBP >20 mmHg or a fall in MAP >10 mmHg in combination with a clinical event (thus without the need for nursing intervention), the prevalence of dialysis hypotension was 18.4% which is still lower compared with the prevalence of 20-30% stated in most reviews. At patient level, as much as 96.8% of patients had a decrease in SBP ≥20mmHg or a decrease in MAP ≥10 mmHg in more than 20% of dialysis sessions. It follows that a decrease in SBP ≥20 mmHg or a fall in MAP≥ 10 mmHg is so common that it is not specific for symptomatic dialysis hypotension. In multivariate analyses, the strongest determinants of dialysis hypotension defined by the full EBPG definition were lower body height and higher ultrafiltration volume. This could be related to an unfavorable balance between ultrafiltration rate and refill rate in smaller patients and underlines our conclusion in chapter 3 that dietary advice including fluid restriction should be individualized.

In **chapter 5** we describe a systemic literature review and a meta-analysis on studies that investigated the prevalence of IDH. In a meta-analysis comprising 4 articles including 1694 patients and 5 articles including 13.189 patients, the prevalence of HD sessions complicated by IDH was 10.1% and 11.6% for the EBPG definition and the Nadir <90 definition (intradialytic SBP <90mmHg) respectively. As also seen in chapter 4 this is much lower than stated in most reviews. The proportion of patients with frequent IDH could not be reliably established because of the wide variation in cut-off values that were used to identify patients with frequent IDH. Major risk factors associated with IDH across studies were diabetes, a higher interdialytic weight gain, female sex and lower body weight.

In **chapter 6** we studied whether the occurrence of IDH according to the EBPG guideline has an influence on the perception of QOL in HD patients. The main finding of this study was that there is no association between IDH as defined according to the EBPG

guideline and QOL. This was factual for the standard EBPG definition as well as when a decrease in SBP of ≥30 or ≥40 mmHg was chosen as the blood pressure decline component, instead of a decrease in SBP ≥20 mmHg or a decrease in MAP ≥10 mmHg. There was an association between QOL and UF-volume, clinical events, and nursing interventions, parameters that are directly or indirectly related to fluid restriction. For some patients this is very difficult to maintain and this may cause stress and anxiety. We also found a significant association between QOL and a simple patient-reported intradialytic symptom score, the PRISS, indicating that the way patients experience HD treatment is indeed of influence on QOL. These findings suggest that a fall in SBP on itself does not have a major impact on QOL in HD patients. The finding that the way patients experience HD treatment is of influence on QOL may underscores the impact of dialysis on their personal life, not only for the patient but, most likely, also for their family members[6].

General discussion and future perspectives

In summary we can conclude that based on our findings in chapter 2 and 3 more pronounced fluid overload leads to higher *pre- intra-* and *post*-dialytic BPs and that intra- and post-dialytic BPs were at their lowest during the third dialysis session of the week, probably because patients are closer to their dry weight. From chapter 3, 4 and 5 we conclude that a higher IDWG, diabetes, lower body height and weight and female sex are important risk factors for the occurrence of IDH. Our results indicate that a dietary advice including fluid restriction should be individualized, taking the weight and gender of the patient into account.

In our population, IDH defined according to the EBPG guideline occurred in 6.7% of HD patients. The results of the meta-analysis in our systematic review also show that the prevalence of IDH according to both the EBPG and the Nadir<90mmHg definition, occurred on average in 10.9% of HD sessions. This is much lower than is mentioned in most reviews with IDH occurring in up to 30% of dialysis sessions. This lack of uniformity could be caused by wide variety in the use of IDH definitions. There is no general consensus regarding the best evidence-based indicators of IDH. As seen in chapter 5, a decrease in SBP ≥20 mmHg or a fall in MAP≥ 10 mmHg is so common that it is not specific for symptomatic dialysis hypotension. This raises the question whether a decrease in SBP ≥20 mmHg or a decrease in MAP≥10 mmHg discriminates between patients with and without symptomatic dialysis hypotension. A definition that uses patients' complaints and/or nursing interventions seems more appropriate to capture the symptom burden. However, a definition based on clinical symptoms and nursing interventions is never free of bias. There can be differences between patients in experiencing and reporting symptoms, depending on how data are collected with 'actively' using questionnaires at each dialysis session yielding a higher prevalence than 'passively' waiting for the patient to report symptoms. Furthermore, the interpretation

of patient complaints as part of the symptomatology of dialysis hypotension as well as the threshold to perform an intervention may differ between nurses and between physicians. An absolute nadir intradialytic BP of SPB <90 mmHg was previously found to be associated with an increased mortality risk, but intradialytic symptoms and/or interventions were not associated with mortality risk[7]. So depending on the purpose of the study, the appropriate definition may differ[8]. Surprisingly, in none of the articles examined, it was stated what the underlying motivation was for the used definition.

An important question which should be further investigated is if whether mortality can be lowered by preventing a fall in SBP to <90 mmHg within a thrice weekly 4 hour dialysis schedule. Increasing dry weight or preventive intradialytic administration of saline carries the risk of chronic overhydration which has a strong negative impact on survival as well[9]. Besides hypovolemia, there may be other dialysis associated factors involved in the pathogenesis of IDH and/or CV stress during hemodialysis[10].

There is no association between QOL and IDH as defined according to the EBPG guideline. However, the significant association between QOL and various parameters related to fluid restriction and the association between QOL and a simple patient questionnaire (PRISS), indicates that the way patients experience the HD treatment is (certainly) of influence on their QOL. The impact of dialysis on the lives of patients and their family members can be overwhelming[6]**.** More research using Patient Reported Outcomes Measures (PROMs) might help to understand the patient burden of the dialysis treatment. This information can be used by the medical and nursing staff to provide a frame of reference to better understand the consequences for the daily life of patients. Such an evidence-based knowledge framework related to UF-volume, clinical events, and nursing interventions can be implemented in nursing as well as in medical education programs, creating awareness that the signs and symptoms related to the influence of HD treatment on QOL are of significant importance.

Parameters that are directly or indirectly related to fluid restriction may cause stress and anxiety or other related experiences of patients. As these experiences seems to be, to some extent, individual and related to the specific patient related condition and circumstance, especially nurses, who often have a long-term relationship with their patients, need to be cognizant and responsive to patients physical and psychological experiences on HD treatment in general, as well as the spectrum of UF-volume related symptoms in particular. Understanding the patients experiences can help to offer accurate interventions and to support the patient in successfully modify their behavior to improve their QOL. This might already influence the QOL for both the patient as well as for their family members[11] and can be a treatment-related factor to decrease mortality. If nurses have full awareness and a knowledge based, patient centered attitude in the field of intradialytic hypotension, research towards their observations and documentation of patients' reflections related to biomedical measurements may lead, on the one hand, to new insights for better patient outcomes and higher scores in QOL

measurements. On the other hand, it may lead to a more focused and evidence-based definition on what can be seen as intradialytic hypotension as well as what can be seen as evidence-based interventions and patient sensitive outcomes. The management should encourage and enable the nursing staff to develop advanced counseling skills and a family centered approach to the care of the patient with ESRD[6-12].

Practical recommendations and needs for improvement

It is obvious that there is a need for a more specific and widely disseminated definition of IDH. The question is whether one optimal definition for IDH exists. We recommend that the definition of IDH should be graded and defined based on the purpose for which the definition is used. E.g. when the goal of the study is to study the relation between IDH and outcome, a nadir definition may be appropriate whereas when the purpose of the study is to investigate the relation between IDH and QOL or/and PROMs, a definition of IDH that incorporates intradialytic (and preferably also post-dialytic) symptoms may be more relevant.

Furthermore, a more personal approach is needed to support the patient in a more individualized dietary advice and fluid restriction. PROMs can help to understand the patient burden of the dialysis treatment and improve the quality of care and the nursing staff should be facilitated to give HD patients personal support.

References

1. Stefansson BV, Brunelli SM, Cabrera C, et al. Intradialytic hypotension and risk of cardiovascular disease. *Clin J Am Soc Nephrol*. 2014;9(12):2124-2132.
2. Https://Www.nierstichting.nl/professionals/factsheets/.
3. Janssen D, Spruit MA, Wouters E, Schols J. Daily symptom burden in end-stage chronic organ failure: A systematic review. *Palliat Med*. 2008;22(8):938-948.
4. Chesterton LJ, Selby NM, Burton JO, McIntyre CW. Cool dialysate reduces asymptomatic intradialytic hypotension and increases baroreflex variability. *Hemodial Int.* 2009;13(2):189-196.
5. Jefferies HJ, Burton JO, McIntyre CW. Individualised dialysate temperature improves intradialytic haemodynamics and abrogates haemodialysis-induced myo cardial stunning, without compromising tolerability. *Blood Purif*. 2011;32(1):63-68.
6. White Y. The biopsychosocial impact of end-stage renal disease: The experience of dialysis patients and their partners. *J Adv Nurs*. 1999-12;30(6):1312-20.
7. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol*. 2014.
8. Assimon MM. Definitions of intradialytic hypotension. *Semin Dial*. 2017 11;30(6):464-472.
9. Zoccali C. Chronic fluid overload and mortality in ESRD. *J. Am. Soc. Nephrol.* 2017-8;28(8):2491-2497.
10. Assa S. Effect of isolated ultrafiltration and isovolemic dialysis on myocardial perfusion and left ventricular function assessed with 13N-NH3 positron emission tomography and echocardiography. *Am. J. Physiol. Renal Physiol*. 2018-01;314(3):445.
11. Barnett T. Fluid compliance among patients having haemodialysis: Can an educational programme make a difference? *J Adv Nurs*. 2008-2;61(3):300-6.
12. McCarley P. Patient empowerment and motivational interviewing: Engaging patients to self-manage their own care. Nephrol Nurs J 2009 Jul-Aug;36(4):409-13.

Nederlandse samenvatting

Nederlandse samenvatting

Dialyse is een vorm van een nierfunctie vervangende behandeling waarmee afvalstoffen en overtollig vocht uit het lichaam wordt verwijderd. Het is een levensreddende behandeling voor mensen bij wie de nieren niet goed meer werken. De kenmerken van de patiënten die dialyse ondergaan zijn in de loop der jaren sterk veranderd. Waar eerst relatief jonge patiënten met nierziekten werden behandeld, omvat de patiëntengroep nu ook oudere mensen met multi-morbiditeit zoals diabetes mellitus en vaatlijden. Dialyse heeft een negatieve invloed op de kwaliteit van leven door de behandeling zelf en door bijkomende klachten en (beperkingen door) leefregels. De meeste patiënten hebben een vochtbeperking en een streng dieet met een laag natrium- en kaliumgehalte. Er is een verhoogd risico op hart- en vaatziekten en de algehele conditie verslechtert vaak na verloop van tijd. Het hemodialysebehandelingsschema en de behandeling zelf hebben ook een grote invloed op het dagelijks leven van patiënten. Het meest gebruikte behandelingsschema bij hemodialyse is drie maal per week 4 uur en veroorzaakt dus grote veranderingen in de samenstelling van het bloed in een relatief korte periode. Het verwijderen van het overtollige vocht kan leiden tot lage bloeddruk tijdens dialyse (dialyse hypotensie) hetgeen vaak met klachten verloopt die nog uren na afloop van de behandeling aan kunnen houden.

Het centrale thema van dit proefschrift is dialyse hypotensie, één van de belangrijkste en meest frequent optredende complicaties van de dialysebehandeling. Het regelmatig optreden van dialyse hypotensie is geassocieerd met een verhoogde kans op aandoeningen aan hart- en bloedvaten en overlijden. In de afgelopen decennia zijn de dialysetechnieken verbeterd en zijn er betere strategieën ontwikkeld om dialyse hypotensie te voorkomen. Desondanks zijn studies over hoe vaak dialyse hypotensie precies voor komt schaars, met als complicerende factor dat in de literatuur uiteenlopende/ verschillende definities worden gebruikt voor dialyse hypotensie. Het is daarom niet duidelijk hoe vaak het voor komt en wat de exacte impact is op patiënten.

Patiënten met een hemodialyseschema van 3 keer per week hebben tijdens de eerste dialysesessie van de week een hoger predialyse gewicht en er wordt meer vocht onttrokken in vergelijking met de tweede en derde dialysesessie van de week. In **hoofdstuk 2** is onderzocht of deze variaties in gewicht en het vocht onttrekken gepaard gaan met een consistent verschil in bloeddrukken voor, tijdens en na de dialyse tussen de eerste en de volgende dialysebehandelingen van de week. De systolische en diastolische bloeddruk vóór de eerste dialyse van de week bleek significant hoger te zijn in vergelijking met de twee andere dialysebehandelingen van de week, waarschijnlijk als gevolg van een meer uitgesproken vochtoverbelasting voor de eerste dialysebehandeling van de week. Een tweede, onverwachte bevinding was dat tijdens de eerste dialyse van de week de bloeddrukken tijdens en na de dialyse ook significant hoger waren in vergelijking met de andere dialysebehandelingen van de week. Identieke resultaten

werden gevonden in een cohort van 789 hemodialyse patiënten uit zes Amerikaanse dialysecentra.

In **hoofdstuk 3** wilden we de belangrijkste factoren van een hoge interdialytische gewichts-toename (vochtinname tussen 2 dialysebehandelingen) (IDG) en de associatie ervan met voedings-parameters identificeren. Bij 138 volwassen hemodialysepatiënten met een drie keer per week hemodialyseschema verzamelden we deze gegevens gedurende 1 week. We vonden dat een hogere IDG was geassocieerd met een jongere leeftijd, mannelijk geslacht, een hoger lichaamsgewicht en -lengte, de aanwezigheid van diurese en lagere plasma natriumconcentraties na de dialyse. Vooral jonge mannelijke dialysepatiënten hadden een hoog IDG. Patiënten met een hoger IDG hadden een significant hogere diastolische bloeddruk hetgeen in lijn is met onze in hoofdstuk 2 beschreven onderzoek waarbij de meer uitgesproken vochtoverbelasting bij de eerste dialysebehandeling van de week geassocieerd was met een hogere bloeddruk voor dialyse. Het is opmerkelijk dat een hogere plasma natriumconcentratie na de dialysebehandeling geassocieerd was met een lager IDG. Dit staat in contrast met de algemene overtuiging dat hogere plasma natriumspiegels na de dialyse leiden tot dorst en vervolgens tot een hogere vochtinname. Onze studie suggereert dat dit verklaard kan worden door het feit dat patiënten met een hoog IDG de hemodialysebehandeling vaak beginnen met een lage plasma natriumconcentratie als gevolg van verdunning waarbij de natriumconcentratie tijdens de dialysebehandeling niet tot een normaal niveau stijgt ondanks de diffusieve natriumoverdracht naar de patiënt tijdens de hemodialyse. Onze resultaten geven aan dat het voedingsadvies, inclusief vochtbeperking, moet worden geïndividualiseerd op basis van leeftijd, lichaamslengte en -gewicht, en diurese.

In **hoofdstuk 4** hebben we onderzocht hoe vaak dialyse hypotensie voorkomt in onze patiëntenpopulatie en welke patiënt- en behandelingsfactoren hierop van invloed zijn. De belangrijkste bevinding van dit onderzoek was dat dialyse hypotensie zoals gedefinieerd volgens de Europese Best Practice Guideline (EBPG) (een daling van de systolische bloeddruk van tenminste 20 mmHg of een daling van de gemiddelde arteriële bloeddruk van tenminste 10 mmHg in combinatie met klachten van de patiënt en de noodzaak van een verpleegkundige interventie) in slechts 6,7% van de dialysebehandelingen plaats vond. Dit staat in contrast met de prevalentie van 30% die in de meeste overzichtsartikelen over dialyse hypotensie genoemd wordt. Dialyse hypotensie op patiëntniveau, gedefinieerd als dialyse hypotensie (EBPG) in meer dan 20% van de dialysebehandelingen werd waargenomen bij 8,1% van de patiënten. Zelfs als we een meer liberale definitie hanteerden, bijvoorbeeld een daling van de systolische bloeddruk van tenminste 20 mmHg of een daling van de MAP van ten minste 10 mmHg in combinatie met een klachten van de patiënt (dus zonder verpleegkundige interventie), kwam dialyse hypotensie in 18,4% van de dialysebehandelingen voor, hetgeen nog steeds lager is dan wat in de meeste overzichtsartikelen wordt vermeld. Op patiëntniveau had maar liefst 96,8% van de patiënten een daling van de systolische bloeddruk van meer

dan 20mmHg of een daling van de MAP van meer dan 10 mmHg in meer dan 20% van de dialysebehandelingen. Hieruit volgt dat een afname van de systolische bloeddruk van meer dan 20 mmHg of een daling van de MAP van meer dan 10 mmHg zo vaak voorkomt dat het niet specifiek is voor symptomatische dialyse hypotensie. In een multivariate analyse bleek dat lagere lichaamslengte en het onttrekken van een groter volume vocht tijdens de dialysebehandeling significant van invloed waren op de frequentie van dialyse hypotensie (gedefinieerd volgens de EBPG-definitie). Dit wordt waarschijnlijk verklaard door een ongunstig evenwicht tussen de snelheid van vocht onttrekken (ultrafiltratiesnelheid) en de plasma refill vanuit de weefsels bij kleinere patiënten en onderstreept onze conclusie in hoofdstuk 3 dat dieetadviezen inclusief vochtbeperking geïndividualiseerd moeten worden.

In **hoofdstuk 5** beschrijven we een literatuuronderzoek en een meta-analyse van studies waarin is onderzocht hoe vaak dialyse hypotensie voor komt. In een meta-analyse van 4 artikelen met in totaal 1630 patiënten bleek dialyse hypotensie volgens de EBPG-definitie voor te komen in 10,1% van de dialysebehandelingen. In een meta-analyse van vijf artikelen met in totaal 13.189 patiënten bleek dat dialyse hypotensie, gedefinieerd als een laagste systolische bloeddruk tijdens dialyse van 90 mmHg of lager, voor kwam in 11,6% van de dialysebehandelingen. Net als beschreven in hoofdstuk 4, is deze prevalentie van dialyse hypotensie veel lager dan in de meeste overzichtsartikelen wordt vermeld. Belangrijke risicofactoren die in alle onderzochte studies geassocieerd waren met dialyse hypotensie waren diabetes, een hogere vochttoename tussen de dialyses, vrouwelijk geslacht en een lager lichaamsgewicht.

In **hoofdstuk 6** hebben we onderzocht of het optreden van dialyse hypotensie volgens de EBPG-richtlijn invloed heeft op de kwaliteit van leven bij dialysepatiënten. De belangrijkste bevinding van dit onderzoek was dat wij geen verband vonden tussen dialyse hypotensie volgens de EBPG-richtlijn en kwaliteit van leven. Wij vonden wel significante verbanden tussen kwaliteit van leven en de hoeveelheid vocht die onttrokken werd tijdens de dialysebehandeling, klachten van de patiënt en verpleegkundige interventies; dit zijn allen parameters die direct of indirect gerelateerd zijn aan de vochtbeperking. Voor sommige patiënten is de vochtbeperking zeer moeilijk vol te houden en dat kan stress en angst veroorzaken. We vonden ook een verband tussen de kwaliteit van leven en een patiënt-gerapporteerde klachtenscore (na iedere dialyse door de patiënt ingevuld waarbij men eventuele klachten tijdens de voorgaande dialysebehandeling aan kon geven) hetgeen aan geeft dat de manier waarop patiënten een dialysebehandeling ervaren inderdaad van invloed is op kwaliteit van leven. Dit onderstreept de impact van hemodialyse op hun persoonlijke leven, niet alleen voor de patiënt zelf, maar waarschijnlijk ook voor hun familieleden.

Conclusie

Samenvattend kunnen we concluderen dat op basis van onze bevindingen in hoofdstuk 2 en 3 meer uitgesproken vochtoverbelasting leidt tot hogere bloeddrukken voor tijdens en na de dialyse en dat de bloedrukken tijdens en na de derde dialysesessie van de week het laagst waren, waarschijnlijk omdat patiënten dichter bij hun droog gewicht zijn. Uit hoofdstuk 3, 4 en 5 concluderen we dat een hogere IDG, diabetes, lagere lichaamslengte en -gewicht en vrouwelijk geslacht belangrijke risicofactoren zijn voor het optreden van dialyse hypotensie. Onze resultaten geven aan dat een dieetadvies inclusief vochtbeperking geïndividualiseerd moet worden, rekening houdend met het gewicht en het geslacht van de patiënt.

In onze populatie kwam dialyse hypotensie gedefinieerd volgens de EBPG-richtlijn voor bij 6,7% van de dialysepatiënten. De resultaten van de meta-analyse in onze literatuur review tonen ook aan dat dialysehypotensie gemiddeld in 10,9% van de dialysebehandelingen voor kwam. Dit is veel lager dan in de meeste reviews wordt vermeld. Dit gebrek aan uniformiteit kan worden veroorzaakt door de grote verscheidenheid in het gebruik van definities voor dialyse hypotensie. Er is geen consensus over de beste evidence-based indicatoren van dialyse hypotensie. Zoals in hoofdstuk 5 blijkt is een daling van de systolische bloeddruk van tenminste 20 mmHg of een daling van MAP van tenminste 10 mmHg zo gebruikelijk dat het niet specifiek is voor symptomatische dialyse hypotensie. Dit roept de vraag op of een daling van de systolische bloeddruk van meer dan 20 mmHg of een daling van de MAP van meer dan 10 mmHg onderscheid maakt tussen patiënten met en zonder symptomatische dialyse hypotensie. Een definitie die gebruik maakt van klachten van patiënten en/of verpleegkundige interventies lijkt meer geschikt om de symptoomlast te vangen. Een definitie op basis van klinische symptomen en verpleegkundige interventies is echter altijd subjectief. Er kunnen verschillen bestaan tussen patiënten in het ervaren en rapporteren van symptomen, afhankelijk van de manier waarop gegevens worden verzameld. Zo zal een 'actief' gebruik van vragenlijsten bij elke dialysesessie waarschijnlijk een hogere prevalentie opleveren dan als de onderzoekers 'passief' wachten op het melden van symptomen door de patiënt. Verder kan de interpretatie van de, door de patiënt ervaren klachten als onderdeel van de symptomatologie van dialysehypotensie en de drempel voor het uitvoeren van een interventie verschillen tussen verpleegkundigen en tussen artsen. Een absoluut laagste systolische bloeddruk van 90 mmHg of lager bleek in eerder onderzoek geassocieerd te zijn met een verhoogd sterfterisico, maar symptomen en/of interventies tijdens de dialyse werden niet geassocieerd met een verhoogd sterfterisico. Dus afhankelijk van het doel van de studie kan de juiste definitie verschillen. Verrassend genoeg werd in geen van de onderzochte artikelen vermeld wat de onderliggende motivatie was voor de gebruikte definitie.

Een belangrijke vraag is of de sterfte kan worden verlaagd door een daling van de systolische bloeddruk tot onder 90 mmHg te voorkomen bij een gebruikelijk

hemodialyseschema van 3 maal per week 4 uur. Het verhogen van gewicht of het preventief toedienen van vocht tijdens de dialyse heeft het risico van chronische overvulling dat op zichzelf weer een sterke negatieve invloed heeft op de overleving. Daarnaast kunnen er andere dialyse-geassocieerde factoren betrokken zijn bij de pathogenese van dialyse hypotensie en/of cardiovasculaire stress tijdens hemodialyse.

Er is geen verband tussen kwaliteit van leven en dialyse hypotensie zoals gedefinieerd volgens de EBPG-richtlijn. Echter, de significante associatie tussen kwaliteit van leven en diverse parameters met betrekking tot vochtbeperking en de associatie tussen kwaliteit van leven en een eenvoudige patiënt vragenlijst, geeft aan dat de manier waarop patiënten de dialyse behandeling ervaren van invloed is op hun kwaliteit van leven. De impact van dialyse op het leven van patiënten en hun familieleden is groot. Meer onderzoek met behulp van patiënten vragenlijsten kan helpen om de last van de dialyse behandeling voor de patiënt te begrijpen. Deze informatie kan door het medisch en verplegend personeel worden gebruikt om een referentiekader te bieden voor een beter begrip van de gevolgen voor het dagelijks leven van patiënten.
Inzicht in de ervaringen van de patiënt kan helpen om de klachten van patiënt te verminderen en samen met de patiënt te onderzoeken wat mogelijk is om de kwaliteit van leven te verbeteren. Deze manier van ondersteuning kan op zich al van invloed zijn op de kwaliteit van leven voor zowel de patiënt als voor hun familieleden. Meer kennis en een betere documentatie van de problematiek rondom dialyse hypotensie en de klachten die dit kan veroorzaken kan ook leiden tot nieuwe inzichten om te komen tot een goede definitie van dialyse hypotensie en hoe dit te voorkomen of te behandelen. Het management dient daarbij de verpleegkundigen in staat te stellen coaching vaardigheden op te doen en een familiegerichte benadering van de zorg voor de dialyse patiënt te ontwikkelen.

Praktische toepasbaarheid
Het is duidelijk dat er behoefte is aan een goed onderbouwde definitie van dialyse hypotensie. De vraag is of er één optimale definitie van dialyse hypotensie bestaat. Onze aanbeveling is om dialyse hypotensie te definiëren op basis van het doel waarvoor de definitie wordt gebruikt. Een laagste systolische bloeddruk tijdens dialyse van 90 mmHg of lager kan gebruikt worden wanneer het doel van het onderzoek is om de relatie tussen dialyse en mortaliteit te bestuderen, terwijl een definitie van dialyse hypotensie die klachten tijdens de dialyse (en bij voorkeur ook na de dialyse) omvat, relevanter kan zijn wanneer het doel is om de relatie tussen dialyse hypotensie en kwaliteit van leven en/of patiënten ervaringen te onderzoeken. Een meer persoonlijke benadering is nodig om de patiënt te ondersteunen in een geïndividualiseerd voedingsadvies en vochtbeperking. Patiënten vragenlijsten kunnen helpen om de impact van de dialyse behandeling te begrijpen en de kwaliteit van de zorg te verbeteren, waarbij verpleegkundigen van groot belang zijn om de dialyse patiënt persoonlijke ondersteuning te geven.

Appendices

Dankwoord

About the author

List of publications

Dankwoord

Dit dankwoord is niet alleen bedoeld voor alle mensen die direct betrokken zijn geweest bij het promotietraject, maar ook voor alle mensen die daar omheen van grote waarde zijn geweest om mij na een periode van ziekte weer op de been te krijgen. De keuze om na mijn ziekte dit traject weer op te pakken is niet de gemakkelijkste geweest. Een promotietraject doorlopen is als het leven zelf: het loopt altijd anders dan verwacht. Meebuigen in de wind en rustig doorgaan is voor mij de beste remedie geweest.

In 2008 ben ik gestart met de opleiding voor researchverpleegkundige. Naast het ondersteunen van medisch wetenschappelijk onderzoek bij dialyse patiënten, ben ik ook gestart met een observationeel onderzoek om te achterhalen hoe vaak dialyse hypotensie voor kwam bij onze eigen patiënten van het Dialyse Centrum Groningen (DCG). Deze vraag is voortgekomen uit het promotieonderzoek van Judith Dasselaar naar de werking van Hemocontrol op dialyse hypotensie. Judith is mijn voorbeeld en inspiratie geweest in het doen van onderzoek, dank daarvoor! Ook wil ik Ronald van der Meer bedanken (destijds hoofd zorg van het DCG) die dit mede mogelijk heeft gemaakt.

Voor dit onderzoek heb ik gedurende 3 maanden gegevens van 136 patiënten verzameld. Daarbij zijn na elke dialyse scorelijsten ingevuld door de patiënten en verpleegkundigen. Hartelijk dank daarvoor! Na een lange periode van het invoeren van al die gegevens (4500 daglijsten en evenzovele scorelijsten) rolde er uiteindelijk een eerste artikel uit over de variabiliteit in bloeddrukken tijdens de verschillende dialyses van de week. Naar aanleiding van dat artikel kwam de vraag of ik niet op het onderwerp dialyse hypotensie zou willen promoveren. Daarover heb ik lang getwijfeld, ik zag bij promovendi met wie ik samenwerkte dat het een enorme klus is om een promotietraject tot een goed einde te brengen en wilde ik dat? Kon ik dat als verpleegkundige? Maar ik had er al zoveel werk voor verricht dat het ook jammer was om het uit handen te geven. Ik heb dus de beslissing genomen en ben ervoor gegaan. In 2013 is het promotietraject in gang gezet met Prof. Dr. Carlo A.J.M. Gaillard als promotor en Dr. Casper F.M. Franssen, Dr. Ralf Westerhuis en dr. Wolter Paans als copromotoren.

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Lieve mam en zussen, wat een rijkdom om jullie allemaal in mijn leven te hebben. Als er iets aan de hand is met één van ons dan voel ik hoe groot onze verbondenheid is in onze zorg voor elkaar en onze naasten. Lieve mam, je kwam er al vroeg in het leven in je eentje voor te staan met een groot gezin. Het vroege overlijden van pap heeft op ons allemaal een grote impact gehad, wat ons als gezin en individueel heeft gevormd. Dat de dag van mijn promotie op paps verjaardag valt vind ik een mooie symboliek en geeft het gevoel dat hij er toch een beetje bij is. Ik heb enorme bewondering en respect voor de manier waarop jij je leven verder vorm hebt gegeven. Altijd in staat bent geweest om de draad weer op te pakken en door te gaan om vooral zo zelfstandig mogelijk je leven te kunnen leiden. Dus, na wéér een heup of een knieoperatie, revalideren, fitness. In beweging blijven is je motto! Wat ben ik ontzettend dankbaar dat je deze dag als 86 jarige, nog in redelijke gezondheid mee mag maken. Sita, de fase waar in jij op dit ogenblik zit maakt mijn promotietraject niet zo belangrijk meer. Op het moment dat ik dit schrijf moet de transplantatie nog plaatsvinden en dat is superspannend. Jij bent een enorme doorzetter. Je wil vooral niet teveel gezeur, maar ik heb diepe bewondering voor jou nuchterheid, de rust die je uitstraalt en de manier waarop je hier mee omgaat. Ik hoop van harte dat je nog heel lang bij ons bent en samen met Aldert kun genieten van jullie pensioen en de kinderen en kleinkinderen. We kunnen je nog niet missen in onze weekenden waar jij vaak niet alleen de oudste, maar toch ook de wijste bent. Tineke, jij bent voor mij het voorbeeld van 'alles kan als je maar wil'. Ik heb diep respect voor jouw carrière switch om je droom te volgen en op je 45ste bij de politie te gaan. Je tomeloze energie en je carrièreplanning is een voorbeeld voor mij geweest. Je bent nooit te oud om te leren en ook vooral nooit te oud om je hart te volgen.

Ook Binie heeft haar hart gevolgd en is via een omweg van douane via psychiatrie, HBO docent geworden. Ik ben daar super trots op. Jullie gastvrijheid op de Valom is altijd weer hartverwarmend. Mams verjaardag, wat elk jaar weer bij jullie gevierd wordt, is een prachtige traditie geworden en dankzij de gastvrijheid van jou en Rein altijd weer enorm gezellig. Ik ben blij dat jij mijn paranimf wilt zijn. Anneke, we schelen maar anderhalf jaar en waren binnen ons gezin 'de kleintjes' We hebben vooral in onze pubertijd een periode veel samen opgetrokken, waar ik goede herinneringen aan heb. Je hebt wat werk betreft ook de bewuste keuze gemaakt om alsnog de HBO-V te gaan doen en deze in maart succesvol afgerond. Hartstikke goed! In mijn ziekteperiode ben jij een aantal keren mee geweest naar ziekenhuis, dat waren niet altijd de gemakkelijkste gesprekken, maar wat was het fijn om jou naast me te hebben, dank daarvoor. Ik wil jullie bedanken voor alle liefde en onvoorwaardelijke steun in de afgelopen jaren. Ondanks onze grote verschillen in karakter en soms ook nog wel in mening is de rode draad dat we er voor elkaar zijn als het nodig is en ik kan daarmee alleen maar blij en dankbaar zijn!

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Lieve Fred. We zijn al 33 jaar samen en deze maand 25 jaar getrouwd. En op de een of andere manier wordt het nooit saai en is het tot nu toe dan ook nog niet gelukt om in een sleur te belanden. We hebben zowat alles beleefd wat er in een relatie aan uitdagingen aan te gaan is en het is niet altijd gemakkelijk geweest, maar we vonden elkaar altijd weer. Ook jij hebt in de loop van het leven op werkgebied allerlei paden bewandeld met daarbij de nodige frustraties, maar je bent nooit bij de pakken neer gaan zitten. Dat jij een hele periode thuis voor gezin en huishouden hebt gezorgd, maakte dat ik meer kon werken en mij daardoor verder kon ontwikkelen. Ook dat hebben we samen gedaan, je was er voor mij, had geen last van ego-problemen omdat jij thuis zat en ik doorging. Dat heb ik enorm gewaardeerd en de kinderen vonden het heerlijk dat jij thuis was. Op je 46ste alsnog gestart met de SPW en een heel aantal jaren met veel plezier in de gehandicaptenzorg gewerkt. In 2017 ook nog 'even' je diploma voor MBO-verpleeg-

kundige in ontvangst mogen nemen. Dat maakt mij super trots! Dat je nu je plek gevonden lijkt te hebben in de palliatieve thuiszorg voelt als een groot cadeau, maar wel één die je helemaal zelf verdiend hebt.
De laatste (promotie)jaren zijn niet gemakkelijk geweest. Mijn ziekteperiodes, die samenvielen met jouw opleiding waren intens. Mijn grote twijfels over het wel of niet doorgaan met de promotie heb ik veelvuldig met jou gedeeld, waarbij je altijd weer een luisterend oor had of een (letterlijk) brede schouder. Na het eerst heel ver weggegooid te hebben en ervan overtuigd te willen stoppen was daar aan het eind van de zomer in 2017 in één keer die knop om, ik moest het afmaken. Ook toen stond je opnieuw voor 100% achter mij. Zonder jouw niet aflatende liefde en steun had ik dit niet gered. Het feit dat jij de lay-out van mijn boekje hebt gemaakt en we samen een prachtige omslag hebben ontworpen een is enorme kers op de taart. Dank.

Someone who really loves you
sees what a mess you can be
how moody you can get
how hard you are to handle
but still wants you in their life
(unknown)

About the author

About the author

Hannie (Johanna) Kuipers was born on November 13th, 1966 in Grootegast, the Netherlands. After finishing the HAVO in Leek, she followed education as a nurse at the 'Stichting Opleiding centrum Gezondheidszorg Oost Groningen' in Winschoten. In 1989 she received her nursing degree while working as a nurse in 'Delfzicht Ziekenhuis' in Delfzijl. After her graduation, she worked as a nurse in Beatrixoord Haren at the department for tuberculosis patients for 2 years and, next, at the Martini Ziekenhuis Groningen at the department of vascular surgery for 6 years. From 1998 to 2000 she worked at the short stay department at Delfzicht Ziekenhuis Delfzijl.

In 2000 she started the Dialysis Nursing specialization at the Dialysis Center Groningen and graduated in December 2001. Next, she worked for 8 years as a dialysis nurse. She became interested in doing research because of the data collection work she did as a member of the vascular access committee. In January 2008 she started with the postgraduate Course 'Clinical Research Coordinator' at the Transfergroup Rotterdam, which she completed successfully in April 2009. She participated as a research nurse in several research projects like studies on the acute effect of hemodialysis on heart function and cerebral blood flow. In 2009 she started an observational study on intradialytic hypotension in hemodialysis patients. In 2013 after the first publication, she started her PhD project on intradialytic hypotension which resulted in this thesis besides her work as a research nurse.

List of publications

1. **Kuipers J**, Usvyat LA, Oosterhuis JK, Dasselaar JJ, de Jong PE, Westerhuis R, Sands JJ, Wang Y, Kotanko P, Franssen CFM. Variability of pre-, intra-, and postdialytic blood pressures in the course of a week: a study in Dutch and US chronic hemodialysis patients. Am J Kidney Dis 2013;62:779-788.

2. **Kuipers J**, Oosterhuis JK, MD, Krijnen WP, Dasselaar JJ, Gaillard CAJM, Westerhuis R, Franssen CFM. Prevalence of intradialytic hypotension, clinical symptoms and nursing interventions - a three-months prospective study of 3818 hemodialysis sessions. BCM Nephrology 2016 Feb 27;17(1):21.

3. Ipema JR, **Kuipers J**, Westerhuis R, Gaillard CAJM, van der Schans CP, Krijnen WP, Franssen CFM. Causes and consequences of interdialytic weight gain.Kidney Blood Press Res 2016;41:710-720.

4. Assa, S, Hummel YM, Voors AA, **Kuipers J**, Groen H, de Jong PE, Westerhuis R, Franssen CFM. Changes in Left Ventricular Diastolic Function During Hemodialysis Sessions. Am J Kidney Dis 2013;62:549-556.

5. Assa S, Hummel YM, Voors AA, **Kuipers J**, Westerhuis R, de Jong PE, Franssen CFM. Hemodialysis-induced regional left ventricular systolic dysfunction: prevalence, patient and dialysis treatment-related factors and prognostic significance. Clin J Am Soc Nephrol, 2012;7:1615-1623.

6. Ettema EM, **Kuipers J**, Groen H, Kema I, Westerhuis R, de Jong PE, Franssen CFM. Vasopressin release is enhanced by the Hemocontrol biofeedback system and could contribute to better haemodynamic stability during haemodialysis. Nephrology Dial Transplant 2012;27:3263-70.

7. Assa S, Hummel YM, Voors AA, **Kuipers J**, Westerhuis R, Groen H,. Bakker SJL, Muller Kobold AC , van Oeveren W, Struck J, de Jong PE, Franssen CFM. Hemodialysis-Induced Regional Left Ventricular Systolic Dysfunction and Inflammation: A Cross-sectional Study. Am J Kidney Dis. 2014 ;64:265-73.

8. Ettema EM, **Kuipers J**, Assa S, Bakker SJ, Groen H, Westerhuis R, Gaillard CA, Gansevoort RT, Franssen CF. Changes in Plasma Copeptin Levels during Hemodialysis: Are the Physiological Stimuli Active in Hemodialysis Patients? PLoS One*. 2015 May 14;10(5):e0127116. doi: 10.1371/journal.pone.0127116.*

9. Ettema EM, Zittema D, **Kuipers J**, Gansevoort RT, Vart P, De Jong PE, Westerhuis R, Franssen CFM. Dialysis Hypotension: A Role for Inadequate Increase in Arginine Vasopressin Levels? A Systematic Literature Review and Meta- Analysis. *Am J Nephrol 2014;39:100–109.*

10. Solmaz Assa, **Hannie Kuipers**, Esmee Ettema, Carlo A. Gaillard, Wim P Krijnen, Yoran M Hummel, Adriaan A Voors, Joost P van Melle, Ralf Westerhuis, Antoon Willemsen, Riemer H.J.A. Slart, Casper FM Franssen. Effect of isolated ultrafiltration an isovolemic dialysis on myocardial perfusion and left ventricular function as sessed with 13N-NH3 PET and echocardiography. *Am J Physiol Renal Physiol, nov 2017, 00368.2017*

11. Polinder-Bos HA, Vállez García D, **Kuipers J**, Elting JWJ, Aries MJH, Krijnen WP, Groen H, Willemsen ATM, van Laar PJ, Strijkert F, Luurtsema G, Slart RHJA, Westerhuis R, Gansevoort RT, Gaillard CAJM, Franssen CFM. Hemodialysis Induces an Acute Decline in Cerebral Blood Flow in Elderly Patients. *J Am Soc Nephrol* in press.

12. Esmee Ettema, **Johanna Kuipers**, Martijn van Faassen, Henk Groen, Arie M. van Roon, Joop D. Lefrandt, Ralf Westerhuis, Ido P. Kema, Harry van Goor, Ron T. Gansevoort, Carlo A.J.M. Gaillard, Casper F.M. Franssen. Effect of plasma sodium concentration on blood pressure regulators during hemodialysis: A randomized crossover study *BMC Nephrology 2018 aug 19:214 doi.org/10.1186/s12882-018-0997-z*

13. Harmke A. Polinder-Bos, Jan Willem J. Elting, Marcel J.H. Aries, David Vállez García, Antoon T.M. Willemsen, Peter J. van Laar, **Johanna Kuipers**, Wim P Krijnen, Riemer H.J.A. Slart, Gert Luurtsema, Ralf Westerhuis, Ron T. Gansevoort, Carlo A.J.M. Gaillard, Casper F.M. Franssen. Changes in cerebral oxygenation and cerebral blood flow during hemodialysis - a simultaneous near-infrared spectroscopy and positron emission tomography study. *Journal of Cerebral Blood Flow & Metabolism dec 2018; doi.org/10.1177/0271678X18818652*