High cutoff versus high-flux haemodialysis for myeloma cast nephropathy in patients receiving bortezomib-based chemotherapy (EuLITE): a phase 2 randomised controlled trial

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Summary

Background In multiple myeloma, severe acute kidney injury due to myeloma cast nephropathy is caused by pathogenic free light chain immunoglobulin in serum. High cutoff haemodialysis (HCO-HD) can remove large quantities of free light chain immunoglobulin from serum, but its effect on clinical outcomes is uncertain. We therefore aimed to assess whether HCO-HD could increase the frequency of renal recovery in patients with de novo multiple myeloma, severe acute kidney injury, and myeloma cast nephropathy relative to treatment with standard high-flux haemodialysis (HF-HD).

Methods In this open-label, phase 2, multicentre, randomised controlled trial (EuLITE), we recruited patients with newly diagnosed multiple myeloma, biopsy-confirmed cast nephropathy, and acute kidney injury that required dialysis from renal services in 16 hospitals in the UK and Germany. Patients were randomly assigned (1:1) by random number generation to receive intensive HCO-HD (in sessions lasting 6–8 h) or standard high-flux haemodialysis (HF-HD) and they were stratified by age and centre. Patients and the medical staff treating them were not masked to treatment allocation. Patients received bortezomib, doxorubicin, and dexamethasone chemotherapy, and were then followed up for 2 years. The primary outcome was independence from dialysis at 90 days after random allocation to groups, which was assessed in an intention-to-treat population. The trial has completed follow-up, and is registered at the ISRCTN registry, number ISRCTN45967602.

Findings Between June 7, 2008, and Sept 18, 2013, we recruited 90 patients, of whom 43 (48%) were randomly assigned to receive HCO-HD and 47 (52%) were randomly assigned to receive HF-HD. All 90 patients were included in the analysis of the primary outcome. One (2%) patient from the HF-HD group withdrew consent before receiving treatment. During treatment, nine (21%) patients from the HCO-HD group and two (4%) patients in the HF-HD group discontinued trial treatment. After 90 days, 24 (56%) patients in the HCO-HD group and 24 (51%) patients in the HF-HD group were independent from dialysis (relative risk 1.09, 95% CI 0.74-1.61; p=0.81). During the 2-year follow-up, 98 serious adverse events were reported in the HCO-HD group and 82 serious adverse events were reported in the HF-HD group. The most common serious adverse events were infections and adverse events related to the cardiovascular and thrombotic and musculoskeletal systems. During the first 90 days, 26 infections were reported in the HCO-HD group and 13 infections were reported in the HF-HD group, including 14 lung infections in the HCO-HD group and three lung infections in the HF-HD group.

Interpretation In this phase 2 study, HCO-HD did not improve clinical outcomes for patients with de novo multiple myeloma and myeloma cast nephropathy who required haemodialysis for acute kidney injury and who received a bortezomib-based chemotherapy regimen relative to those receiving HF-HD. These results do not support proceeding to a phase 3 study for HCO-HD in these patients.

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Research in context

Evidence before this study

In patients with multiple myeloma, severe acute kidney injury that requires dialysis has previously been associated with very poor survival and low rates of recovery from dependence on dialysis. Patients who recover independent renal function have better survival than those who do not. Most patients with severe acute kidney injury have myeloma cast nephropathy caused by a pathogenic immunoglobulin light chain, so it is logical to test treatments that can immediately reduce concentrations of immunoglobulin light chain by its direct removal from the blood. The largest published trial of plasma exchange showed no benefit of this treatment. However, high cut-off haemodialysis (HCO-HD) removes more free light chains from serum than plasma exchange. We searched PubMed for work published on or before Dec 21, 2018, by use of the search terms "(high AND cutoff) OR (high AND cut-off) OR (high AND cut AND off OR HCO OR Theralite AND ('multiple myeloma' OR ('multiple' AND 'myeloma') OR 'multiple myeloma' OR 'myeloma')", with no language restrictions. This search identified eight retrospective studies that reported use of HCO-HD in ten patients or more, in which 145 (64%) of 226 patients were shown to have recovered independent renal function. There has been one prospective randomised controlled trial that compared HCO-HD with standard high-flux haemodialysis (HF-HD), which found no difference in the primary outcome of independent renal function at 90 days but increased renal recovery in patients who received HCO-HD.

Added value of the study

We did not find a clinical benefit of HCO-HD relative to standard dialysis treatment, including no additional effect on recovery of kidney function in our primary outcome of independence from dialysis at 90 days or on overall renal recovery. We found an increased mortality over the study and 2 years of follow-up in the HCO-HD group relative to those receiving standard dialysis, and we found that blood concentrations of immunoglobulin light chain did not significantly differ between treatment groups, except for at 4–6 days when lower concentrations were reported in patients who had been treated with HCO-HD and had a pathogenic immunoglobulin λ-light chain.

Implication of all the available evidence

In the previous randomised controlled trial and ours, HCO-HD did not improve renal recovery at 90 days in patients with de novo multiple myeloma, myeloma cast nephropathy, and severe acute kidney injury. Increased overall renal recovery in patients who received HCO-HD was found in the previous study but not in ours. Bortezomib-based chemotherapy is highly effective for early reductions in free light chains in the serum of patients with myeloma cast nephropathy and could explain the improved outcomes reported in patients with acute kidney injury and myeloma cast nephropathy relative to patients with acute kidney injury and myeloma cast nephropathy before the introduction of bortezomib.

Introduction

Multiple myeloma is a cancer of the plasma cells that affected 85 people per 1 million in the UK in 2015.[1] Approximately 20% of patients have renal insufficiency that fulfils the CRAB criteria[2] for renal end-organ damage (defined as a serum creatinine concentration of more than 173 µmol/L [2 mg/dL]),[2] and up to 5% of patients have severe acute kidney injury that requires dialysis.[3,4]

Before the introduction of modern chemotherapy, less than 25% of patients who required dialysis for multiple myeloma and acute kidney injury recovered sufficient renal function to no longer be dependent on dialysis, with a median overall survival of less than 1 year.[5–7] Since 2009, survival in patients with multiple myeloma who require dialysis at presentation has improved,[3,4] which might be because of the better disease responses enabled by modern chemotherapy regimens and better supportive care.[8–10]

Up to 90% of patients with multiple myeloma and severe acute kidney injury have myeloma cast nephropathy,[11] a renal lesion that is caused by pathogenic 25-kDa κ or 50-kDa λ free light chain (FLC) clonal immunoglobulin.[12] These molecules are freely filtered by the glomerulus into the renal tubules and, when serum levels exceed 500 mg/mL, they can co-precipitate with uromodulin (also known as Tamm-Horsfall protein) to form insoluble casts within the distal tubule, leading to tubule obstruction and rupture and an associated tubulo-interstitial inflammation.[13] The lesion is rapid in onset and causes such severe injury that irreversible renal failure requiring long-term dialysis treatment can develop in weeks to months.[14] Modelling studies have shown that rapid reductions in FLC clonal immunoglobulin in serum (herein, serum free light chain [sFLC]) in the first 3 weeks after the start of treatment is associated with an increased likelihood of recovery of kidney function.[15]

Because of the pathogenicity of FLC clonal immunoglobulin, there has been a longstanding interest in supplementing chemotherapy with extracorporeal removal of sFLC, originally by plasma exchange, the largest study[16] of which showed no clinical benefit. Since 2007, there has been a focus on high cutoff haemodialysis (HCO-HD) for removal of sFLC; HCO-HD relies on use of a highly permeable dialysis membrane that is very effective in clearing both FLC isotypes[17] and is more effective than plasma exchange because it can be used for longer treatment sessions.[18] Uncontrolled clinical trials[11,19–21] have shown a high frequency of renal recovery in patients who were dialysis-dependent and received HCO-HD. However, the effect of novel chemotherapy was not evaluated in these studies, and a 2017 randomised controlled trial,[22] in which all patients received a multiple myeloma treatment containing bortezomib and dexamethasone, showed no differences in the primary outcome of independence from dialysis at 90 days between the group randomly assigned to receive HCO-HD and the group randomly assigned to receive high-flux haemodialysis (HF-HD), although increased overall renal recovery was reported in patients who received HCO-HD. HF-HD is the standard dialysis treatment for patients with severe acute kidney injury of any cause that requires dialysis treatment.

The European trial of light chain removal (EuLITE) was designed to compare the effects of HCO-HD versus standard HF-HD in patients with severe acute kidney injury caused by biopsy-proven cast nephropathy and requiring dialysis. Patients in both groups received a regimen comprising modified bortezomib (PS-341), doxorubicin, and dexamethasone (PAD). The study included 2 years of follow-up and aimed to assess the effects of the HCO-HD on renal recovery, patient survival, and change in sFLC concentrations during the first 3 weeks of the study.

Methods

Study design and participants

In this open-label, phase 2, multicentre, randomised controlled trial (EuLITE), we recruited patients under the inpatient care of renal services at 16 hospitals in the UK (14 hospitals) and Germany (two hospitals). Patients were enrolled by clinical research staff employed at the hospitals. Patients aged 18 years and older were eligible to participate if they fulfilled diagnostic criteria for the diagnosis of symptomatic multiple myeloma; had an abnormal sFLC ratio and an sFLC concentration of the involved light chain isotype of more than 500 mg/L; had myeloma cast nephropathy, as demonstrated by kidney biopsy; were dialysis-dependent, as defined by an estimated glomerular filtration rate (eGFR) of less than 15 mL/min per 1·73 m^2, and required dialysis treatment; and had presented to the enrolling renal unit within the past 10 days. Exclusion criteria included known advanced chronic kidney disease; previous treatment of multiple myeloma with chemotherapy; cardiac disease (myocardial infarction in the last 6 months, unstable angina, New York Heart Association class III or IV heart failure, clinically relevant pericardial disease, or cardiac amyloidosis); a history of allergic reaction attributable to compounds containing boron or mannitol; peripheral neuropathy or neuropathic pain of grade 2 or higher (as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events); liver dysfunction (defined as a bilirubin concentration of more than 1·8 mg/dL or 30 μmol/L); active uncontrolled infection; presence of amyloid or light-chain deposition disease on a kidney biopsy; or an inability to give informed consent. The trial was approved by the Leeds Multicentre Research Ethics Committee and the Ethik-Komission of the University of Tubingen, and regulatory approvals were obtained before the enrolment of any study participants. All participants provided written informed consent. The protocol has previously been published.[23]

Randomisation and masking

Patients were randomly assigned (1:1) to receive dialysis with extended HCO-HD or standard HF-HD. Participants were randomly assigned to groups with a web-based system with random number generation by use of Datinf RandGen software. A minimisation algorithm described by Pocock and Simon[24] was used to ensure balance between the intervention age groups (18–55, 56–65, 66–75, and more than 75 years) and study centre. The algorithm included a random component with a 66·7% probability of allocating patients to the preferred group. Patients and the medical staff treating them knew which groups they had been allocated to.

Procedures

HCO-HD was done with two Baxter Gambro HCO 1100 dialysers in series at a blood flow of 250 mL/min and a dialysate flow of 500 mL/min. 60 g of human serum albumin was administered during the last hour of each dialysis. Patients received HCO-HD for 6 h on day 0, then 8 h on days 2, 3, 5–7, 9, and 10. After day 12, patients received 8 h of HCO-HD on alternate days and, from day 21, HCO-HD dialysis was given for 6 h three times a week. Dialysis treatment with HCO-HD continued for up to 90 days. If the patient did not become independent from dialysis by 90 days, the patient was treated with standard HF-HD from this point. Standard HF-HD was given at intervals that were determined on a clinical basis by the nephrologist supervising care, with a minimum recommended prescription of 4 h dialysis treatment three times a week.

The decision of when to discontinue treatment with dialysis was delegated to the nephrologist responsible for the care of the patient, with the recommendation that a patient with a pre-dialysis eGFR of more than 20 mL/min and a good urine output should discontinue dialysis. The definition for independence from dialysis was an eGFR of more than 15 mL/min per 1·73 m^2 2 weeks after the last dialysis session. Chemotherapy was given to both groups. The first six patients entered into the study were assessed for the safety of the modified-dose PAD regimen.[25] The chemotherapy regimen comprised bortezomib (1 mg/m^2 intravenously on days 1, 4, 8, and 11 of a 21-day cycle), doxorubicin (9 mg/m^2 intravenously on days 1 and 4 of the 21-day cycle), and dexamethasone (40 mg orally on days 1–4, 8–11, and 15–18 for the first 21-day cycle and on days 1–4 only on subsequent cycles). The chemotherapy was given for a maximum of eight cycles; the number of cycles given was determined by the response criteria for multiple myeloma, as stated in the methods paper.[23] A safety assessment was done, which was independent of the renal therapy group to which the patients were assigned, and the results of this assessment were reported to the regulatory authorities.

As specified in the protocol, all participants were given 480 mg co-trimoxazole three times per week or alternative pneumocystis jirovecii prophylaxis, as per local institutional practice; 150 mg ranitidine twice daily while receiving dexamethasone; 10–20 mg metoclopramide three times daily, as required (20 mg given before chemotherapy on day 1); 100 mg allopurinol orally daily; and 200 mg aciclovir twice daily.

Outcomes

The outcome measures are identified in the protocol.[23] The primary outcome measure was independence from dialysis at 90 days after random allocation to groups. Patients who became independent from dialysis and subsequently required further dialysis support during the first 90 days, and patients who withdrew or for whom the data was unavailable, had their treatment classified as failed. The secondary outcome measures were the efficacy of HCO-HD in the first 21 days in decreasing sFLC, the duration of requirement of haemodialysis, disease response at 6 and 12 months, stem cell transplantation at 12 months, and overall survival at the end of the study (2 years of follow-up). Pre-planned sensitivity analyses for all outcome measures controlled for age at randomisation, which was a stratification factor used in the randomisation algorithm to ensure the validity of conclusions. Another pre-planned sensitivity analysis for the primary outcome measure excluded patients who withdrew their consent to data collection before the time of assessment of the primary outcome (full withdrawal). Post-

hoc analyses were done to assess the incidence of lung infections during the first 3 months and the stage of chronic kidney disease.

Statistical analysis

Sample size calculations were based on the primary outcome. Data from published studies[5,17] at the time of study design suggested a recovery frequency of 25% in control groups that received dialysis with HF-HD, and that an improvement to 55% in the treatment group was a realistic expectation. Assuming a two-sided α error level of 5%, 41 patients were required in each treatment group to detect this difference with 80% power. The sample size was adjusted to allow for a 10% dropout, giving a target recruitment of 90 patients.

Efficacy analyses were done on an intention-to-treat basis, analyses of adverse events were done for patients who started allocated treatment, and analyses of sFLC data were done with available case data.

Independence from dialysis at 90 days, the proportion of participants who had received a peripheral blood stem cell transplant by 12 months, and myeloma response outcomes were analysed by use of a chi-squared test with Yates' correction for continuity, and they were summarised by use of a risk ratio (RR) with 95% CIs. Multivariable logistic regression was used to examine the effect of adjustment by age at randomisation. A Kaplan- Meier estimation[26] and log-rank test were used to compare the time to independence from dialysis and overall survival between the two treatment groups. Hazard ratios with CIs were derived from a Cox regression model; assumptions were assessed by use of the log(–log[survival]) versus the log of survival time and Schoenfeld residuals. Deaths were not counted as competing risks for the time to independence from dialysis outcome and were censored at that time.

sFLC data were log-transformed for predefined time analyses. For patients in whom more than one pre-dialysis or non-dialysis day sFLC concentration datapoint was available, the mean sFLC concentration during that predefined duration (days 4–6, 8–10, and 20–22) was calculated. The change from baseline in log-sFLC concentrations within a prespecified time was compared by use of regression adjusted for the baseline values. A mixed-effects model was used to analyse available log-FLC data over time (days 0–22), controlling for baseline measurement and time. Random effects were assigned at the patient level.

The proportion of patients with at least one serious adverse event relating to a lung infection was analysed as per the primary outcome measures. This adverse event analysis was not prespecified. Chronic kidney disease stage during follow-up was summarised by the standard classification system of chronic kidney disease. Results were considered statistically significant at the 5% level. Analyses were done with Stata (version 14).

An independent data monitoring committee was used to review recruitment data and data on adverse outcomes and adverse events when 50% of the recruitment target had

been achieved, representing a descriptive analysis to assess patient safety. The trial has completed follow-up, and it is registered at the ISRCTN registry, number ISRCTN459676

Role of funding source

Gambro were the main funder for the study, and the Binding Site produced and provided the Freelite assay used for the quantification of sFLC. Employees of both companies, as academic collaborators, contributed to the study design, data interpretation, and writing of the report. However, these funders had no role in data collection or data analysis. Janssen provided the bortezomib that was used in the study but had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 7, 2008, and Sept 18, 2013, 90 patients were recruited by local clinical research staff and randomly assigned to groups; 43 (48%) patients were allocated to the HCO-HD (intervention) group and 47 (52%) patients were allocated to the HF-HD (control) group (figure 1). Three (7%) patients from the HCO-HD group and three (6%) patients from the HF-HD group withdrew from the study and did not provide follow-up data from time of withdrawal, but all other patients were followed up for 2 years or until their death.

Demographic and clinical characteristics were evenly distributed across the treatment groups, except for the number of patients with myeloma type IgG (table 1). The mean age of participants was 65 years (SD 11), 51 (57%) were male, and 77 (86%) were white. Potential precipitating factors for cast nephropathy are also shown in table 1; 48 (53%) patients—23 (53%) patients in the HCO-HD group and 24 (53%) patients in the HF-HD group—had one or more precipitating factors. Only two patients (in the HF-HD group) had an sFLC concentration of less than 1000 mg/L, both of which were of λ isotype. 31 (72%) patients in the HCO-HD group and 32 (68%) patients in the HF-HD group had received one or more dialysis treatments before the study, but information on dialysis before the study was not available for one patient (in the HF-HD group). All other patients needed to start dialysis for severe acute kidney injury at the time of entering the study. The mean creatinine concentration of patients who had not received dialysis before entering the study was 623 (241) µmol/L in the HCO-HD group and 499 (127) µmol/L in the HF-HD group. The mean dialysis duration per session was 7 (0·5) h in the HCO-HD group and 3·7 (0·7) h in the HF-HD group.

The median reduction in sFLC concentration was assessed for the first full dialysis session (8 h in the HCO-HD group, 4 h in the HF-HD group), to determine the efficacy of a single treatment in removing the pathogenic FLC isotype. The clearance of k-sFLC and l-sFLC across a HCO-HD dialyser are different,[18] therefore all analyses relating to sFLC levels were done by isotype. These data were analysed for 18 (95%) of 19 patients in the HCO-HD group and 19 (90%) of 21 patients in the HF-HD group with a k isotype and 23 (96%) of 24 patient in the HCO-HD group and 24 (92%) of 26 patients in the HF-HD group with a l isotype, after exclusion of one patient with a k isotype who had their first full dialysis treatment after 3 weeks of enrolment in the study. These median reductions in sFLC concentrations were -77% (IQR -82 to -64) in the HCO-HD group and -20% (-41 to -

8) in the HF-HD group for k-sFLC (p<0.0001) and -72% (-82 to -68) in the HCO-HD group and -7% (-20 to -1) in the HF-HD group for l-sFLC (p<0.0001).

For patients who remained dialysis-dependent at the pre-defined timepoints, we had data at baseline and on at least one pre-dialysis or non-dialysis day on κ-sFLC concentration for 19 (100%) patients in the HCO-HD group and 18 (95%) patients in the HF-HD group at days 4–6; for 17 (89%) patients in both groups on days 8-10; and for 11 (85%) patients in the HCO-HD group and 16 (84%) in the HF-HD groups at days 20-22. For λ-sFLC concentration, we had data at baseline and on at least one pre-dialysis or non-dialysis day for 24 (100%) patient in both groups at days 4-6; for 23 (100%) patients in both groups at days 4-6; for 23 (100%) patients in the HCO-HD group and 21 (88%) in the HF-HD group on days 8-10; and for 17 (100%) patients in the HCO-HD group and 18 (100%) patients in the HF-HD group at days 20-22.

24 (56%) patients in the HCO-HD group and 24 (51%) patients in the HF-HD group became independent from dialysis by 90 days. The RR for independence from dialysis was 1·09 (95% CI 0·74–1·61; p=0·81). Three (7%) patients in the HCO-HD group and two (4%) patients in the HF-HD group withdrew consent to further data collection before 90 days and were therefore considered to have failed treatment. The mean difference in change of log κ-sFLC concentration from baseline was –0·42 (95% CI –1·04 to 0·02; p=0·17) to days 4–6, –0·46 (–1·37 to 0·45; p=0·31) to days 8–10, and –0·31 (–2·11 to 1·49; p=0·72) to days 20–22. The mean difference in change of log λ-sFLC concentration from baseline was –0·65 (–1·27 to 0·02; p=0·04) to days 4–6, –0·60 (–1·41 to 0·20; p=0·14) to days 8–10, and –0·27 (–1·50 to 0·96; p=0·65) to days 20–22. The change in sFLC concentration between baseline and days 4–6, 8–10, and 20–22 and the model fit based on predictions from a linear mixed-effects model incorporating restricted cubic splines for κ-sFLC and λ-sFLC (days 0–22) are shown in figure 2. Repeated measures analyses of log-sFLC including all time points (days 0–22) showed a change of 0·027 (95% CI –0·39 to 0·34; p=0·88) in log κ-sFLC and –0·31 (–0·77 to 0·14; p=0·18) in log λ-sFLC. Adjustment for age at randomisation did not change our conclusions (data not shown).

For patients with a pathogenic κ-sFLC who remained on dialysis at 21 days but who became independent from dialysis by 90 days, the median sFLC concentration at days 20–22 in three patients receiving HCO-HD was 683 mg/L (IQR 53–18 500) and the median sFLC concentration at days 20–22 in seven patients receiving HF-HD was 164 mg/L (145–1145). Of patients who remained on dialysis at 21 days and had not become independent of dialysis by 90 days, eight patients receiving HCO-HD showed a median sFLC concentration at days 20–22 of 2689 mg/L (1773–6907), and nine patients receiving HF-HD showed a median sFLC concentration at days 20–22 of 3250 mg/L (1260–9870). For patients with a pathogenic λ-FLC who remained on dialysis at 21 days but who became independent from dialysis by 90 days, the median sFLC concentration at days 20–22 in nine patients receiving HCO-HD was 129 mg/L (70–755) and the median sFLC concentration at days 20–22 in nine patients receiving HF-HD was 803 mg/L (145–1145). Of patients who remained on dialysis at 21 days and had not become independent of dialysis by 90 days, eight patients receiving HCO-HD showed a median sFLC concentration at days 20–22 of 1422 mg/L (496–11081) and nine patients receiving HF-HD showed a median sFLC concentration at days 20–22 of 719 mg/L (623–1610).

The median time to independence from dialysis was 51 days (95% CI 26 to not reached) for those in the HCO-HD group and 61 days (35 to 175) for those in the HF-HD group. The HR for time to independence from dialysis was 0·91 (0·54–1·54; p=0·72; figure 3). The assumption of proportional hazards was not infringed. The HR for independence from dialysis, adjusted for age at randomisation, was 0·92 (95% CI 0·54–1·57; p=0·76).

27 (63%) patients in the HCO-HD group and 34 (72%) patients in the HF-HD group showed a myeloma response at 6 months (table 2). There was no evidence of a difference in response at 6 months between the treatment groups (RR 0·87, 95% CI 0·65–1·16; p=0·46). However, at 12 months, 18 (42%) patients in the HCO-HD group and 32 (68%) patients in the HF-HD group showed a disease response, which indicated a difference between the groups (RR 0·62, 95% CI 0·41–0·92; p=0·022).

Ten (23%) patients in the HCO-HD group and 12 (26%) patients in the HF-HD group had received a peripheral blood stem cell transplant 12 months after randomisation (RR 0·91, 95% CI 0·439–1·890; p=0·10). An additional three (7%) patients in the HCO-HD group and nine (19%) patients in the HCO-HD group could might have been considered for a stem cell transplant by 12 months, by use of criteria that patients be younger than 70 years and have a disease response at 6 and 12 months.

Deaths reported up to 25 months of follow-up were included in the analysis (figure 4). After 2 years of follow-up, 16 (37%) patients in the HCO-HD group and nine (19%) patients in the HF-HD group had died. The overall survival at 90 days was 0·95 (95% CI 0·82–0·99) in the HCO-HD group and 0·98 (0·85–1·00) in the HF-HD group. The unadjusted HR of overall survival was 2·17 (0·96–4·91; log-rank p=0·058 in the HCO-HD group versus the HF-HD group. The most common causes of death were advanced myeloma (seven [44%] of 16 patient deaths in the HCO-HD group and four [44%] of nine patient deaths in the HF-HD group) and infection (five [31%] of 16 patient deaths in the HCO-HD group and three [33%] of nine patient deaths in the HF-HD group); other causes of death are shown in table 3. Two (5%) patients in the HCO-HD group and one (2%) patient in the HF-HD group who recovered independent renal function subsequently returned to requiring dialysis treatment. These patients subsequently died during the follow-up period of the study, two patients (one [2%] HCO-HD, one [2%] HF-HD) died of advanced myeloma and one (2%) patient (HF-HD) died of complications from a subdural haematoma.

There were 364 adverse events: 191 (52%) events occurred in patients receiving HCO-HD and 173 (48%) events occurred in patients receiving HF-HD. 180 grade 3–5 serious adverse events (SAEs) were reported: 98 (54%) SAEs in the HCO-HD group and 82 (46%) SAEs in the HF-HD group (table 4). 39 (91%) patients in the HCO-HD group and 35 (76%) patients in the HF-HD group had one or more SAEs, at a median of two SAEs (IQR 1–3) in the HCO-HD group and one (1–3) SAE in the HF-HD group.

14 lung infections in 13 patients were reported in the first 90 days in the HCO-HD group and three lung infections in three patients were reported in the HF-HD group (RR of at

least one lung infection 4·636, 95% CI 1·42–15·20; p=0·008) In reported lung infections in the first 90 days, the most common symptoms were cough and at least one other symptom of a lower respiratory tract infection in nine patients from the HCO-HD and two patients from the HF-HD group, which was consistent with the definition in the UK National Institute for Health and Care Excellence pneumonia guideline (CG191) of a lower respiratory tract infection. The clinical team reported two cases of pneumonia (one in each group). Five (38%) of 13 patients who received HCO-HD and who had a lung infection in the first 90 days subsequently died: three of these patients died of myeloma (at 196, 383, and 737 days) and two patients died of infection (at 146 and 383 days). None of the three patients with lung infections who received HF-HD died during follow-up.

Seven (4%) adverse events in the HCO-HD group and eight (5%) adverse events in the HF-HD group were related to peripheral neuropathy, but only one of these was an SAE (grade 3, HCO-HD group). 14 cases (six cases in the HCO-HD group and eight cases in the HF-HD group) were reported as grade 1 or grade 2 adverse events, and one case was reported as a grade 3 SAE.

Chronic kidney disease (CKD) stage was classified at 6, 12, and 24 months. CKD stages 1–2 corresponded to an eGFR of at least 60 mL/min per 1·73 m^2; stage 3 indicated an eGFR of 30–59 mL/min per 1·73 m2; stage 4 indicated an eGFR of 15–29 mL/min per 1·73 m^2; stage 5 indicated an eGFR of less than 15 mL/min per 1·73 m^2; and stage 5D indicated dialysis dependence. After 6 months, five patients in the HCO-HD group and four patients in the HF-HD group had chronic kidney disease stages 1–2, six patients in the HCO-HD group and ten patients in the HF-HD group had chronic kidney disease stage 3, 11 patients in the HCO-HD group and 12 patients in the HF-HD group had chronic kidney disease stage 4, one patient in the HCO-HD group and one patient in the HF-HD group had chronic kidney disease stage 5, 12 patients in the HCO-HD group and 12 patients in the HF-HD group had chronic kidney disease stage 5D, eight patients in the HCO-HD group and seven patients in the HF-HD group had died or withdrawn, and the status of one patient in the HF-HD group was unknown. After 12 months, three patients in the HCO-HD group and four patients in the HF-HD group had chronic kidney disease stages 1–2, six patients in the HCO-HD group and 12 patients in the HF-HD group had chronic kidney disease stage 3, nine patients in the HCO-HD group and ten patients in the HF-HD group had chronic kidney disease stage 4, two patients in the HCO-HD group and one patient in the HF-HD group had chronic kidney disease stage 5, eight patients in the HCO-HD group and ten patients in the HF-HD group had chronic kidney disease stage 5D, 14 patients in the HCO-HD group and nine patients in the HF-HD group had died or withdrawn, and the status of one patient in each group was unknown. After 24 months, two patients in the HCO-HD group and three patients in the HF-HD group had chronic kidney disease stages 1–2, seven patients in the HCO-HD group and 12 patients in the HF-HD group had chronic kidney disease stage 3, ten patients in the HCO-HD group and 11 patients in the HF-HD group had chronic kidney disease stage 4, six patients in the HCO-HD group and nine patients in the HF-HD group had chronic kidney disease stage 5D, 17 patients in the HCO-HD group and 11 patients in the HF-HD group had died or withdrawn, and the status of one patient in each group was unknown.

One (2%) patient in the HCO-HD group and seven (15%) patients in the HF-HD group became independent from dialysis after 90 days. Overall, 25 (58%) patients in the HCO-HD group and 31 (66%) patients in the HF-HD group became independent of dialysis. A sensitivity analysis was done that excluded the patients who withdrew consent for further data collection before 90 days, which showed no difference between the groups regarding independence from dialysis with this exclusion (RR 1·07, 95% CI 0·73–1·59; p=0·89). The adjusted analysis for age did not change the conclusions. A sensitivity analysis adjusting for age at randomisation altered our findings of the difference in change to log λ-sFLC lambda from baseline to days 4–6 to –0·57 (95% CI –1·21 to 0·06; p=0·076).

At 6 months, six (14%) patients in the HCO-HD group and five (11%) patients in the HF-HD group who became independent of dialysis by 90 days had stable or progressive disease, were not assessed, or had died or withdrawn. At 12 months, 12 (28%) patients in the HCO-HD group and five (11%) patients in the HF-HD group who became independent of dialysis by 90 days had stable or progressive disease. 14 (33%) patients in the HCO-HD group and 16 (34%) patients in the HF-HD group had a peripheral blood stem cell transplant during the 2 years of follow-up. When adjusted by age at randomisation, the overall survival HR was 2·63 (95% CI 1·13–6·15; p=0·03) in the HCO-HD group versus the HF-HD group. A sensitivity analysis was done that censored data at 24 months of follow-up and our conclusions remained the same. The assumption of proportional hazards was not broken (data not shown). Adjustment for age at randomisation did not change our conclusions regarding myeloma response at 6 or 12 months or risk of peripheral blood stem cell transplantation at 12 months (data not shown).

Discussion

Our study showed that, compared with HF-HD, HCO-HD did not improve renal recovery in patients with newly presenting multiple myeloma and severe acute kidney injury caused by myeloma cast nephropathy that required dialysis treatment. At the prespecified timepoints of 4–6 days, 8–10 days, and 20–22 days, the only significant difference in pre-dialysis treatment session sFLC between the treatment groups was a lower λ-sFLC in the HCO-HD group at 4–6 days. Overall survival was lower in the HCO-HD group.

The results from EuLITE are consistent with the high frequency of renal recovery reported in retrospective open label studies[11,19–21] of patients receiving HCO-HD; however, the results of our randomised controlled trial showed that a higher frequency of renal recovery, defined in this study as independence from dialysis, is not associated with treatment with HCO-HD versus treatment with HF-HD. Regarding our primary outcome of independence from dialysis at 90 days, the results are consistent with a 2017 trial (MYRE)[22] that showed no significant difference in renal outcome after 3 months, reporting recovery in 41% of patients receiving HCO-HD and 33% of patients receiving HF-HD. The MYRE study reported increased renal recovery beyond 3 months in patients

receiving HCO-HD, although this finding was not associated with differences in mortality at 12 months. The different findings relating to renal recovery might reflect a difference in inclusion criteria: MYRE incorporated a screening period of 4–15 days to include administration of high-dose steroids, correction of dehydration, and treatment of hypercalcaemia, if present. Patients who still required dialysis after this period were eligible for recruitment. Additionally, chemotherapy was less intensive in MYRE, comprising a doublet regimen (bortezomib and dexamethasone) with reinforcement by cyclophosphamide after 3 months if indicated, whereas EuLITE used a triplet regimen (comprising bortezomib, doxorubicin, and dexamethasone).

The EuLITE and MYRE trials also differed in the dose of prescribed HCO-HD (and, therefore, sFLC removal) in the treatment groups. In the first 10 days, patients in the HCO-HD group of EuLITE were treated with HCO-HD for 6 h at the first dialysis and 8 h for subsequent dialysis sessions, whereas patients in MYRE were treated for 5-h dialysis sessions. During the first 10 days, patients in the HCO-HD group in EuLITE received seven dialysis sessions and patients in MYRE received eight dialysis sessions. Therefore, patients in EuLITE had a 40% greater treatment duration with HCO-HD in the first 10 days of the study than patients in MYRE. Beyond this time, patients in EuLITE continued to receive a higher dose of HCO-HD than in MYRE; in MYRE, patients continued with dialysis three times a week to the end of the third cycle of chemotherapy, whereas patients in EuLITE continued with HCO-HD for up to 3 months.

In EuLITE, two 1·1 m^2 HCO dialysers in series were used to provide a surface area of 2·2 m^2 but, in MYRE, a single membrane 2·1 m^2 dialyser (Theralite) was used. Although there are no direct published comparisons of sFLC removal between the two regimes, modelling for the use of two 1·1 m^2 HCO dialysers in series shows comparable sFLC removal of the κ isotype and more λ isotype clearance compared with the manufacturer's data on sFLC removal by Theralite.[18,27] The regimen used in EuLITE was started before the Theralite dialyser became commercially available and, for standardisation of dialysis dose, we did not change the dialysis protocol during the study. Detailed modelling studies on the quantification and kinetics of sFLC clearance by HCO-HD, including measurement of FLC in the dialysate fluid have been done, so these studies[15,18] were not repeated in our trial. The effects of HCO-HD on serum albumin were also measured in these previous studies and were used to inform the study protocol. Dialysate albumin levels with HCO-HD have previously been quantified in the setting of acute kidney injury.[28]

Despite the effectiveness of HCO-HD treatment for sFLC removal, the failure of the HCO-HD regime used in improving renal recovery compared with HF-HD is consistent with an early and deep tumour response to the chemotherapy used in the study. We used a bortezomib, doxorubicin, and dexamethasone regimen, in accordance with the evidence base for a regimen with the highest clinical efficacy for multiple myeloma and severe acute kidney injury and consistent with the recommendations of the International Myeloma Working Group.[29] The results of EuLITE are broadly consistent with a 2016 open-label study[10] that used a bortezomib, doxorubicin, and dexamethasone regimen and in which HCO-HD was not used; this study reported that 15 of 31 patients who required dialysis recovered independent renal function.

The activity of the chemotherapy used in EuLITE is clearly shown by the sFLC concentrations in patients during the first 3 weeks of treatment. Previous studies[25] have shown the activity of the PAD regimen for intact immunoglobulin in which, by the end of cycle one (21 days), there is a reduction in intact immunoglobulin concentration of 50% from pre-treatment concentration. Intact IgG has a serum half-life of around 21 days, which contrasts with the shorter half-life of sFLC of around 18 h in a nephrectomised animal, around ten times that seen in people with normal kidney function.[30] We found a profound early response in sFLC concentration to chemotherapy such that, in patients who remained dependent on dialysis by 20–22 days, these concentrations were around 10% of the concentrations before the study. These findings indicate the activity of the chemotherapy regimen in reducing the production of the pathogenic molecules, despite our modification of the dose of bortezomib from 1·3 mg/m^2 to 1 mg/m^2 per dose.

The SAEs in the first 90 days differed between the two groups: we found an increased incidence of respiratory tract infections in the HCO-HD group. There was also a lower disease response at 12 months in the HCO-HD group. In vitro modelling indicates that HCO-HD could reduce the bortezomib concentration in the blood;[31] however, the drug was given on non-dialysis days, so it was unlikely that this phenomenon contributed to these results. We found increased mortality in the HCO-HD group relative to the HF-HD group, which became increasingly apparent during the second year of the follow-up period. However, since the numbers in each group are small, the analysis might not be reliable. The absence of any clear dominant cause of mortality makes it less likely that this was a true finding.

The main analyses presented were not adjusted for the stratification factors (age and centre), as was prespecified in the analysis plan. However, this approach can cause biased standard errors,[32] meaning that p values from the unadjusted analyses might change on adjustment. Adjusting for age in the sensitivity analysis changed the significance of the p value: the main (unadjusted) mortality analysis showed no significant difference (p=0·058), whereas the sensitivity analysis (adjusted) indicated a significant difference (p=0·026).

The overall outcomes in the study are much better than those historically reported for patients with multiple myeloma and severe renal failure and are consistent with a 2018 population-based study.[4] This analysis of patients in England who had a first coded diagnosis of multiple myeloma and were required to have their first in-centre dialysis treatment within 1 month of diagnosis showed substantial improvements in overall survival between 2006 and 2014, a period when UK practice moved from use of conventional chemotherapy (alkylating drugs) to novel drugs, with adoption of bortezomib-based chemotherapy as the standard of care for patients with multiple myeloma and severe acute kidney injury.

Our study had several limitations: staff and patients were not masked to their treatment group, and we did not control for dialysis dose. Additionally, the study was powered on the basis of a large treatment effect (an improvement in renal recovery from 25% to 55%), so the overall sample size implies that the trial has low power to detect a more

realistic treatment effect. The criteria for a trial without dialysis were not fully defined but were left to the clinical judgement of the local team. Despite these limitations, there were few differences in sFLC responses in patients who remained dialysis-dependent at prespecified measurement times; these findings provide supportive evidence for why HCO-HD, the most effective treatment available for extracorporeal removal of sFLC, did not have an effect on the frequency of renal recovery in patients with myeloma cast nephropathy and severe acute kidney injury in our study.

Further improvements to the clinical outcomes of patients with myeloma cast nephropathy and multiple myeloma who receive bortezomib based chemotherapy will require the rapid identification of the lesion in patients and prompt commencement of chemotherapy. This disease presentation is a time-critical emergency, and haematology and nephrology teams must work closely together to ensure that local protocols are in place to deliver rapidly acting treatment.

In conclusion, in our study, HCO-HD was not associated with an improvement in renal recovery relative to HF-HD in patients with a new diagnosis of multiple myeloma and myeloma cast nephropathy who received modified-dose bortezomib-containing chemotherapy. There was a sustained early reduction in sFLC in both groups, providing a biological basis for the clinical outcomes reported in the study.

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Contributors

CAH, PC, ARB, LF, MS, KW, NH, and MC devised and designed the study. CAH, PC, VM, ARB, LF, MDJ, JW, CGW, KW, NH, and MC acquired the data, which was analysed by PC and VM and interpreted by CAH, PC, VM, ARB, LF, JDG, CGW, MS, KW, NH, and MC. PC and VM wrote the initial draft, and all authors were involved in manuscript revision and approved the final manuscript.

Declaration of interests

PC reports grants from Gambro and supply of bortezomib for the EuLITE study from Janssen Pharmaceutica and Binding Site during the conduct of the study and personal fees from Gambro and Janssen Pharmaceutica outside the submitted work. ARB reports being a non-executive director and minor shareholder of Binding Site, which produced and provided the assay used for measurement of serum free light chains (Freelite). MS is an employee of Baxter International. KW reports personal fees and non-financial support from Celgene during the conduct of the study; grants from Celgene and Janssen Pharmaceutica outside the submitted work; and personal fees and non-financial support from Celgene, Janssen Pharmaceutica, Bristol-Myers Squibb, Onyx, Amgen, Takeda, and Novartis outside the submitted work. NH reports personal fees from Ablynx, Alexion, Baxter, and Novartis and grants from Chiesi outside the submitted work. MC reports grants from Gambro, supply of bortezomib for the EuLITE study from Janssen Pharmaceutica, and non-financial support from Binding Site during the conduct of the study; personal fees from Janssen Pharmaceutica, Celgene, Takeda, AbbVie, Amgen, Chugai, and Jazz Pharmaceuticals outside the submitted work; grants from Celgene outside the submitted work; and non-financial support from Takeda and Amgen outside the submitted work. CAH, VM, LF, JDG, MDJ, JW, and CGW declare no competing interests.

Data sharing
The original data for this paper is available from the time of publication, on request to the corresponding author.

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Figure 1

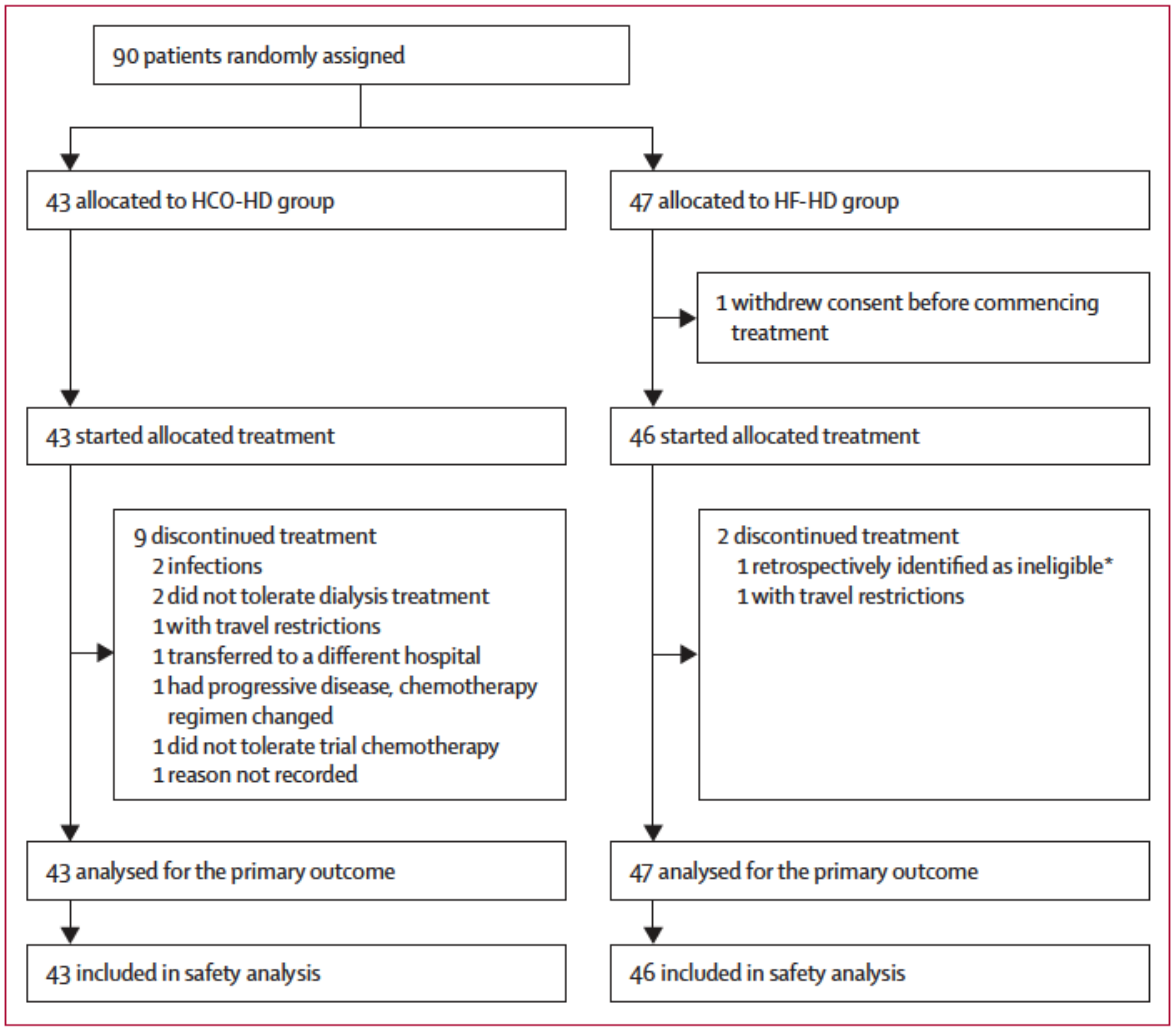

Figure 1: **Trial profile**
HCO-HD=high cutoff haemodialysis. HF-HD=high-flux haemodialysis. *Identified at day 6 of treatment.

Figure 2

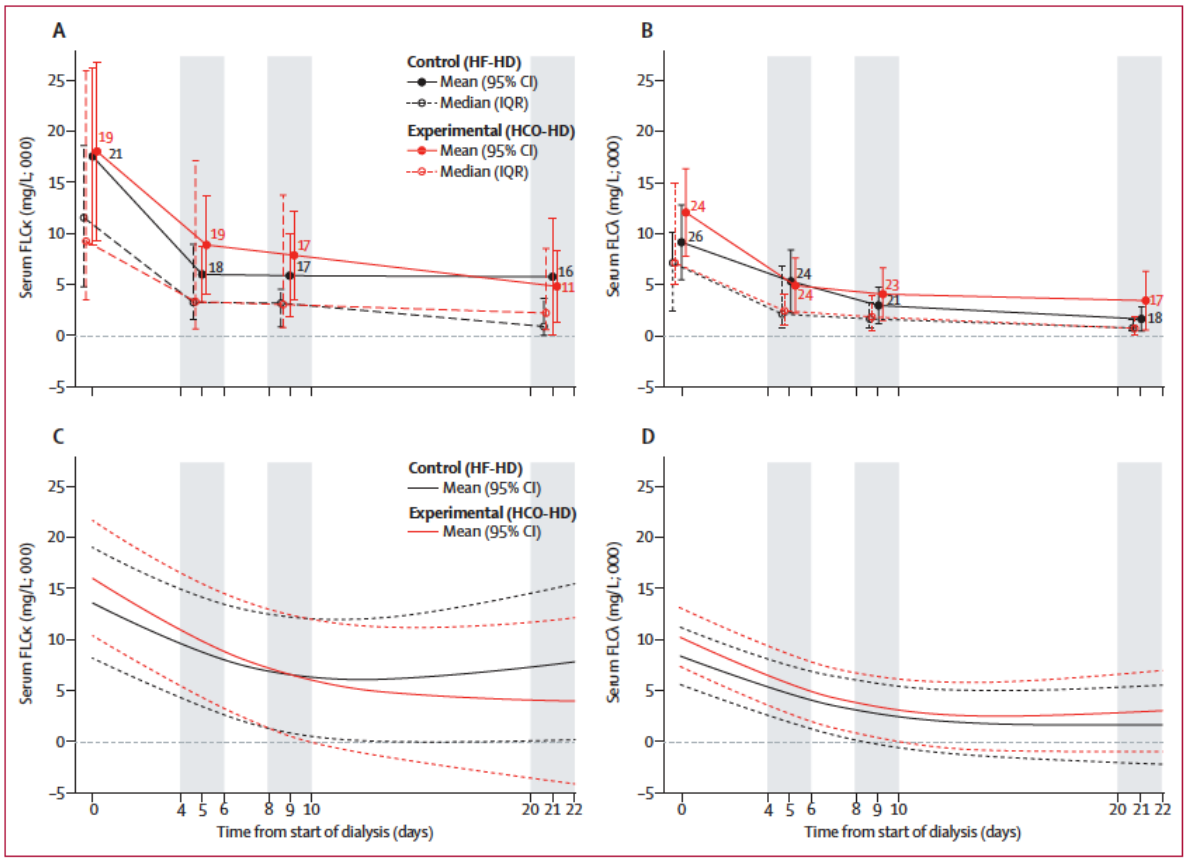

Figure 2: **Change in κ-sFLC and λ-sFLC concentration at days 4–6, 8–10, and 20–22**

Data are the observed mean change (95% CI) in (A) κ-sFLC and (B) λ-sFLC concentration at baseline and days 4–6, 8–10, and 20–22 and the model fit based on predictions from a linear mixed-effects model incorporating restricted cubic splines for (C) κ-sFLC and (D) λ-sFLC on days 0–22. HCO-HD=high cutoff haemodialysis. HF-HD=high-flux haemodialysis. sFLC=serum free light chain immunoglobulin.

Figure 3

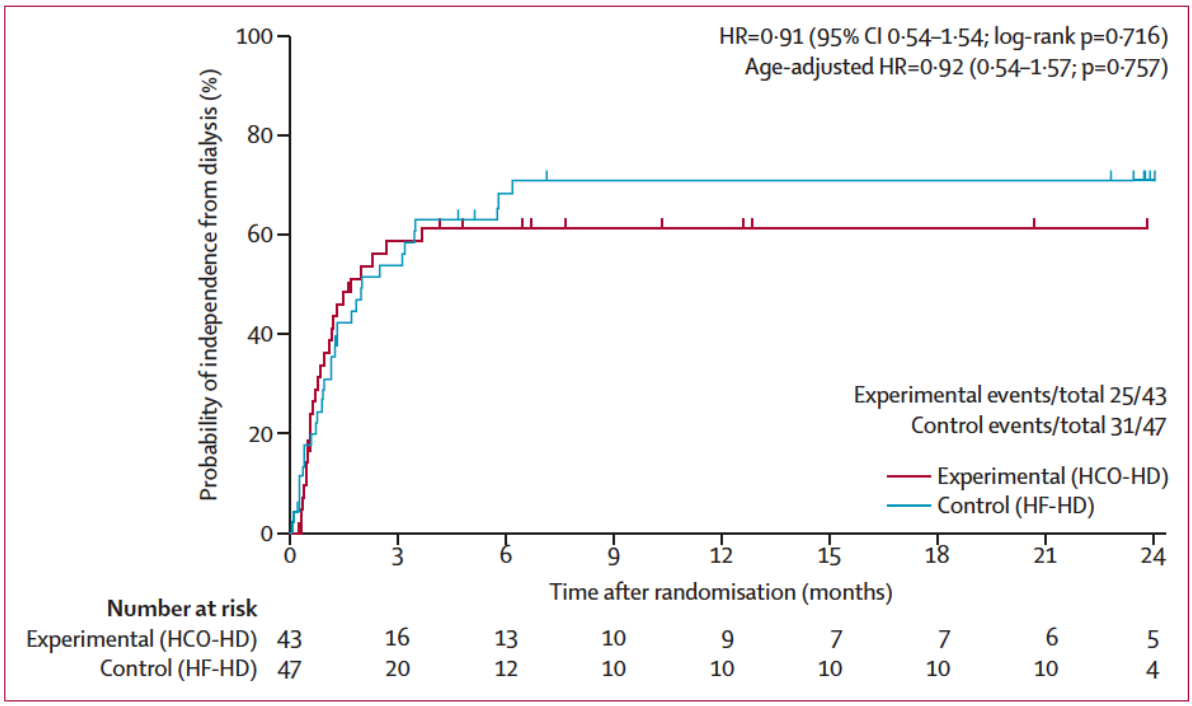

Figure 3: **Reverse Kaplan-Meier graph of time to independence from dialysis by treatment group**
HCO-HD=high cutoff haemodialysis. HF-HD=high-flux haemodialysis. HR=hazard ratio.

Figure 4

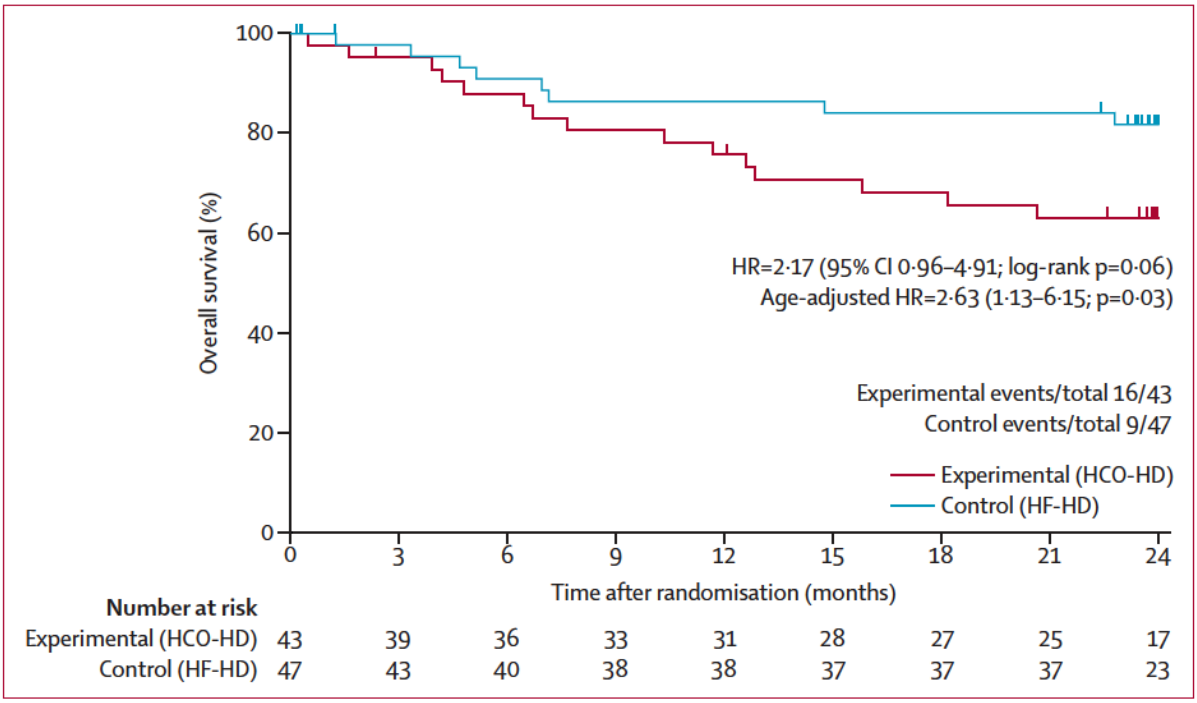

Figure 4: **Kaplan-Meier graph of overall survival by treatment group**
HCO-HD=high cutoff haemodialysis. HF-HD=high-flux haemodialysis. HR=hazard ratio.

Table 1: Baseline demographic and laboratory characteristics

Baseline demographic and laboratory characteristics		
Characteristic	**HCO-HD (N=43)**	**HF-HD (N=47)**
Gender (male)	26 (60%)	25 (53%)
Age (years)	66 (11)	65 (10)
18-54	6 (14%)	10 (21%)
55-65	17 (40%	15 (32%)
66-75	13 (30%)	17 (36%)
75+	7 (16%)	5 (11%)
Race		
White	36 (84%)	41 (87%)
Black	5 (12%)	2 (4%)
South-Asian	2 (5%)	4 (9%)
Comorbidity ($)		
Previous known kidney disease	3 (7%)	1 (2%)
Hypertension	17 (40%)	22 (47%)
Diabetes Mellitus	8 (19%)	9 (19%)
Potential precipitating factors		
Hypercalcaemia (>2.5 mmol/L)	20 (47%)	14 (30%)
NSAID	4 (9%)	4 (9%)
ACEi/ARB	8 (19%)	10 (21%)
Aminoglycoside	1 (2%)	1 (2%)
Loop diuretic	1 (2%)	2 (4%)
>1 precipitating factor	7 (16%)	5 (11)%
Dexamethasone pre-randomisation	5 (12%)	8 (17%)
Dialysis pre-randomisation	32 (74%)	31 (66%)
Dialysis days pre-bortezomib regime	5.7 (3.6)	5.7 (3.7)
Dialysis sessions $	3 (2-4)	3 (2-4)
eGFR (ml/min/1.73m^2)	7 (2)	7 (3)
Calcium (mmol/L) $	2.5 (2.4-2.7)	2.4 (2.2-2.6)

Table 1: Baseline demographic and laboratory characteristics (cont)

Baseline demographic and laboratory characteristics		
Albumin (g/L) $	36.8 (7.7)	38.1 (5.9)
Haemoglobin (g/L)	90 (10)	91 (14)
Bone marrow plasma cells (%)	48 (23)	50 (25)
Myeloma type		
IgG	9 (21%)	19 (40%)
IgA	9 (21%)	4 (9%)
IgD	2 (5%)	4 (9%)
Light Chain Only (LCO)	23 (53%)	24 (51%)
LC isotype		
kappa	19 (44%)	21 (45%)
lambda	24 (56%)	26 (55%)
Serum LC level (mg/L)		
kappa	9300 (3570-25954)	11600 (5277-19118)
lambda	7150 (4696-15650)	7155 (2818-10840)

Data are: n (%); mean (standard deviation (SD)); median (interquartile range (IQR)); eGFR; estimated glomerular filtration; Ig, Immunoglobulin; LC, light chain. $ = missing data (n); kidney disease (2), hypertension (2), diabetes mellitus (1); dialysis sessions (1), Calcium level (1), Albumin level (1)

Table 2: disease response category by treatment arm at 6 and 12 months

Myeloma response at 6 and 12 months				
Disease response	**6 months***		**12 months****	
	HCO-HD (N=43)	HF-HD (N=47)	HCO-HD (N=43)	HF-HD (N=47)
Complete Response	6 (14%)	14 (30%)	12 (28%)	16 (34%)
Very Good Partial Response	10 (23%)	15 (32%)	3 (7%)	13 (28%)
Partial Response	11 (26%)	5 (11%)	3 (7%)	3 (6%)
Stable Disease	1 (2%)	0 (0%)	3 (7%)	1 (2%)
Progressive Disease	3 (7%)	3 (6%)	8 (19%)	3 (6%)
Not Assessed	3 (7%)	1 (2%)	2 (5%)	2 (4%)
Death or withdrawal	9 (22%)	9 (19%)	12 (27%)	9 (20%)

*risk ratio for disease response was 0.87 (95% CI: 0.65 to 1.16; P=0.46), for HCO-HD vs HF-HD
**risk ratio for disease response 0.62 (95% CI: 0.41-0.92; P=0.022) for HCO-HD vs HF-HD

Table 3: causes of death

	HCO-HD (N=43)	HF-HD (N=47)
Numbers (% of participants)	16 (37%)	9 (19%)
Cause and % of deaths		
Advanced myeloma	7 (44%)	4 (44%)
Infection	5 (31%)	3 (33%)
Renal Failure	2 (13%)	0
Cardiac disease	0	1 (11%)
Other	2 (13%)	1 (11%)

Table 4. Grade 3-5 adverse events, by time of onset

	Total	HCO-HD (43)	HF-HD (47)
SAE onset date 0-90 days	**78**	**45**	**33**
Infections	**39 (50%)**	**26 (38%)**	**13 (39%)**
Catheter Related	8 (10%)	5 (11%)	3 (9%)
Lung	17 (22%)	14 (31%)	3 (9%)
Sepsis	3 (4%)	1 (2%)	2 (6%)
Other	11 (14%)	6 (13%)	5 (15%)
Not-infections	**39 (50%)**	**19 (42%)**	**20 (61%)**
Cardiovascular & thrombotic	6 (8%)	3 (7%)	3 (9%)
Gastrointestinal	4 (5%)	3 (7%)	1 (3%)
Haematological	0	0	0
Musculoskeletal	8 (10%)	5 (11%)	3 (9%)
Neurological	2 (3%)	1 (2%)	1 (3%)
Other organ systems	19 (24%)	7 (16%)	12 (36%)
SAE onset date 91 days – 12 months	**67**	**33**	**34**
Infections	**27 (40%)**	**10 (30%)**	**17 (50%)**
Catheter Related	2 (3%)	1 (3%)	1 (3%)
Lung	6 (9%)	2 (6%)	4 (12%)
Sepsis	6 (9%)	3 (9%)	3 (9%)
Other organ systems	13 (19%)	4 (12%)	9 (26%)
Not-infections	**40 (60%)**	**23 (70%)**	**17 (50%)**
Cardiovascular & thrombotic	4 (6%)	2 (6%)	2 (6%)
Gastrointestinal	7 (10%)	4 (12%)	3 (9%)
Haematological	2 (3%)	0	2 (6%)
Musculoskeletal	6 (9%)	3 (9%)	3 (9%)
Neurological	7 (10%)	5 (15%)	2 (6%)
Other organ systems	14 (21%)	9 (27%)	5 (15%)

Table 4 (cont.) Grade 3-5 adverse events, by time of onset

	Total	HCO-HD (43)	HF-HD (47)
SAE onset date 12-24 months	**35**	**20**	**15**
Infections	14 (40%)	8 (40%)	6 (40%)
Catheter Related	0	0	0
Lung	8 (23%)	5 (25%)	3 (20%)
Sepsis	0	0	0
Other organ systems	6 (17%)	3 (15%)	3 (20%)
Not infections	21 (60%)	12 (60%)	9 (60%)
Cardiovascular & thrombotic	0	0	0
Gastrointestinal	3 (9%)	2 (10%)	1 (7%)
Haematological	1 (3%)	1 (5%)	0
Musculoskeletal	3 (9%)	2 (10%)	1 (7%)
Neurological	3 (9%)	1 (5%)	2 (13%)
Other organ systems	11 (31%)	6 (30%)	5 (33%)