Effects of Hemodiafiltration versus Conventional Hemodialysis in Children with ESKD: The HDF, Heart and Height Study

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ABSTRACT

Background Hypertension and cardiovascular disease are common in children undergoing dialysis. Studies suggest that hemodiafiltration (HDF) may reduce cardiovascular mortality in adults, but data for children are scarce.

Methods The HDF, Heart and Height study is a nonrandomized observational study comparing outcomes on conventional hemodialysis (HD) versus postdilution online HDF in children. Primary outcome measures were annualized changes in carotid intima-media thickness (cIMT) SD score and height SD score.

Results We enrolled 190 children from 28 centers; 78 on HD and 55 on HDF completed 1-year follow-up. The groups were comparable for age, dialysis vintage, access type, dialysis frequency, blood flow, and residual renal function. At 1 year, cIMT SD score increased significantly in children on HD but remained static in the HDF cohort. On propensity score analysis, HD was associated with a +0.47 higher annualized cIMT SD score compared with HDF. Height SD score increased in HDF but remained static in HD. Mean arterial pressure SD score increased with HD only. Factors associated with higher cIMT and mean arterial pressure SD-scores were HD group, higher ultrafiltration rate, and higher β2-microglobulin. The HDF cohort had lower β2-microglobulin, parathyroid hormone, and high-sensitivity C-reactive protein at 1 year; fewer headaches, dizziness, or cramps; and shorter postdialysis recovery time.

Conclusions HDF is associated with a lack of progression in vascular measures versus progression with HD, as well as an increase in height not seen in the HD cohort. Patient-related outcomes improved among children on HDF correlating with improved BP control and clearances. Confirmation through randomized trials is required.

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Children with ESKD and on dialysis have a very high burden of cardiovascular risk factors, including chronic fluid overload and mineral dysregulation with hyperphosphatemia and hyperparathyroidism.[1,2] Preclinical cardiovascular disease (CVD), measured through surrogate markers such as carotid intima-media thickness (cIMT), pulse wave velocity (PWV), and left ventricular hypertrophy, is prevalent in CKD,[3,4] with accelerated progression on dialysis.[1,5–8] Vascular calcification,[6,7,9] cIMT,[9] hypertension, and cardiovascular function[10] all worsen with increasing time on dialysis, implying that the dialysis milieu, including biochemical derangements and hemodynamic stresses, lead to a rapidly worsening cardiovascular risk profile; 30% of deaths in children on dialysis are due to cardiovascular events.[11] Even within a short period of 3 months on conventional hemodialysis (HD), biomarkers of inflammation, oxidative stress, and endothelial dysfunction were shown to increase.[12] Clearly, the *sine qua non* is prevention, but no studies in children have shown how to prevent the inexorable progression of CVD in patients on dialysis.

Outcomes on dialysis cannot be further improved by increasing the flux or efficiency of HD.[13] Hemodiafiltration (HDF) utilizes a combination of diffusive and convective solute transport through a highly permeable membrane,[14–17] thereby achieving clearance of middle-molecular-weight solutes unlike conventional HD. In addition, HDF is shown to achieve better intradialytic hemodynamic stability[18] and the ultrapure dialysate that is used in HDF reduces low-grade endotoxemia, which can develop in patients on HD.[14] In adults on dialysis, a recent randomized, controlled trial (RCT), the Estudio de Supervivencia de Hemodiafiltración Online (ESHOL) study, has shown a survival benefit of HDF compared with high-flux HD.[19] ESHOL, as well as pooled data[20] from the Convective Transport study (CONTRAST),[21] Turkish Online Haemodiafiltration[22] studies and French Convective versus Hemodialysis in Elderly (FRENCHIE)[23] have indicated a critical dose-response relationship between the magnitude of the convection volume and survival.

HDF has been used in children for four decades, but there are few data on outcomes. Small, single-center, retrospective analyses have shown an association with improved nutrition and growth,[24] reduced inflammation,[12,25,26] regression of left ventricular hypertrophy,[25,27,28] and improved anemia control,[25] but these studies utilized daily HDF, variably with pre- or postdilution techniques. We performed a multicenter, prospective, observational cohort study to test the hypothesis that HDF dialysis modality is associated with an improved cardiovascular risk profile, growth, and quality of life, compared with use of conventional HD in children.[29] The HDF, Heart and Height (3H) study includes the largest cohort of children and adolescents on dialysis to date, and compares cardiac and vascular function, growth, biochemical markers, and patient-related outcome measures in children receiving postdilution online HDF versus conventional HD.

Significance Statement

Although studies suggest that hemodiafiltration (HDF) may reduce cardiovascular mortality in adults, data in children are sparse. In this observational multicenter study, the authors compared HDF and hemodialysis (HD) in children with ESKD, finding that annualized changes in well validated subclinical markers of cardiovascular disease, including carotid intima-media thickness SD scores, were lower in HDF and associated with lower 24-hour ambulatory BP and intradialytic weight gain. Height increased only in the HDF cohort. Compared with the HD cohort, the HDF cohort also had better self-reported outcomes, with fewer headaches, less dizziness or cramps, and shorter recovery time after dialysis sessions. The study provides proof-of-concept data that HDF is a safe treatment that may have benefits over conventional HD in children. A randomized trial is required to confirm these findings.

METHODS

Cohort

3H is a multicenter, nonrandomized, parallel-arm intervention study performed within the International Pediatric Hemodialysis Network. Details of the dialysis procedures, study organization, investigational plan, data acquisition and handling, and statistical analyses have been previously described.[29] The trial is registered with Clinicaltrials.gov, under identifier NCT02063776. This study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by both a central medical research committee and local ethics boards at each participating center. Written informed consent was obtained from all parents, and assent from children, where appropriate.

Inclusion criteria were incident and prevalent patients between 5 and 20 years of age undergoing postdilution HDF or HD on a 4 hours per session, three times per week schedule. A minimum follow-up of 12 months was required. Children in whom a living donor kidney transplant was planned, those on predilution HDF, and prevalent patients on HD in whom the single pool Kt/V was <1.2 in the month preceding recruitment were excluded. The coprimary end points were an annualized change in cIMT SD score and height SD score. Multiple exploratory end points relating to cardiovascular measures, nutrition, growth, and quality of life were assessed as previously described.[29]

Dialysis Procedures

The decision to perform HD or HDF was left to the treating physicians and made according to usual center practice. Seventeen out of 28 (61%) centers included both patients on HD and those on HDF, whereas seven centers had only patients on HD and four centers had only patients on HDF. Standardized procedures for HD and HDF were provided.[29] Efforts to achieve the highest possible blood flow rate in both groups, and a target convection volume of 12–15 L/m^2 body surface area in the HDF cohort was aimed for. Ultrapure dialysate (defined as containing <0.1 CFU/ml and <0.03 endotoxin unit/ml) was used for all HDF and some HD procedures

(Table 1), depending on center availability. Water quality was measured every 3 months locally, and every 6 months in a central laboratory. All dialysis-related parameters are expressed as the average of the previous four midweek dialysis sessions.

Investigational Plan and Study Organization

All imaging studies (cIMT, PWV, and echocardiogram) and 24-hour ambulatory BP monitoring for mean arterial pressure (MAP) were performed annually, and anthropometric measures, biochemical testing, and health-related quality of life

Table 1. Demographics of children at study entry (only includes those with 1-year follow-up)

Demographics	HD	HDF	*P*-Value
Number	78	55	
Age, yr, *n* (%)			0.45
5–10	17 (21.8)	14 (25.5)	
10–15	27 (34.6)	23 (41.8)	
15–20	34 (43.6)	18 (32.7)	
Females, *n* (%)	32 (41.0)	31 (56.4)	0.08
Race, %			
White/Asian/black/Mixed or other	75.6/6.4/5.2/12.8	70.9/10.9/10.9/7.3	0.48
Anthropometry			
Height SD score	−2.24 (−3.08 to −1.04)	−1.66 (−2.94 to −0.91)	0.21
Body mass index SD score	−0.11 (−0.85 to +0.92)	−0.17 (−0.96 to +0.77)	0.61
Underlying renal diagnosis, %			
Dysplasia/GN/cystic kidney disease/others or unknown	42.3/20.5/3.9/33.3	38.2/20.0/5.5/36.3	0.66
Comorbidity/genetic conditions, *n* (%)			0.76
Impaired cognitive development	15 (19.2)	13 (23.6)	
Impaired motor development	5 (6.4)	6 (10.9)	
Ocular or hearing abnormalities	12 (15.4)	11 (20.1)	
Cardiopulmonary	5 (6.4)	7 (12.7)	
Other abnormalities	20 (25.6)	13 (23.6)	
Genetic disorder/defined syndrome	17 (21.8)	17 (30.9)	
Previous dialysis			
Incident patients in study, %	52 (66.7)	28 (51)	0.11
If previous dialysis			
PD/HD/HDF/HD and PD sequentially	13/7/1/5	12/3/7/4	0.43
Time on dialysis before start of 3H study			
Incident patients, mo	1.03 (0.2–1.7)	1.4 (0.61–1.9)	0.69
Prevalent patients, mo	24.5 (18–52)	29.5 (17–53.3)	0.91
Previous transplant			
Yes, %	14 (18.0)	15 (27.3)	0.20
Time with functioning graft, mo	30 (14–72)	72 (10–119)	0.34
Vascular access, *n* (%)			
Central venous line/arteriovenous fistula/arteriovenous graft	49 (62.8)/28 (35.9)/1 (1.3)	30 (54.6)/23 (41.8)/2 (3.6)	0.48
Blood flow, ml/min	200 (180–250)	200 (170–250)	0.38
Blood flow corrected for body surface area	190.3 (157.7–214.8)	183.7 (141.2–225.1)	0.96
Residual renal function (urine volume in ml; %)			
0	32 (41.0)	21 (38.2)	
0–200	18 (23.1)	7 (12.7)	0.32
201–500	11 (14.1)	9 (16.4)	
500+	17 (21.8)	18 (32.7)	
Dialysis prescription			
Time on dialysis, h/wk	12 (11.83–12.20)	12 (11.81–12.22)	0.96
Dialyzer, high/mid/low flux (%)	57 (73)/9 (15)/12 (12)	55 (100)	<0.001
Water quality, ultrapure (%)	40 (51.2)	55 (100)	<0.001
Dialysate sodium, %			0.39
≤138 mmol/L versus ≥138 mmol/L	56 (71.8)/22 (28.2)	37 (67.3)/18 (32.7)	
Dialysate calcium			0.78
1.25 versus 1.5 versus 1.75 mmol, %	48 (62)/24 (30)/6 (8)	34 (62)/18 (33)/3 (5)	
Dialysate bicarbonate <34 versus 34–36 versus >36 mmol/L, %	34 (44)/34 (44)/10(12)	23 (41)/34 (56)/10 (4)	0.74

Data are presented as number (*n*) with percentage or as median and interquartile range. All dialysis-related parameters are expressed as the mean of the previous four midweek dialysis sessions. PD, peritoneal dialysis.

questionnaires were assessed 6-monthly, with 6-monthly data entry throughout the study period. All vascular scans and blood tests were performed before a midweek dialysis session. Six regional coordinators, who were centrally trained and provided with portable ultrasound and Vicorder for PWV measurement, visited the study centers annually to perform vascular scans, collect blood samples, and complete data entry. Observers performing the vascular measures were not blinded to the patients' dialysis modality, but all analyses was performed offline by blinded assessors. In addition, to ensure optimal reproducibility and validity of the cIMT data, 20 pairs (baseline–follow-up) of scans were reanalyzed by a second blinded observer, removing all identifiers and the pairing sequence, with intraobserver and interobserver coefficient of variation <3.5%.

Statistical Analyses

A detailed statistical analysis plan is previously described[29] and detailed in the Supplemental Material.

RESULTS

Patient Characteristics at Baseline

From September 2013 to January 2016, 190 children were recruited from 28 pediatric dialysis centers in ten countries (Turkey, 48; United Kingdom, 40; France, 22; Italy, 20; Germany, 19; Greece, 16; Serbia, eight; Canada, eight; Poland, seven; and Czech Republic, two). A total of 78 (74%) children on HD and 55 (77%) on HDF completed 1-year follow-up (Figure 1). There were 44 dropouts; 35 (80%) after transplantation. The transplanted cohort was comparable to those who completed 1-year follow-up in all demographic characteristics. Four children moved from HDF to HD, mainly because of issues with water quality in their center. Both incident (median 1 month on dialysis before study start) and prevalent patients were included. Baseline characteristics of children who completed 1-year follow-up are shown in Table 1.

Details of Dialysis Therapy

The median blood flow rate (standardized to body surface area) was similar between groups (Table 1) and independent of the type of vascular access. The median convection volume achieved in the HDF group was 13.2 (interquartile range, 12.1–14.3) L/m^2. There was no significant correlation between the convection volume (adjusted to body surface area) and age, weight, and the type of vascular access but it correlated with the blood flow rate/body surface area ($P<0.001$; $R^2=0.32$). There were no significant intraindividual changes in the type of dialyzers used, water quality, blood flow, or convective volume over the study duration, but the number of children with a dialysate sodium >138 mmol/L decreased from 33% to 24% in the HDF group and increased from 28% to 37% in the HD group.

A total of 34% on HD and 35% on HDF ($P=0.98$) had a decrease in their urine output (categorized into four groups; Table 1), whereas 66% had no change in urine output over the study period. The interdialytic weight gain percentile (IDWG%; expressed as the mean of the previous four midweek dialysis sessions) was consistently lower in HDF compared with HD, and this was reflected in lower ultrafiltration

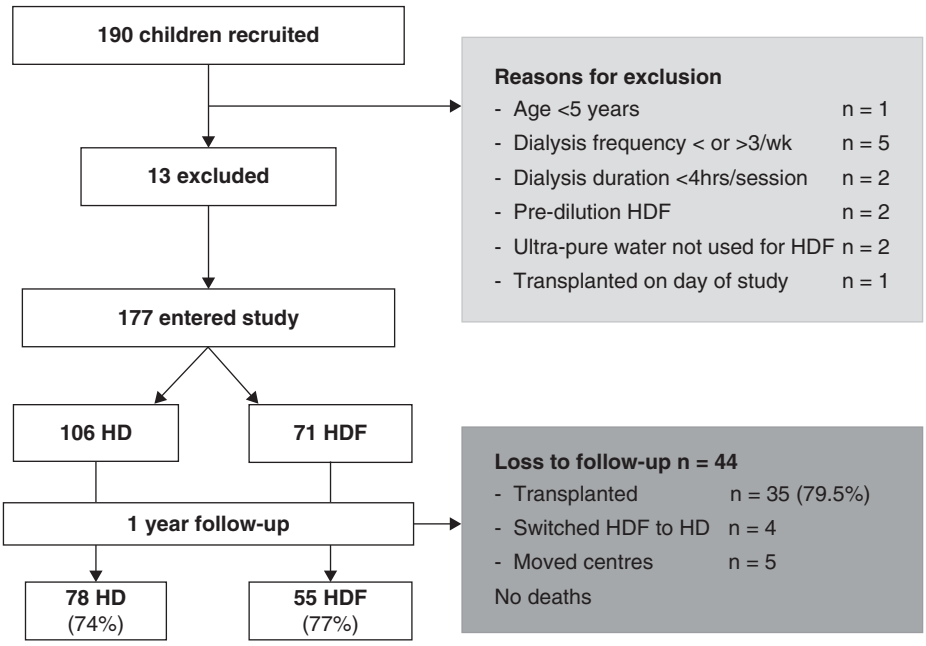

Figure 1. Flow chart of study populations, including the number of children who were screened, underwent randomization, and completed 1-year follow-up in the HD and HDF arms.

rates (adjusted to body surface area) in HDF (Supplemental Table 1). Both incident and prevalent patients on HDF had lower IDWG% and ultrafiltration rates compared with HD (P=0.04 and P=0.03, respectively).

Primary Outcome Measures

Annualized Change in cIMT SD Score

At baseline there was no difference in the cIMT SD score between groups (Figure 2A, Supplemental Table 1). At 1-year follow-up, the cIMT SD score increased by median 0.41 in the HD group and decreased by −0.07 in the HDF group (P=0.02), resulting in a significant difference between groups at 12 months (P<0.01). After adjusting for potential confounders, age, sex, country, blood flow, and water quality, using the propensity score approach, children on HD had a +0.47 greater increase in annualized cIMT SD score change (95% confidence interval [95% CI], 0.07 to 0.87; P=0.02) compared with those on HDF. Predictors of higher cIMT SD score at 12 months were HD group, higher IDWG% and ultrafiltration rate, higher systolic BP, and higher β2-microglobulin.

Among incident patients on HD and HDF, there was no difference in cIMT SD score at baseline (P=0.14; Figure 2B). Prevalent patients on HD had a significantly higher cIMT SD score at baseline compared with HDF (P=0.04; Figure 2C). cIMT SD score increased significantly from baseline in incident and prevalent patients on HD (Δ=+0.64; P<0.001 and; Δ=+0.34, P=0.002, respectively), but was static in

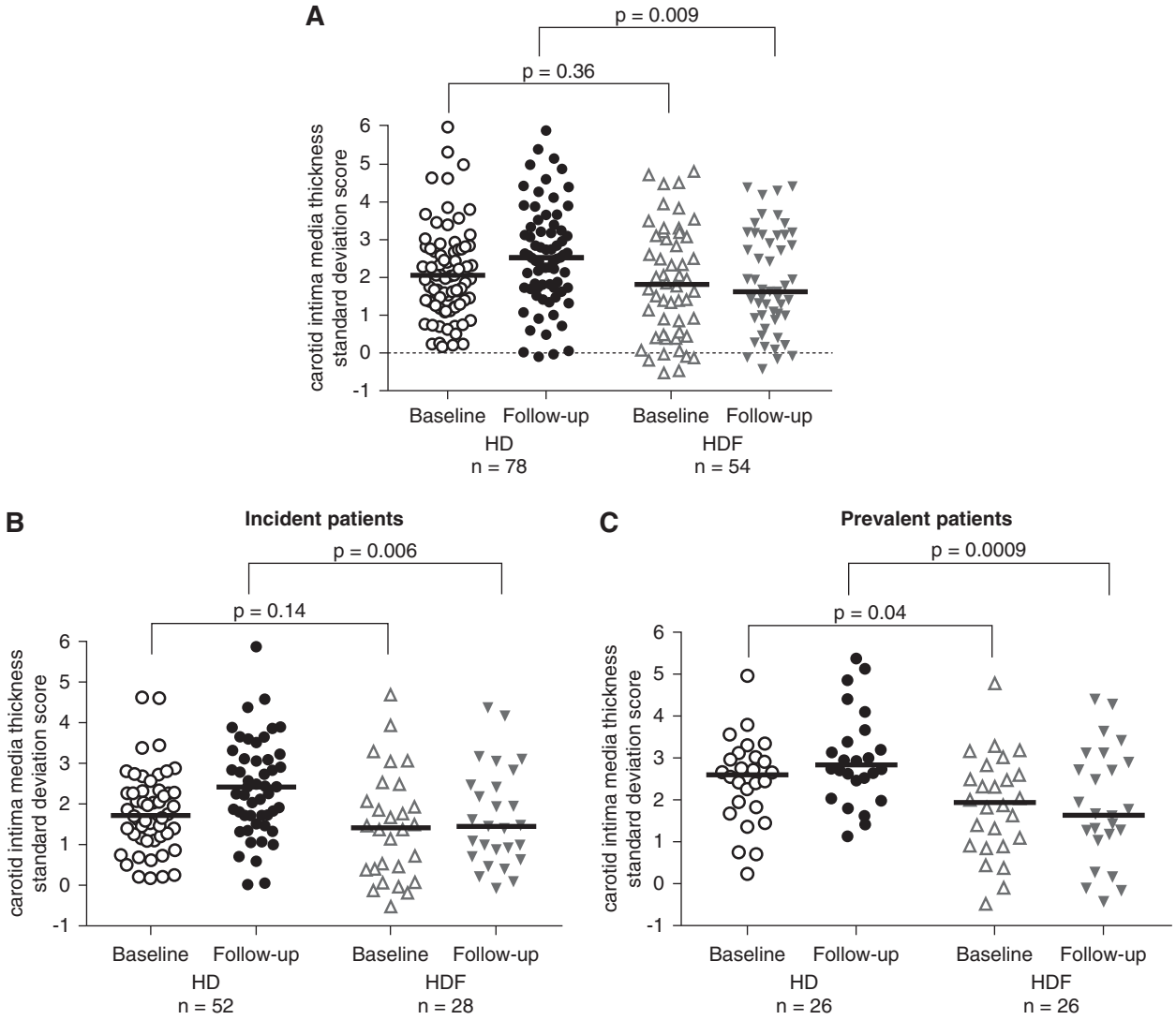

Figure 2. At 12 months the cIMT SD score increased in the HD group and remained static in the HDF group. (A) cIMT SD scores at baseline and 12 months for HD and HDF cohorts are shown. cIMT increases significantly from 0 to 12 months in the HD cohort (P=0.02) but remains static in HDF (P=0.89), with a significant difference between groups at 12 months (P=0.009). (B and C) cIMT SD score at baseline and 12 months in incident and prevalent patients on HD and HDF. Data are shown as median and interquartile range. Within-group analyses performed by Wilcoxon matched-pairs signed-rank test (see Supplemental Table 1) and HD versus HDF cohorts compared by Mann–Whitney U test.

patients on HDF (Δ=−0.13, *P*=0.85 and Δ=−0.04, *P*=0.58, respectively).

Annualized Change in Height SD Score

At baseline, there was no difference in the height SD score of children on HD or HDF (Figure 3, Table 1). The annualized change in height SD score remained static in HD, but showed a small but statistically significant increase in HDF (Δ=−0.16; *P*=0.02), so that patients on HDF were taller than patients on HD at 12 months (*P*=0.04). Although pubertal status was not assessed, in children above 13 years of age (*n*=49 on HD and *n*=32 on HDF), the median annualized change in height SD score was significant between groups (HD Δ=−0.01 and HDF Δ=+0.15; *P*=0.005).

A total of 15% on HD and 25% on HDF (*P*=0.18) were on growth hormone treatment (GH-Rx; Supplemental Table 2); there was a similar change in height SD score in the GH-Rx HDF group compared with the HD group (*P*=0.08). On propensity score–adjusted analysis (that adjusted for GH-Rx) the annualized change equated to a 0.18 SD score greater increase in height in the HDF group compared with the HD group (95% CI, 0.02 to 0.33; *P*=0.03). There was an inverse association between final height SD score and β2-microglobulin levels (β=−0.07 per 10 mg/L higher level; 95% CI, −0.14 to 0; *P*=0.05).

Exploratory End Points of Cardiovascular Status

Details of PWV, 24-hour MAP, and left ventricular mass index (LVMI) are described in Figure 4 and Supplemental Table 1.

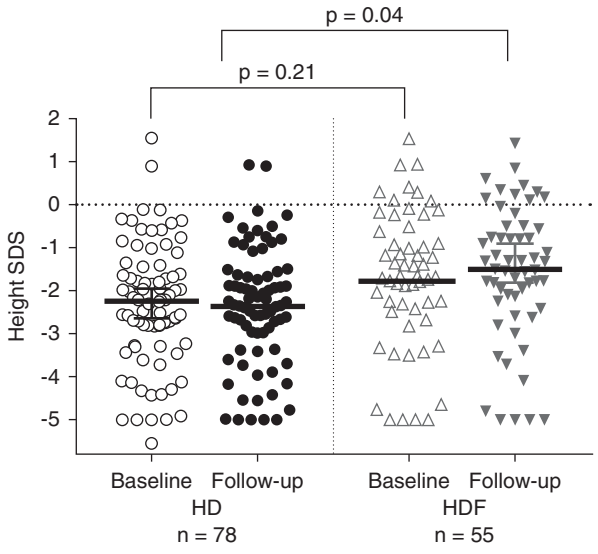

Figure 3. Improved height SD score in HDF compared to HD. The figure shows change in height SD score in the HD and HDF arms at baseline and 1-year follow-up. Data are shown as median and interquartile range. Within-group analyses performed by Wilcoxon matched-pairs signed-rank test and HD versus HDF cohorts compared by Mann–Whitney *U* test. At 12 months the height SD score in the HDF group was higher than in the HD group (*P* = 0.04).

PWV SD score was higher in HD compared with HDF both at baseline and 12 months. In both groups, PWV SD score decreased over the study period, but there was no significant difference in the annualized change in PWV SD score between groups (*P*=0.49). On propensity score analysis, there was no difference in PWV SD score change between HD and HDF cohorts (0.58; 95% CI, −0.2 to 1.36; *P*=0.15). Predictors of higher PWV SD score at 12 months were higher IDWG%, higher systolic and diastolic BP SD score, lower hemoglobin, and higher parathyroid hormone (PTH). Among incident patients, the baseline PWV SD score was higher in HD compared with HDF cohorts, and decreased over 12 months in both groups. However, prevalent patients on dialysis showed no difference in PWV SD score at baseline, and no change over 12 months in either group.

MAP SD score, derived from 24-hour ambulatory BP monitoring performed in the midweek interdialytic interval, was higher in patients on HD compared with patients on HDF both at baseline and 12 months (*P*<0.001 for both). In patients on HD, the MAP SD score increased from baseline to 12 months (*P*<0.001), whereas in patients on HDF it remained static (*P*=0.35). At 12 months, 61 (81%) children on HD and 20 (37.7%) on HDF had an MAP SD score above 2 D of normal (*P*<0.001). On propensity score analysis, the HD cohort had a 0.65 (95% CI, 0.16 to 1.13; *P*=0.01) higher annualized MAP SD score change compared with the HDF group. There was no correlation with dialysate sodium levels. Predictors of higher MAP SD score at 12 months were HD group, higher IDWG%, higher β2-microglobulin, and higher PTH values. Both incident and prevalent patients on HD increased their MAP SD score 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).

LVMI at baseline was comparable between HD and HDF (*P*=0.07), and although it did not show a significant increase over 12 months in either group (*P*=0.40 for HD and *P*=0.55 for HDF), the LVMI was higher in patients on HD at 12 months (*P*=0.02). On propensity score analysis, the HD cohort had a 5.6 (95% CI, −0.79 to 11.99; *P*=0.09) higher LVMI change compared with the HDF group, but this did not reach statistical significance. Predictors of higher LVMI at 12 months were HD group, higher IDWG% and ultrafiltration rate, higher MAP SD score, higher PTH, lower hemoglobin, and higher body mass index SD score. Incident patients on HD had an increase in LVMI (*P*=0.004), whereas no change was seen in incident patients on HDF (*P*=0.73), or any prevalent patients (*P*=0.08 for HD and *P*=0.43 for HDF) from 0 to 12 months.

Sensitivity Analyses

All analyses were repeated using a standard adjustment approach with univariable and multivariable analyses for potential confounders of vascular measures (Supplemental Tables 3 and

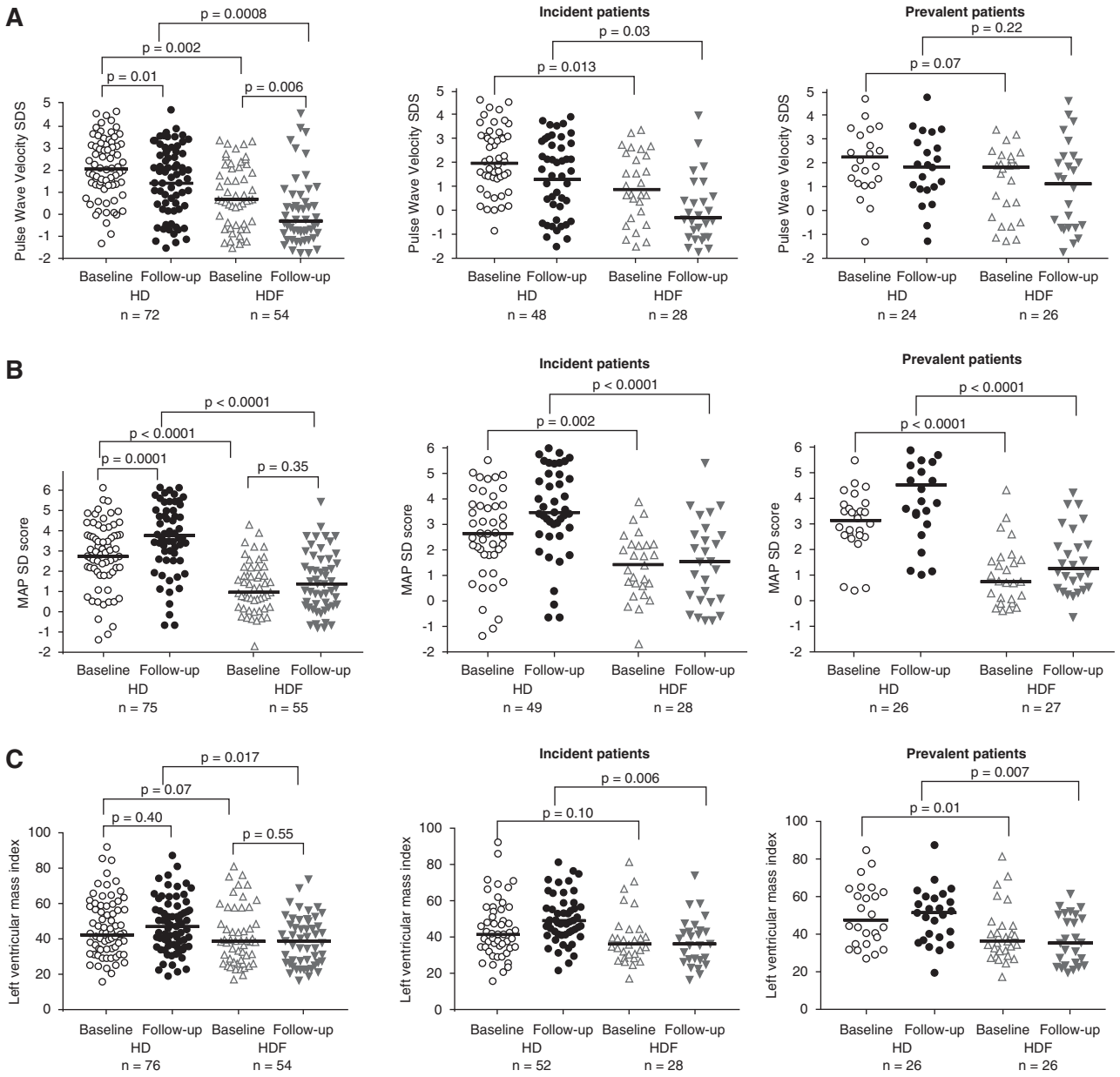

Figure 4. Changes in secondary outcome measures. (A) PWV SD score, (B) 24-hour MAP SD score, and (C) LVMI at baseline and 12 months in the HD and HDF cohorts. PWV SD score, MAP SD score, and LVMI at baseline and 12 months in incident and prevalent patients on HD and HDF. Data are shown as median and interquartile range. Within-group analyses performed by Wilcoxon matched-pairs signed-rank test (see Supplemental Table 1) and HD versus HDF cohorts compared by Mann–Whitney *U* test.

4). All results were consistent for HDF versus HD comparison, except for the inclusion of baseline LVMI, which unmasked an association between ΔLVMI and modality (β=5.96; 95% CI, 1.49 to 10.44; P=0.009). Within-center comparisons on incident patients on HD and incident patients on HDF at baseline was performed in the five largest centers, contributing 28 (36%) patients on HD and 18 (33%) patients on HDF. There was no difference in patient demographics, PWV SD score, or MAP SD score between patients on HD and patients on HDF in any center (P>0.05 for all).

Biochemical Measures and Medications in Patients on HD and Patients on HDF

Biochemical values measured predialysis at baseline and 12 months are shown in Figure 5 and Supplemental Table 2.

Dialysis Dose and Middle Molecule Clearance

The Kt/V and urea reduction ratio were comparable at baseline in HD and HDF groups, and did not change over the study period in either group. β2-microglobulin levels were lower in HDF compared with HD, both at baseline (only in prevalent

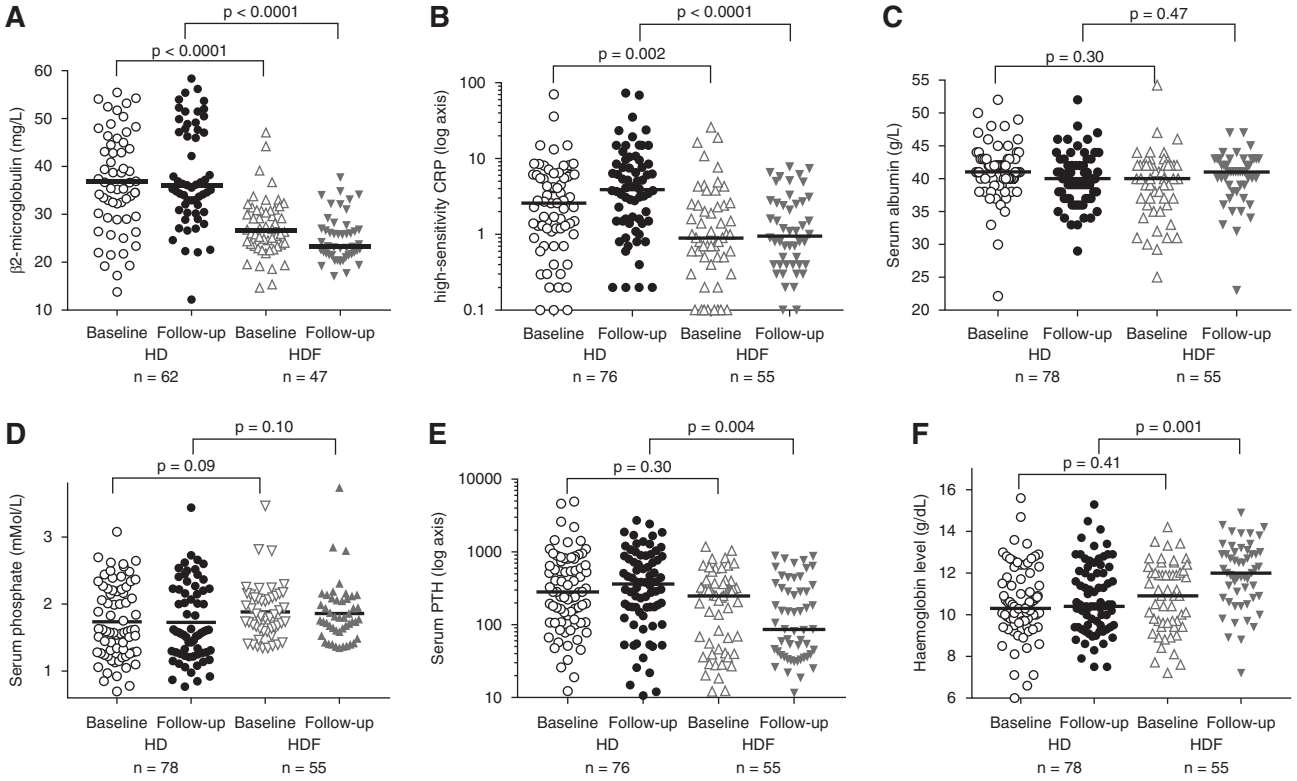

Figure 5. Predialysis biochemical measurements in HD and HDF groups at baseline and 12-months follow-up. (A) β2-microglobulin level, (B) hs-CRP (log10 axis), (C) serum albumin levels, (D) serum phosphate levels, (E) serum PTH levels (log10 axis), and (F) serum hemoglobin levels. Data are shown as median and interquartile range. Within group analyses performed by Wilcoxon matched-pairs signed-rank test (see Supplemental Table 2) and HD versus HDF cohorts compared by Mann–Whitney *U* test.

HD and HDF groups) and 12 months ($P<0.001$ in both groups; Figure 5A). Over the study period, β2-microglobulin levels were unchanged in the HD cohort ($P=0.57$) but decreased from month 0 to month 12 in HDF ($P=0.02$). There was no correlation between convection volume (adjusted to body surface area) and β2-microglobulin in the HDF cohort. In HD, β2-microglobulin levels were comparable in patients on high- and low-flux dialyzers. In a subgroup of patients with >500 ml loss of urine volume from 0 to 12 months, β2-microglobulin increased in the HD cohort but was unchanged in the HDF cohort.

Inflammation

High-sensitivity C-reactive protein (hs-CRP) levels increased in HD but remained static in HDF over the study period (Figure 5B), with a significant difference between groups both at baseline and 12 months. Incident patients on HDF also had lower hs-CRP levels compared with HD ($P=0.03$). In patients on HD, hs-CRP levels were not associated with use of ultrapure versus pure water. There was no difference in serum albumin between groups and no change from 0 to 12 months in either group (Figure 5C).

CKD–Mineral and Bone Disorder Measures

Serum phosphate levels were similar between HD and HDF cohorts (Figure 5D), but a significant difference in PTH (Figure 5E) was noted: PTH levels declined in the HDF cohort over 12 months ($P=0.03$) but remained static in HD ($P=0.13$), resulting in lower levels in the HDF group compared with the HD group at 12 months ($P=0.004$). There was no difference in the type of phosphate binders or cinacalcet use, and serum and dialysate calcium levels, and 25-hydroxy vitamin D levels were similar between groups.

Anemia and Its Management

Hemoglobin levels were comparable between groups at baseline, and remained unchanged in HD but increased in HDF from 0 to 12 months, resulting in significantly higher hemoglobin levels at 12 months between groups (Figure 5F). There was no difference in ferritin levels, type of iron supplementation or its dosage between groups. There was no difference in erythropoietin dosage between groups. There was a lower prevalence of darbepoetin use in HD compared with HDF but the dose of darbepoetin was higher in HD at baseline and 12 months.

Hospitalization

There was no difference in the number of hospitalizations: 24 (30.8%) admissions in 19 patients with HD and 19 (34.5%) admissions in 17 patients with HDF ($P=0.76$). The reasons for

hospitalization were access-related issues (15.4% patients with HD and 18.2% patients with HDF), infections (five in each group), and uncontrolled hypertension and hyperkalemia (two in each group).

Patient-Related Outcome Measures

Children or their parents completed 6-monthly questionnaires in their local language, reporting on the impact of dialysis on their lives. The postdialysis recovery time was longer in the HD compared with HDF cohort (Figure 6A), with 70% patients on HDF reporting no postdialysis symptoms or a recovery time of only a few minutes compared with 32% patients on HD. On multiple ordinal regression analysis (adjusted for country) the significant predictors of a shorter postdialysis recovery time were the dialysis modality (adjusted odds ratio, 4.81; 95% CI, 2.29 to 10.12; $P<0.001$) and the interdialytic weight gain percentage (adjusted odds ratio per 1% change, 0.79; 95% CI, 0.67 to 0.93; $P=0.005$). At final follow-up, children on HDF were more active (Figure 6B), with 44% of children on HDF playing sport compared with only 13% of children on HD. School attendance was higher in patients on HDF (Figure 6C): 15% of patients on HD versus 3% of patients on HDF reported that they did not feel well enough to attend school after dialysis. Additional schooling on dialysis was available to approximately 60% in each group and 23% in each group attended special needs schools.

At final follow-up, symptoms relating to fluid status, including headaches, dizziness, and cramps, were less common in the HDF cohort compared with the HD cohort (Figure 6, D–F). Symptoms of headaches and dizziness were most significant in those with the highest ultrafiltration volume per session, although those with the lowest tertile for hemoglobin also had the most severe dizziness. These symptoms correlated with postdialysis recovery time, but were independent of residual renal function and MAP SD score. There was no difference in sleep disturbances, pruritus, or restless leg syndrome between groups (Figure 6, G–I).

DISCUSSION

The 3H study has shown that subclinical CVD is prevalent in children on dialysis, and an attenuated progression of vascular changes is seen in a cohort of children receiving HDF compared with children receiving conventional HD. Within 1 year of conventional HD the cIMT increased by 0.41 SD score, whereas there was no change in patients on HDF. On fully adjusted analyses the annualized changes in both cIMT SD score and MAP SD score were significantly lower in patients on HDF compared with HD, correlating with improved fluid removal as well as clearance of middle-molecular-weight uremic toxins by HDF. Childrens' tolerance of HDF treatment was significantly better, although children were not blinded to treatment modality. Children are uniquely suited to study the effects of dialysis treatment on the cardiovascular system because of the absence of secondary pathologies typically present in adults, such as long-standing hypertension, diabetes, smoking, and preexisting CVD.

Although a number of biologically plausible explanations have been suggested for improved outcomes with HDF, observational studies, registries, and RCTs provide conflicting results, which to some extent can be explained by differences in the convection volume,[20] with patients achieving the highest convection volumes benefiting most. Detailed analysis of the CONTRAST study has shown that most of the variation in convection volume is explained by practice patterns, not patient characteristics.[30] In 3H we demonstrated that a high convection volume of 12–15 L/m^2 body surface area, equating to 20–23 L/session in adults, can be achieved in children by optimizing blood flow and setting a high filtration fraction (up to 33%) without increasing treatment time, as shown in adult patients on HDF.[31] Second, it has been suggested that optimal vascular access, and therefore improved blood flows, are associated with superior outcomes, irrespective of HD or HDF modality,[32] and randomization imbalance by vascular access may have confounded some previous RCTs.[19,23,32] In 3H, blood flow rates were comparable in both arms and independent of vascular access type, implying that any perceived benefits of improved blood flow alone did not account for improved outcomes.

In the 3H study, patients on HDF had lower ultrafiltration rates compared with HD. A low ultrafiltration rate facilitates vascular refilling during the dialysis session, reducing the propensity for hypotensive episodes, which in turn allows better patient tolerance with fewer headaches, dizziness, or cramps. Also, 3H showed that patients on HDF had a lower interdialytic weight gain, a surrogate for sodium mass removal rate, which has been associated with reduced left ventricular hypertrophy in children on dialysis.[33] Importantly, we measured the 24-hour mean ambulatory BP, the gold standard of BP measurement, whereas all of the RCTs on HDF and most cohort studies in adults have relied on single predialysis BPs. Ambulatory BP samples the patient over a range of extracellular fluid volume and uremic states, has greater prognostic significance, and correlates better with end-organ damage including left ventricular hypertrophy.[34,35] ESHOL, FRENCHIE, and several observational studies have shown that HDF improves intradialytic hemodynamic stability compared with HD.[18,19,23] Intradialytic hypotension reduces myocardial perfusion, and recurrent episodes may eventually lead to myocardial fibrosis, even in children.[36]

Because of the small number of children on dialysis (there are only approximately 450 children on extracorporeal dialysis in Europe[37]), both incident and prevalent patients on dialysis were included, reflecting the "real-life" situation of pediatric dialysis across Europe. The "incident" patients in our cohort were on dialysis for a median of 1 month, to stabilize and achieve the optimal dialysis program before the first study measures were recorded. We found that functional vascular measures that are exquisitely sensitive to changes in fluid status, such as MAP and PWV, were lower in incident patients on

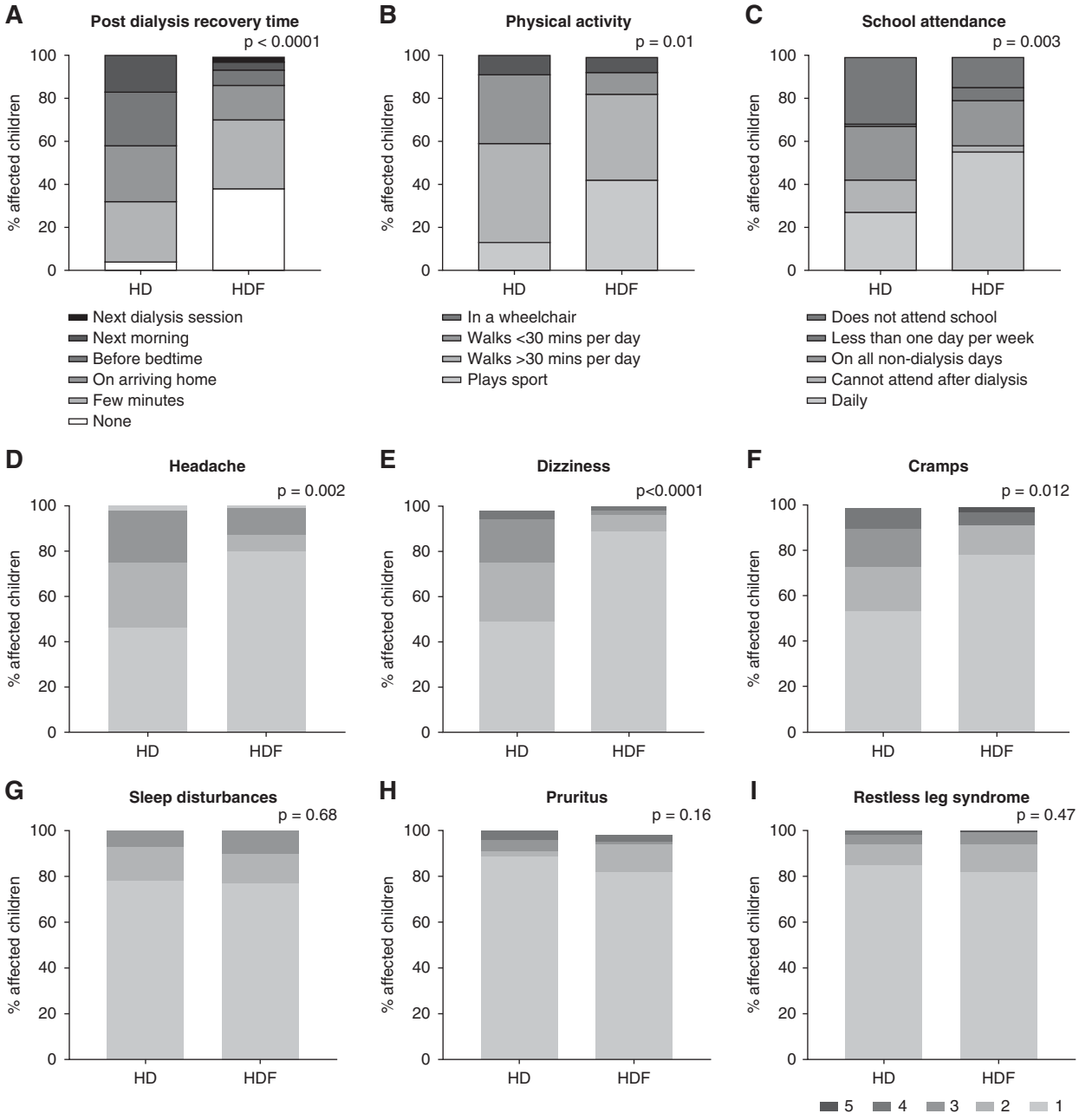

Figure 6. Improved patient-related outcome measures on HDF compared to HD. (A) Postdialysis recovery time, (B) physical activity index, and (C) school attendance, (D) Headaches, (E) dizziness, (F) cramps, (G) sleep disturbances, (H) pruritus, and (I) restless legs; individual scales for each measure shown on the figure. Graded on a scale of 1–5 (5 being most severe or frequent). Stacked bar charts showing the percentage of affected children on HD and HDF for each symptom with comparison between groups made by chi-squared test.

HDF compared with HD, with no further improvement over 1 year. A cohort study in adults has shown that HDF may improve vascular stiffness, although mechanisms remain unclear.[38] Similarly, biochemical measures including β2-microglobulin and hs-CRP were lower in incident patients on HDF. In SWITCH we have shown that in children who received HD for at least 3 months and were then switched to HDF, keeping all dialysis-related parameters and dialysis time constant, there was a significant improvement in inflammation, antioxidant capacity, and endothelial risk profile even within a short time (3 months) on HDF compared with HD.[12] Although there are no RCTs with only incident patients on dialysis, in a cohort study with over 1000 incident adult patients on dialysis, those on high-volume postdilution HDF had a 24% and 30% reduction in all-cause and cardiovascular mortality, respectively, compared with patients on high-flux

HD after propensity score matching to correct for indication bias.[39] Similarly, other national cohort studies have shown that HDF may have an additional survival benefit in incident patients.[40,41] On the basis of these data we suggest that HDF may be associated with an early improvement in fluid status and associated cardiovascular measures, and should be considered at initiation of maintenance dialysis.

We found a consistently lower β2-microglobulin level in patients on HDF, both at baseline and reducing further during the study period. Moreover, patients on HDF who had a significant loss in residual renal function during the study period were able to maintain constant β2-microglobulin levels, whereas levels increased in patients on HD. Our data are comparable with the CONTRAST and FRENCHIE studies.[21,23] We suggest that convective clearance by HDF compensates for the loss of residual kidney function. Further arguments for improved middle-molecular-weight clearance are the reduction in hs-CRP and PTH in patients on HDF, although of course, mechanisms other than clearance alone can modify their levels. Fibroblast growth factor 23, also a middle-molecular-weight substance, is shown to reduce by 32% on HDF.[42] Moreover, in the SWITCH study we have shown that when patients on HD were switched to HDF, using the same dialyzer, dialysis water quality, dialysis time, and blood flow speeds, within a period of 3 months there was a significant reduction in β2-microglobulin and hs-CRP, suggesting that improved clearances on HDF led to an improved biomarker profile.[12] Importantly, we did not see a fall in serum albumin levels in our study, and others have also reported a significant and sustained reduction in CRP with stable albumin levels, suggesting that HDF is a safe and well tolerated dialysis modality in the long term.[19,23,43,44]

Growth rate is a sensitive overall health parameter in children. We found a significant increase in height SD score in patients on HDF compared with patients on HD that was independent of GH-Rx. A single-center, retrospective study has shown impressive catch-up growth in children on an intensive 6 days per week regimen of HDF,[24] providing a large convective mass transport component. Convection may clear IGF-1–binding proteins and their metabolites that dampen the response to endogenous somatomedin and gonadotropins.[45,46] We were unable to assess the pubertal status of the children, and differences in height SD score do not take this into account. Interestingly, we showed an inverse correlation between height SD score increase and β2-microglobulin, suggesting that clearance of middle-molecular-weight compounds may partly alleviate GH-Rx resistance in patients on dialysis.

A further consideration for HDF over HD is the improved health-related quality of life perceived by children on HDF, but because the study is not blinded, results must be interpreted with caution. We found that patient-related outcome measures that are primarily associated with fluid status, such as the postdialysis recovery time, headaches, dizziness, and cramps, were less frequent and less severe in the HDF cohort compared with the HD cohort. Dialysis recovery time is a quantifiable, validated measure[47–49] that has been associated with long-term fatigue, depression, sedentary behavior, and mortality[50] and can reduce exercise and participation in social activities in adult studies.[47,48] We showed that lower interdialytic weight gain on HDF, implying lower ultrafiltration rates per session and greater hemodynamic stability, was strongly associated with fewer symptoms. This is supported by the FRENCHIE study wherein fewer symptomatic intradialytic hypotensive episodes and muscle cramps were reported in a vulnerable population of elderly patients on dialysis.[23] Similarly, ESHOL report a lower risk of stroke attributed to improved intradialytic hemodynamic stability in HDF.[19,51] However, in a randomized crossover trial where patients were blinded to dialysis type, there was no difference in postdialysis recovery time or health-related quality of life scores,[52] but this study had a higher incidence of intradialytic complications, including symptomatic hypotension and clotting,[52] than reported in most HDF studies. The Standardized Outcomes in Nephrology–Hemodialysis workgroup has identified fatigue as one of the most highly prioritized outcomes for dialysis patients and clinicians,[53] and we suggest that it is included in future studies in adults or children on dialysis.

This study provides evidence that can be used to inform the design of an RCT, which would provide definitive evidence of the effect of HDF on vascular and height outcomes in children. As this is the first large-scale study of HDF in children, it has demonstrated that HDF is a safe and feasible treatment, and that high convective volumes can be achieved in children. Also, it is feasible to follow a large, international cohort of children on dialysis, and perform a wide range of surrogate vascular measures with central data analysis and collection and analysis. We also caution that high loss to follow-up as a consequence of progression to transplantation must be anticipated. Although this censoring of follow-up is likely to be noninformative, it poses challenges with regards to the anticipated study sample size, and requires careful consideration of appropriate analysis techniques. Annualized change in cIMT SD score is an appropriate primary endpoint for such a clinical trial, but other important outcomes such as BP control may also be considered. The challenges of large RCTs in relatively rare diseases is well recognized, and so innovative RCT designs such as adaptive designs or Bayesian analysis approaches may need to be considered.

Given the risk of center bias, a propensity score approach was used to adjust for key end points, and adjustments for country were made, but given small patient numbers in many centers, we could not adjust at center level. Also, not all centers were able to offer both HD and HDF modalities, such that 71% of the cohort were treated in centers offering both dialysis modalities. However, when subgroup analysis was performed examining the cohort who were treated in centers that offered both dialysis modalities, there was no difference in demographics between those receiving HD or HDF. A randomized study as discussed above would preclude the need for propensity score adjustment, and remove the possibility of

center bias. Children were not blinded to the dialysis modality, and this may have influenced their perception of the symptoms on dialysis. However, an objective measure of school attendance was improved on HDF compared with HD. Second, the distinct clustering of symptoms related to volume status (headaches, dizziness, and cramps) that showed improvement on HDF, with no change in other symptoms (such as pruritus, restless legs, or sleep disturbances), makes it less likely to be biased reporting by children. Indeed, blinding children to the modality of dialysis would require a curtain or screen to hide the machine from the patient, and current set-up of dialysis units, safety, and infection-control procedures, and the natural curiosity of children would make this virtually impossible in a 1-year study.

Our study was designed to have a short follow-up period of only 1 year as high transplantation rates in children preclude a longer study. However, we had a higher than predicted drop-out rate, mostly due to transplantation, so the study was underpowered for the number of patients on HDF. Biochemical parameters were only measured on a single occasion at baseline and 12 months, with analysis in a central laboratory. However, this meant that averaging of repeated measurements to control for within-individual variability was not possible. As with all pediatric studies, the scarcity of hard end points for cardiovascular outcomes necessitates studies of surrogate markers. cIMT is a well established surrogate for the extent of coronary artery disease, and correlates with hard end points such as myocardial infarction and stroke in adults without CKD[54] and cardiovascular events in patients with CKD[55] and patients on dialysis.[56] These intermediate end points must be interpreted with caution.[57] Also, the predictive value of pediatric data for CKD-related CVD events in adulthood is unknown.

In conclusion, 3H, the largest pediatric dialysis study to date, suggests an association between HDF modality and lack of progression in vascular measures, increase in height, and self-reported improvement in patient-related outcomes compared with HD. Children on HDF had improved BP and hemodynamic stability, reduced inflammatory markers, and lower β2-microglobulin compared with children on HD. The annualized change in vascular measures correlated with improved BP control and clearances on HDF. Confirmation through randomized trials is required.

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The study was performed according to the principles of the declaration of Helsinki. It has been approved by the National Research Ethics Service Committee London– Bloomsbury, a research ethics committee established by the Health Research Authority, England. Approval from local institutional review boards was obtained for each participating site. Full written informed consent has been obtained from all parents or carers, and assent from children, where applicable. A part of the work took place in the Biomedical Research Centre at Great Ormond Street Hospital for Children National Health Service Foundation Trust and University College London.

R.S. is the Principal Investigator, designed the study and obtained funding. R.S. drafted the paper. A.K.B., K.A., D.B., S.A.B., and L.O. performed the vascular scans and collected data from local centers. C.D. designed and performed the quality of life measures. C. Smith performed the statistical analyses. All authors read and approved the final manuscript.

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Fresenius Medical Care approved the study protocol, but had no role in data collection, data analysis, or drafting the present manuscript.

DISCLOSURES

R.S. and C.P.S. have received speaker honoraria from Fresenius Medical Care and Amgen.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi: 10.1681/ASN.2018100990/-/DCSupplemental.

Supplemental Methods. Statistical analysis.

Supplemental Table 1. Fluid status and vascular measures in patients on HD and patients on HDF.

Supplemental Table 2. Laboratory results, medications, and changes in measures in patients on HD and patients on HDF.

Supplemental Table 3. Sensitivity analyses for factors associated with annualized change in vascular measures, using a standard multivariable adjustment approach.

Supplemental Table 4. Comparison of study results, when using different propensity score methods to adjust for potential confounders.

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AFFILIATIONS

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