Hemodiafiltration maintains a sustained improvement in BP compared to conventional hemodialysis in children - the HDF, Heart and Height (3H) study

Abstract

Background Hypertension is prevalent in children on dialysis and associated with cardiovascular disease. We studied the blood pressure (BP) trends and the evolution of BP over 1 year in children on conventional hemodialysis (HD) vs. hemodiafiltration (HDF).

Methods This is a post hoc analysis of the "3H – HDF-Hearts-Height" dataset, a multicenter, parallel-arm observational study. Seventy-eight children on HD and 55 on HDF who had three 24-h ambulatory BP monitoring (ABPM) measures over 1 year were included. Mean arterial pressure (MAP) was calculated and hypertension defined as 24-h MAP standard deviation score (SDS) ≥95th percentile.

Results Poor agreement between pre-dialysis systolic BP-SDS and 24-h MAP was found (mean difference −0.6; 95% limits of agreement −4.9–3.8). At baseline, 82% on HD and 44% on HDF were hypertensive, with uncontrolled hypertension in 88% vs. 25% respectively; $p < 0.001$. At 12 months, children on HDF had consistently lower MAP-SDS compared to those on HD ($p < 0.001$). Over 1-year follow-up, the HD group had mean MAP-SDS increase of +0.98 (95%CI 0.77–1.20; $p < 0.0001$),

Key words:

Hemodialysis (HD); Hemodiafiltration (HDF); children; blood pressure (BP); mean arterial pressure (MAP); ambulatory blood pressure monitoring (ABPM)

Introduction:

Hypertension is common among children on dialysis[1], is often inadequately controlled[2], and is causally associated with adverse cardiovascular outcomes[3,4]. Hypertension (HTN) can cause left ventricular hypertrophy (LVH) and vascular stiffness[5], that are key pathogenic mechanism for early cardiovascular events [6,7]. Appropriate management of blood pressure (BP) in children with chronic kidney disease (CKD) and on dialysis is important to prevent cardiovascular morbidity and reduce mortality[8]. Recently two large, prospective multicenter studies in children with CKD have shown that HTN is highly prevalent and associated with LVH and vasculopathy even in early CKD[9,10], with an increase in prevalence of HTN as CKD progresses.

Previous studies have not identified therapeutic modifications to control BP adequately and around 30% of children with CKD on antihypertensive treatment have uncontrolled hypertension. The "3H - HDF-Hearts-Height" study, a multicenter, longitudinal study in children receiving hemodiafiltration (HDF) compared to conventional hemodialysis (HD), showed that subclinical cardiovascular disease is prevalent in children on dialysis, with attenuated progression of vascular changes in children receiving HDF compared to conventional HD.[11,12] HTN was significantly more common in HD compared to HDF patients, but the risk factors for HTN and effects of different dialysis modalities in controlling BP were not explored. In addition, 3H is one of the only studies in adults or children on HDF that has utilized 24-hour ambulatory BP monitoring (ABPM) to characterize HTN, uniquely allowing an in-depth analysis of the BP profile, daytime and nocturnal HTN, as well as comparing ABPM with the routinely used pre-dialysis systolic and diastolic BP measurements.

In this study we perform a post-hoc analysis of the 3H data in order to determine the risk factors associated with the evolution of BP over a one-year follow-up.

Methods:

Data collection

This is a post-hoc analysis of the '3H – HDF, Hearts and Height' dataset. 3H was a multicenter, non-randomized, parallel-arm intervention study that was performed across 28 pediatric dialysis centers in 10 countries, following for one year children who were receiving renal replacement therapy with either HD or HDF. Full details are described in the publications on study design[6] and primary outcomes[8]. Here we focus on BP control, the evolution of hypertension over the 12 months follow-up, risk factors for hypertension including dialysis related parameters and effect of anti-hypertensive medications in BP control.

Of 177 children recruited, 133 children (78 [74%] on HD and 55 [77%] on HDF) completed 12 months' follow-up and were included in this post-hoc analysis. Of the 44 children excluded, 35 (80%) progressed to transplantation and 9 moved center or were lost to follow-up. As previously described, at baseline the HD and HDF patients were comparable for age, sex, race, underlying kidney disease, time on dialysis before start of the 3H study, previous transplantation, type of vascular access and residual renal function[8,6]. At baseline, 26 (33%) on HD and 27 (49%) on HDF were on dialysis at the, with a median of dialysis vintage of 24.5 (18–52) and 29.5 (17–53.3) months respectively (p = 0.91). As with all dialysis studies, incident patients were allowed a period of stability on dialysis before inclusion in the 3H study and had a median dialysis vintage of 1.03 (0.2–1.7) and 1.4 (0.61–1.9) months in the HD and HDF groups (p = 0.69) respectively. As previously described[8], within-center comparisons on incident patients on HD and HDF in the five largest centers, contributing 28 (36%) patients on HD and 18 (33%) on HDF, showed no difference in patient demographics or MAP-SD score between patients on HD and HDF (p>0.05 for all).

Measurements

Children underwent 24-h ambulatory BP monitoring (ABPM) using the Spacelab ABPM portable device (Spacelabs 90,207–2Q) as previously described[9]. ABPM and all BP measures were recorded in the mid-week dialysis period. All patients had three ABPM measurements (baseline, 6 and 12 months). The 24-hour BP measurements were obtained every 15 min during the day and every 30 min at night. For further analysis ABPM profiles were divided into daytime (08:00 to 20:00 h) and nighttime periods (24:00 to 06:00 h). Routine measurements of systolic and diastolic BP measured by auscultation with a standard sphygmomanometer before the start of dialysis were collected, and the mean over the previous 4-weeks

was used for analysis. Office and ambulatory BP were normalized for age, sex and height and expressed as standard deviation scores (SDS)[9]. Systolic and diastolic BP SDS were derived from the National High Blood Pressure Education Program Working Group (NHBPEP) Fourth report[10].

Definition of variables

The time–averaged 24-h MAP was used for primary analyses and hypertension defined as 24-h time–integrated MAP exceeding the 95th percentile[9]. Patients on antihypertensive medication were referred to as having controlled or uncontrolled hypertension if their 24-hour MAP was below or above the 95th percentile respectively. Hypertension was also defined based on systolic and diastolic BP SDS according to the European Society of Hypertension guidelines[11] that define hypertension as a persistently elevated systolic or diastolic BP above the 95th percentile for sex, age and height measured on at least three separate occasions. The cut-off age considered in these guidelines is 16 years, beyond which the absolute values for defining hypertension in adults must be used11. More recently, the American Heart Association (AHA) guidelines have moved this age cut-off to 13 years[12,13]. The European Society of Hypertension guidelines have been used throughout this document, but comparison made with the AHA guidelines. As for MAP, uncontrolled hypertension was defined as presence of hypertension (above the 95th percentile) when the patient was on anti-hypertensive therapy. Masked hypertension was defined as normal pre-dialysis systolic BP SDS but elevated 24-hour MAP SDS; white coat hypertension was defined as elevated pre-dialysis BP SDS but without MAP-hypertension.

SDS for height, weight and BMI were calculated, using the Centers for Disease Control and Prevention growth charts[14]. Interdialytic weight gain percentile (IDWG%), ultrafiltration volume per session and dialysate sodium levels, all expressed as the mean of the previous four mid-week dialysis sessions were recorded at baseline, 6 months and 12 months of follow-up. The 24-hour urine output measured in the inter-dialytic period at the same time intervals of 0, 6 and 12 months was recorded. and dialysate sodium levels.

Statistical analysis

MAP-SDS and pre-dialysis systolic and diastolic BP-SDS at 0 and 12 months are presented using box plots, stratified by age and dialysis modality. Univariable linear regression analysis was used to screen for parameters potentially associated with MAP-SDS at baseline. Parameters with p-value < 0.15 in univariable analysis were selected for a multivariable analysis. In addition, ultra-filtration rate was

excluded *a priori* from all multivariable analyses due to correlation with IDWG. Analyses considering the presence or absence of MAP-SDS defined hypertension at baseline were then performed using logistic regression. Analyses were then repeated considering daytime MAP, nighttime MAP and office BP. However, as office BP was not Normally distributed, we instead considered the presence/absence of hypertension using logistic regression, considering systolic or diastolic BP ≥ 95th percentile.

The evolution of MAP-SDS over the one year study period was examined considering all measurements taken on children at 0, 6 and 12 months. This was first examined descriptively, considering the exact time since baseline that the 6- and 12- months MAP measurements were taken. These were divided into five groups (5 – 7 months, 8 – 10 months, 11 -13 months, and 14 – 18 months plus baseline values) and plotted using a box plot, stratified by dialysis modality. Next, a multi-level linear regression model was conducted with an outcome of 24-hour MAP, using all available measurements from participants over the study period. An unstructured correlation matrix was used to account for repeated observations on individuals, with a random intercept and time since baseline. Changes over time were investigated and found to follow an approximately linear relationship, so was fit as a continuous variable, with an interaction to account for any differences in rate of change over time according to dialysis modality. The robustness of these results was examined in a sensitivity analysis, by fitting a linear regression model with generalized estimating equations (GEE) and found to be consistent. Daytime and nighttime MAP and office BP measurements were available at baseline and 12 months. Therefore, evolution of these measures was evaluated by considering the 12-month values using standard linear regression techniques.

The agreement of MAP-SDS with pre-dialysis systolic BP SDS both at baseline and month 12 was assessed using a Bland–Altman analysis. Statistical analysis was performed using the SPSS software version 25.0 (SPSS, Chicago, IL) and SDS version 9.3 (SAS Institute Inc, Cary, NC). Differences indicated by a two-sided p value of <0.05 were considered statistically significant.

Results:

Prevalence of hypertension at baseline

Blood pressure measured using ABPM at baseline The MAP-SDS was higher in patients on HD compared to those on HDF in all age groups (Figure 1A). Age, baseline IDWG%, baseline ultrafiltration volume and urine output were significantly associated with a baseline MAP-SDS ≥ 95th percentile on univariable analysis (Table 1), with higher baseline IDWG% (0.25; [95%CI 0.04 to 0.28]; p = 0.03) remaining associated in multivariable analysis. Overall 64 (82%) of children on HD and 23 (42%) patients on HDF had MAP-SDS > 95th percentile at baseline (Supplemental Table 1). In sub-group analyses of incident vs prevalent dialysis patients at baseline, no risk factors for MAP-SDS were found in the incident cohort, but in prevalent dialysis patients the IDWG% was a significant and independent risk factor (0.47; [95%CI 0.15 to 0.50]; p = 0.001; Supplemental Table 2) .

Ambulatory Blood Pressure at baseline In children on HD the systolic BP-SDS was significantly higher in the 5-10-year age group compared to older children (p = 0.02), whereas no difference was seen in the HDF cohort (p = 0.56; Supplemental Figure 1A). There was no difference in diastolic BP-SDS between HD and HDF patients in any age category (Supplemental Figure 2A). Using systolic BP-SDS based definitions, hypertension was present in 51 (65%) HD and 13 (24%) HDF patients at baseline. Hypertension using systolic BP-SDS was more common for those aged 5 to 10 years compared to > 15 years (OR 6.07; 95%CI 2.04 – 18.0; p=0.001) and higher baseline ultrafiltration volume (OR 1.07; 95%CI 1.02 - 1.13; p=0.01; Supplemental Table 3).

Longitudinal analyses

Evolution of BP status

The evolution of MAP-SDS over time is shown in Figure 4, showing an increase over time among those receiving HD, with a flatter change for those receiving HDF. In a longitudinal analysis (Table 2), 24-hour MAP-SDS increased in both HD and HDF patients over the 12-month study period, but with a significantly greater increase in HD (mean=+0.98 [95%CI 0.77 – 1.20] SDS; p<0.0001) compared to HDF (mean +0.15 [95%CI -0.10 to +0.40] SDS; p = 0.23). In addition, higher MAP-SDS was associated with higher IDWG% (0.13 [95%CI 0.06 to 0.19]; p = 0.0003) on multivariable analysis (Table 2).

Prevalence of hypertension at 12-months follow-up 69 (88%) of children on HD and 23 (42%) patients on HDF had MAP-SDS > 95th percentile at 12-months (Supplemental Table 1). The MAP-SDS was higher in patients on HD compared to those on HDF in all age groups (Figure 1B). As previously published, both incident and prevalent patients on HD increased their MAP-SDS from baseline to 12 months (p =0.007 and p =0.004, respectively), whereas there was no change in incident or prevalent patients on HDF (p = 0.38 and p =0.11, respectively)[8]. At 12-months, risk factors for systolic BP-SDS >95th percentile was the HD modality (OR 0.33; [95%CI 1.30 to 2.67]; p < 0.001; Supplemental Table 4). When the same analysis was performed using presence of systolic BP-SDS>95th centile as the dependent variable, HD modality (OR 4.92 vs HDF; 95% CI 2 – 12.1; p= 0.001), female gender (OR 3.47; 95% CI 1.5 – 7.7; p= 0.002) were independent risk factors for hypertension.

Daytime and Nighttime MAP-SDS analyses On multivariable analysis independent risk factors for day-time MAP hypertension at baseline was an higher IDWG% (0.22 [95%CI 0.04 to 0.4]; p = 0.01) , whereas on the 12-month analysis the HD modality and age > 15 years compared 5-10 years increased the risk for day-time hypertension at 12 months (0.25 [95%CI 0.13 to 0.36]; p = 0.00) and (0.26 [95%CI 0.06 to 0.45; p = 0.01) respectively. (Supplemental Tables 5A and 6A)

When night-time hypertension was considered the independent risk factors for hypertension at baseline was an higher IDWG% (0.26 [95%CI 0.09 to 0.43]; p = 0.003). On the 12-month analysis, the HD modality (0.47 [95%CI 0.32 to 0.63]; p = 0.001) and age > 15 years compared 5-10 years (0.25 [95%CI 0.07 to 0.42]; p = 0.01) were independent risk factors for nighttime hypertension at 12 months (Supplemental Tables 5B and 6B respectively).

Agreement between MAP-SDS and systolic BP-SDS

In both HD and HDF treatment modalities the agreement between systolic BP-SDS and MAP-SDS was investigated by a Bland Altman analysis (Figure 3A). At baseline the mean difference between MAP-SDS and systolic BP-SDS was -0.6 (95% Limits of Agreement (95% LoA) -4.9 to 3.8). Consistent results were found for the 12-month values (mean difference -1.42; 95% LoA -6.28 to 3.44; Figure 3B), suggesting poor agreement between the two measures. When the definition of hypertension was

considered as per the new AHA guidelines[13], only three children diagnosed as hypertensive with the European definition[11] were high-normal by AHA guidelines.

Anti-hypertensive treatment At baseline 43 (55%) of HD and 23 (42%) of HDF patients were on anti-hypertensive medications, but uncontrolled hypertension was present in 38 (88%) of HD and 6 (25%) of HDF patients (Figure 4A). At 12-months 45 (58%) on HD and 22 (40%) on HDF required anti-hypertensive medications, and uncontrolled hypertension was present in 42/45 (93.3%) on HD and 8/22 (36.3%) on HDF (Figure 4B).

11 (16.7%) children started one anti-hypertensive medications (9 on HD) and 2 (3%) of children on HD required two anti-hypertensive medications. Calcium channel blockers were the most commonly used (52 children; 39%), followed by angiotensin converting enzyme inhibitors or angiotensin II receptor blockers (36 children; 18.8%), beta blockers (22; 11.5%) and diuretics (5; 3.8%) of children. During the study period 47 (80%) of children who were not on anti-hypertensive therapy at baseline remained off anti-hypertensives; of these 27/33 (82%) on HD and 15/33 (45%) on HDF were hypertensive. Of the children taking one or more anti-hypertensives at baseline, 13 (19.4%) stopped all medications (2 on HD and 11 on HDF) and 10 (7.3%; 3 on HD and 7 patients in HDF) reduced the number of anti-hypertensive medications at 12 months.

Discussion

In this study we have shown that hypertension is prevalent in children on dialysis, and is significantly more common and increases more rapidly in children on conventional HD compared to a matched cohort on HDF. Over a 1-year follow-up the MAP-SDS increased by 1.03 SDS in HD patients while there was an attenuated and non-significant increase of 0.17 SDS in HDF patients. Significant and independent risk factors that correlated with change in the MAP-SDS were the dialysis modality, with xx greater risk of hypertension in the HD cohort, and the IDWG%%. Despite the use of antihypertensive medications, 86% on HD and 30% on HDF had uncontrolled hypertension, challenging their effectiveness in dialysis patients. Pre-dialysis BP measurements showed a poor correlation with ABPM and cannot be relied on in dialysis patients.

Although hypertension and its causal effects on LVH and cardiovascular disease are widely prevalent in dialysis patients, few studies have addressed the risk factors for hypertension in this unique cohort of pediatric dialysis patients, nor examined interventions to attenuate its progression. The high prevalence of hypertension in our cohort confirms previous studies showing that there is little improvement in the diagnosis and management of hypertension in children with CKD over the past decade despite recent guidelines20, and a better understanding of the risks of hypertension related cardiovascular disease1,10,14. The 3H study is the first multicenter, prospective, parallel-arm observational study in children that studies the evolution of hypertension and associated risk factors in children on HD and HDF.

Routine office BP measurements, the current cornerstone of hypertension management, do not reflect the true BP load recorded by the "gold standard" method of ABPM21. Given that the circadian BP rhythms are markedly impaired and that the burden of nocturnal hypertension is high among patients with CKD21, it is to be expected that ABPM provides a more accurate estimate of hypertension. As ABPM facilitates the identification of specific BP phenotypes (such as masked, white coat and isolated nocturnal hypertension), the wider adoption of this technique may also improve the management of hypertension, particularly in children on dialysis. 24-hour ambulatory BP samples the patient over a range of extracellular fluid volumes and uremic states, and therefore has a greater prognostic significance, and correlates better with end-organ damage, including left ventricular hypertrophy, than a single pre-dialysis BP measurement22,23. In the 3H study we measured the 24-hour mean ambulatory BP at three key study points, whereas all other randomized trials and most

cohort studies on HDF in adults have relied on a single pre-dialysis BP reading to define hypertension. Indeed, when comparing hypertension determined by ABPM and pre-dialysis BP, we found that of the children with ambulatory hypertension, only 57% on HD and 26% on HDF were identified by pre-dialysis systolic BP, even when mid-week pre-dialysis systolic BPs were averaged over a 4-week period. Two recent multicenter prospective studies in children with CKD have shown a similarly high proportion of masked hypertension (15 - 35%)5,21, stressing the importance of performing regular ABPM measurements. The Cardiovascular Comorbidity in CKD (4C) study has shown that approximately 20% of children with CKD3-5 have masked hypertension5, with similar rates of 37% with masked hypertension in the Chronic Kidney Disease in Childhood (CKiD) study21. However, in a sub-group analysis of the CKiD study the same authors report that in a cohort of CKD patients not on dialysis the clinic BP taken in a protocol-driven setting were not inferior to ABPM in the discrimination of BP-related adverse outcomes of LVH or progression of CKD24.

We found that a significant risk factor for hypertension was a high IDWG%% implying that hypertension in dialysis patients is closely related to their volume status. IDWG%% is a surrogate for sodium mass removal rate, a key factor in the management of patients on chronic HD, both because a high IDWG% leads to a supra-physiological expansion of extracellular water, leading to volume overload, and also, because excessive ultrafiltration during HD carries the risk of relative hypovolemia, reduction of myocardial perfusion and myocardial stunning, with negative effects on cardiac status25.. A lower IDWG%% suggests lower ultrafiltration rates per session and greater hemodynamic stability. As shown in the 3H outcomes paper, a lower IDWG%% was directly associated with fewer symptoms of headaches, dizziness or cramps, fewer hypotensive episodes and a shorter post-dialysis recovery time13 , all of which led to improved school attendance and greater physical activity in children on HDF compared to those on conventional HD. In addition to improved fluid removal, greater clearance of middle-molecular-weight uremic toxins by HDF may also play a role in greater hemodynamic stability on HDF. A pediatric study evaluated the inflammatory state and the changes in myocardial function in children on conventional HD after 6 months of switching to HDF, and showed that HDF significantly reduced the high sensitivity-CRP and improved diastolic function, but this did not correlate with improved BP.26 Fischbach et al have shown that pre-dilution HDF performed 6 days per week leads to normalization of BP and amelioration of LVH27 but it is not clear if increased dialysis frequency or HDF per se resulted in improvement in the fluid status. Other authors report that there are no difference in BP control between HDF and HD patients28,29;

randomized trials are required to definitively answer this question. Myocardial stunning, the development of segmental wall motion abnormalities with ventricular dysfunction due to decreased coronary artery perfusion, has been documented in children on conventional HD30,31 and associated with higher ultrafiltration rates, and negatively with cooled dialysate. A recent cross-over trial comparing myocardial perfusion by intradialytic MRI in 12 adults treated by HD and HDF did not show any difference in the rates of myocardial stunning when equal levels of cooling were employed32.

In our cohort the use of antihypertensive medications on extracorporeal dialysis (HD or HDF) did not improve BP control - 88% of children on HD and 42% on HDF had uncontrolled hypertension at 12-months follow-up. Several studies have confirmed that antihypertensive medications are not useful in dialysis patients33,34,35,36, yet a significant number of dialysis patients in our multicenter study were prescribed antihypertensive medications. The key to BP control in dialysis patients is much more related to maintaining a good fluid balance34,35. It is important to avoid an overestimation of the optimal weight that can lead to an inadequate ultrafiltration prescription, resulting in chronic fluid overload and left ventricular strain, an important predictor of cardiovascular morbidity and mortality37,38. On the other hand, underestimation of dry weight puts patients at risk of higher ultrafiltration rates, resulting in intradialytic hypotension symptoms. High ultrafiltration rates in children on HD have been correlated with higher left ventricular mass index LVMI39; and children with an IDWG% of >4 % are at high risk of LVH39,40. Bioimpedence spectroscopy improve the clinical assessment of hydration status in children on dialysis and correlates with established biomarkers such as NT proBNP as well as peripheral pulse pressure and left ventricular end-diastolic diameter41.

There are some limitations of our study, partly related to small numbers of pediatric dialysis patients, even though 3H included 40% of the pediatric extracorporeal dialysis cohort in Europe. 3H was a non-randomized study, largely because all centers were not able to offer both HD and HDF modalities. Given the small numbers of children on dialysis, both incident and prevalent patients on dialysis were included; however, the two groups were comparable and on sub-group analysis there were no significant differences in the risk factors for hypertension in the two groups. 3H study was designed to have a short follow-up period of only 1 year as high transplantation rates in children preclude a longer study. There were a higher than predicted drop-out rate, mostly due to transplantation, so the study was underpowered for the number of patients on HDF. Data on systolic and diastolic BP and antihypertensive therapy were not available for the 6-month follow-up and this limited our

analysis. Cooling of dialysate in the HD cohort was not performed as the original 3H study design aimed to compare HDF with conventional HD, however, this is an area for future study. Body composition monitoring was not performed due to a lack of machine availability in some centers.

In conclusion, our study of BP control in children on HD and HDF shows that hypertension is prevalent in children on dialysis, but patients on HDF have an attenuated increase in BP compared to those on HD, with an almost 1 SD greater increase in MAP in HD compared to HDF cohorts. Improved fluid management, as indicated by lower IDWG%%, rather than antihypertensive medications was associated with normal MAP-SDS. HDF may be a superior dialysis modality for in-centre dialysis, confirmation through randomized trials is required.

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All authors to declare COI

Figure Legends

Figure 1. 24 hour mean arterial BP (MAP) SDS by treatment modality and age groups at baseline **(1A)** and 12-months **(1B).** MAP-SDS is consistently lower in HDF compared to HD patients in all age categories both at baseline and 12-months. When compared by treatment modality, there is no difference in MAP-SDS in HD or HDF patients in the three age groups (baseline p=0.19 and p=0.17 respectively and 12-months p=0.07 and p=0.13 respectively). Box plots show the median, the 25^{th} and 75^{th} percentile within the shaded box area. The 5^{th} and 95^{th} percentile are shown as extremes of the whisker plots. The dotted line shows the SDS $\geq$ 1.65.

Figure 2. Changes in MAP-SDS over time calculated with the mixed-model. We measured the p values for the difference between every time points in HD and HDF children. For HD (baseline – 6 months p = 0.015; 6 months – 9 months p = 0.89; 9 months – 12 months p = 0.006; 12 months – 15 months p = 0.77). For HDF (baseline – 6 months p = 0.069; 6 months – 9 months p = 0.9; 9 months – 12 months p = 0.058; 12 months – 15 months p = 0.79)

Figure 3. Bland–Altman plot compares the systolic BP-SDS measurements vs MAP-SDS measurements at baseline by plotting the difference between the two measurement techniques against their averages. The mean deviation (dotted line) and the 95% confidence interval of the mean (continuous lines) are shown.

Figure 4. Distribution of hypertension in HD and HDF patients based on MAP-SDS at baseline (4A) and 12-months (4B). The Y-axis indicates the percentage of patients in each category. Striped columns represent BP < 95° percentile and filled columns represent BP > 95° percentile.

Table Legends

Table 1. Univariable and multivariable linear regression analysis of risk factors for MAP-SDS at baseline.

Table 2. Univariable and multivariable multi-level regression analysis of risk factors for MAP-SDS during the 12-month study period

Table 1 - Univariable and multivariable linear regression analysis of risk factors for MAP-SDS at baseline.

	Univariable analysis n = 133			Multivariable analysis n = 133		
	Beta	95% CI	p value	Beta	95% CI	p value
Gender (male vs female)	0.38	-0.17, 0.95	0.17			
Age						
5 – 10 years	0.00	-	0.03	-		
10 -15 years	-0.03	-0.74, 0.68		-0.05	-0.26, 0.15	0.63
> 15 years	0.75	0.04, 1.45		0.15	-0.07, 0.36	0.18
Ethnicity, Caucasian	0.44	-0.19, 1.07	0.16			
Underlying renal diagnosis						
Dysplasia	0.00	-				
Glomerulonephritis	0.05	-0.12,0.23	0.57			
other	-0.11	-0.27, 0.07	0.24			
Previous transplant (yes vs no)	0.45	-0.21, 1.12	0.19			
Baseline BMI (per 1 SDS higher)	0.05	-0.13, 0.22	0.58			
Baseline ultrafiltration rate (per 1L higher)	0.3	0.1, 0.47	0.001			
Baseline sodium dialysate (per 1 higher)	0.09	-0.08, 0.26	0.31			
Baseline IDWG (per 1% higher)	0.27	0.09, 0.4	0.002	0.25	0.04-0.28	0.03
Urine output (24h)						
< 200 ml	0.00	-		0.00	-	
200 – 500 ml	-0.06	-0.17, 0.16	0.94	0.04	-0.14-0.22	0.65
> 500 ml	-0.17	-0.35, 0.1	0.06	-0.14	-0.32-0.06	0.10

Table 2 - Univariable and multivariable multi-level regression analysis of risk factors for MAP-SDS during the 12-month study period

	Univariable analysis n = 133			Multivariable analysis n = 133		
	Beta	95% CI	p-value	Beta	95% CI	p-value
Annual Increase on HDF	0.17	-0.08, 0.41	0.19	0.15	-0.10, 0.40	0.23
Annual Increase on HD	1.03	0.82, 1.24	<0.0001	0.98	0.77, 1.20	<0.0001
Difference in annual increase (HD vs HDF)	0.87	+0.54, +1.19	<0.0001	0.83	+0.51, +1.15	<0.0001
Gender (male vs female)	+0.54	-0.06, +1.15	0.08	+0.44	-0.08, 0.97	0.10
Age						
5-10 years	0.00	-	0.01	0.00	-	0.10
10-15 years	+0.16	-0.62, -0.94		0.14	-0.54, 0.83	
>15 years	+1.04	0.26, 1.81		0.66	-0.02, 1.34	
Underlying diagnosis						
Dysplasia	0.29	-0.40, 0.97	0.56			
Glomerulonephritis	0.42	-0.42, 1.25				
other	0.00	-				
Previous transplant (yes vs no)	0.46	-0.27, 1.20	0.22			
Baseline BMI (per 1 SDS higher)	0.08	-0.14, 0.30	0.45			
Current ultrafiltration rate (per 1L higher)	0.27	0.14, 0.40	<0.0001			
Current sodium dialysate (per 1 higher)	0.04	-0.02, 0.10	0.20			
Current IDWG (per 1% higher)	0.18	0.11, 0.26	<0.0001	0.13	0.06, 0.19	0.0003
Urine output (24h)						
<200	0.73	0.37, 1.09	0.0003	0.30	-0.03, 0.63	0.16
200-500	0.34	-0.06, 0.73		0.29	-0.05, 0.63	
>500	0.00	-		0.00	-	

Figure 1 A

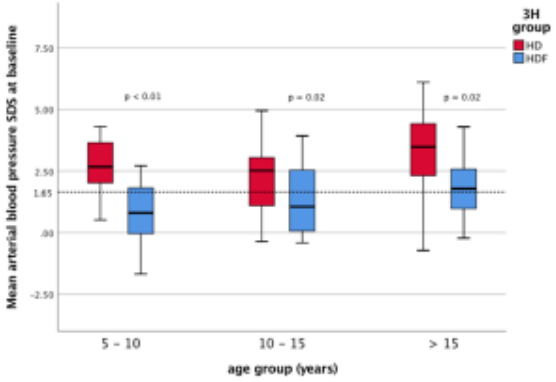


Figure 1 B

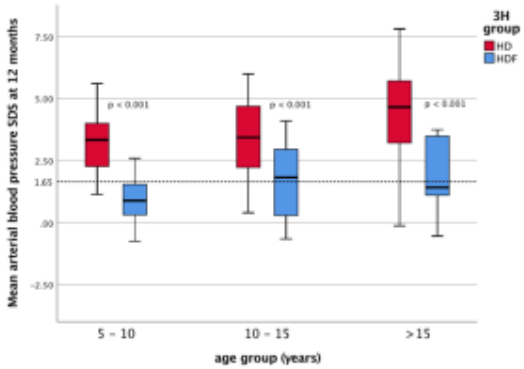


Figure 2

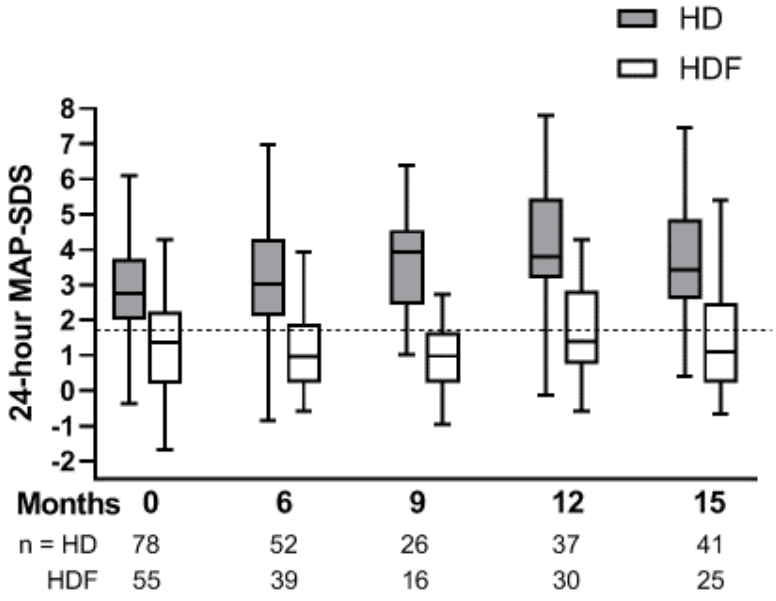


Figure 3A

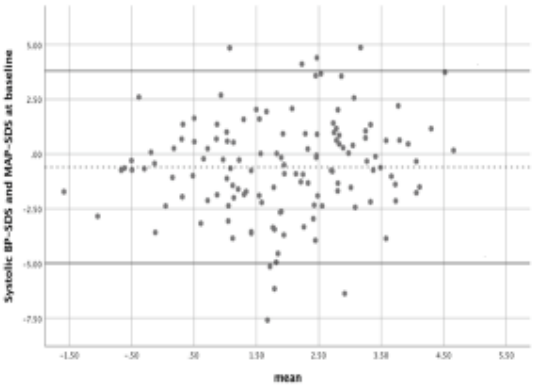


Figure 3B

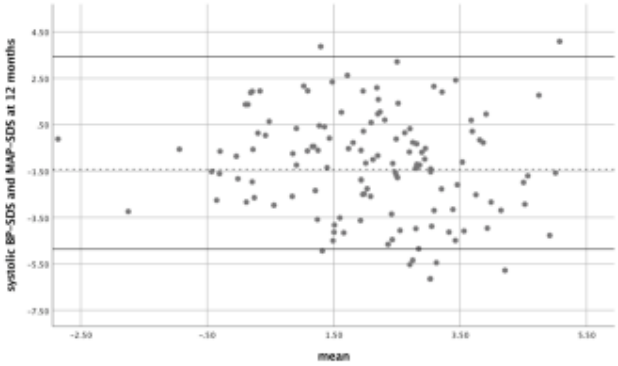


Figure 4A

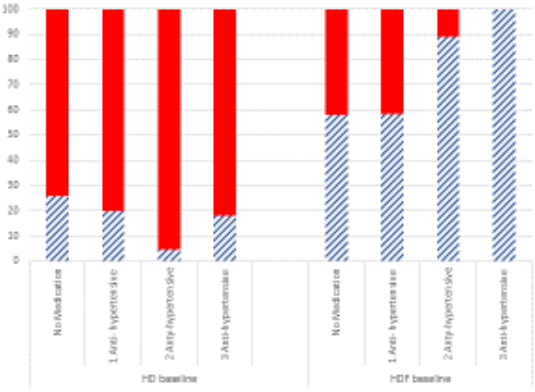
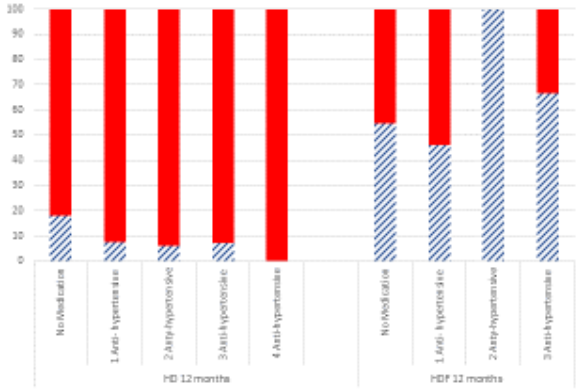


Figure 4B



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