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ORIGINAL ARTICLE

Effectiveness of cold HD for the prevention of HD hypotension and mortality in the general HD population

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ABSTRACT

Background. Cold hemodialysis (HD) prevented intradialysis hypotension (IDH) in small, short-term, randomized trials in selected patients with IDH. Whether this treatments prevents IDH and mortality in the HD population at large is unknown.

Methods. We investigated the relationship between dialysate temperature and the risk of IDH, i.e. nadir blood pressure <90 mmHg (generalized estimating equation model) and all-cause mortality (Cox's regression) in an incident cohort of HD patients ($n = 8071$). To control for confounding by bias by indication and other factors we applied instrumental variables adjusting for case mix at facility level.

Results. Twenty-seven percent of patients in the study cohort were systematically treated with a dialysate temperature ≤35.5°C. Over a median follow-up of 13.6 months (interquartile range 5.2–26.1 months), a 0.5°C reduction of the dialysate temperature was associated with a small (–2.4%) reduction of the risk of IDH [odds ratio (OR) 0.976, 95% confidence interval (CI) 0.957–0.995, $P = .013$]. In case-mix, facility-level adjusted analysis, the association became much stronger (OR 0.67, 95% CI 0.63–0.72, risk reduction = 33%, $P < .001$). In contrast, colder dialysate temperature had no effect on mortality both in the unadjusted [hazard ratio (HR) (0.5°C decrease) 1.074, 95% CI 0.972–1.187, $P = .16$] and case-mix-adjusted analysis at facility level (HR 1.01, 95% CI 0.88–1.16, $P = .84$). Similar results were registered in additional analyses by instrumental variables applying the median dialysate temperature or the facility percentage of patients prescribed a dialysate temperature <36°C. Further analyses restricted to patients with recurrent IDH fully confirmed these findings.

Conclusions. Cold HD was associated with IDH in the HD population but had no association with all-cause mortality.

Keywords: cold hemodialysis, hemodialysis hypotension, kidney failure, mortality

INTRODUCTION

In the face of the unquestionable benefits of hemodialysis (HD) for correcting the metabolic alterations of end-stage kidney disease and for the control of fluid overload, HD treatment *per se* induces several intradialysis complications of which HD hypotension (IDH) [1] is the most concerning. The adverse effects of HD on the heart [2] and nervous system [3] have been investigated in landmark studies by McIntyre *et al.* These studies coherently linked myocardial and brain injury to HD exposure. In these studies ultrafiltration rate and intradialytic blood pressure (BP) falls were apparently the main mediators of HD-induced myocardial and brain dysfunction. Interestingly, these noxious effects of HD were prevented by cold dialysis [4, 5]. These pathophysiological observations go along with a randomized clinical trial by Maggiore *et al.*, in 95 patients [6], which clearly showed that cold dialysis substantially reduces the risk for IDH. Other small trials confirmed the findings of Maggiore *et al.* and a meta-analysis in 2015 collating a total of 484 patients showed that cold HD has distinct hemodynamic advantages as compared with standard HD [7]. On average the duration of these trials was relatively short and ranged from 2 to 24 dialysis sessions [7], and no major clinical events like death could be investigated in these trials. A cluster randomized trial embedded in clinical practice (MyTEMP) testing the effect of cold HD on clinical outcomes is ongoing in 84 dialysis centers in Ontario, Canada [8] and the results of this trial are expected by 2023. Whether cold dialysis may serve to prevent IDH and all-cause mortality in the HD population at large rather than in selected patients

KEY LEARNING POINTS

What is already known about this subject?

- Cold hemodialysis (HD) prevented intradialysis hypotension (IDH) in small, short-term, randomized trials in selected patients with IDH.
- Whether this treatments prevents IDH and mortality in the HD population at large is unknown.
- We investigated the relationship between dialysate temperature and the risk of IDH (generalized estimating equation model) and all-cause mortality (Cox's regression) in an incident cohort of HD patients ($n = 8071$).

What this study adds?

- Over a median follow-up of 13.6 months, a 0.5°C reduction of the dialysate temperature was associated with a small (−2.4%, not significant) reduction of the risk of IDH. In an instrumental variable (the dialysis units) based analysis adjusted for case mix the association became much stronger (risk reduction = 33%, $P < .001$).
- In contrast, colder dialysate temperature had no effect on mortality both in the unadjusted and case-mix-adjusted analysis.
- Cold HD effectively prevents IDH in the HD population but has no effect on all-cause mortality.

What impact this may have on practice or policy?

- While confirming on a large scale and in the real world clinical practice that cold HD prevents IDH, our study suggests that it is unlikely that this intervention reduces mortality in the HD population.

with IDH has never been explored in observational studies. In the absence of golden standard studies, i.e. randomized clinical trials, these studies represent a valuable source of information [9].

With this background knowledge in mind we performed a study based on an incident cohort extracted from the Fresenius NephroCare data base of two countries, Spain and Portugal, which are part of the European Middle East Africa (EMEA) network of the same company. The cohort includes over 8000 patients and the scope of the present study is that of describing the relationship of dialysate temperature with the incidence of IDH and with all-cause mortality. In order to control for bias by indication we applied two instrumental variables [10, 11], namely the case-mix-adjusted dialysate temperature by facility and the case-mix-adjusted facility percentage of patients prescribed a dialysate temperature <36°C.

MATERIALS AND METHODS

The study was conducted along the principles of the Helsinki Declaration and written informed consent was obtained by each participant.

The study cohort was formed by patients treated in the Fresenius NephroCare dialysis centers network, operating in two European countries, Spain and Portugal. Data were retrieved from the central European Clinical Database version 5 (EuCliD5) database, which integrates patient characteristics as well as day-by-day treatment data, laboratory parameters and medications. Along with KDOQI guidelines [12] in the NephroCare network cold dialysis is formally included in a set of interventions recommended for the treatment of severe, recurrent IDH (see Supplemental appendix, Fresenius manual). However, apart from these selected cases, background dialysate temperature at center level is decided by the Directors of individual clinics and no specific general recommendation for dialysate temperature is given to these doctors. Dialysate temperature during each dialysis treatment as well as all BP and heart-rate measurements and information on blood flow and other technical parameters is systematically (automatically) transferred from the haemodialysis monitors to the EuCliD clinical database, thereby ensuring complete case ascertainment.

In this study we included incident patients who received haemodialysis (HD) treatments for at least 30 days from January 2018 until December 2021. In order to be included in the study cohort patients had to have had a constant value of the dialysate temperature during the month preceding the study i.e. during the preceding 12 HD sessions. All patients consented their pseudo-anonymized data be used for statistical analyses.

Along the study by Flythe *et al.* [13] which found that the nadir BP during the HD session was the sole definition to be related with the risk of death, we defined IDH as a nadir BP <90 mmHg during the HD session. Pre-dialysis fluid excess was quantified by applying bioimpedance analysis (Body Composition Monitor, Fresenius Medical Care) [14]. The detailed definitions of demographic and clinical data and dialysate temperature data acquisition, the analytical plan and statistical analysis are described in the Supplemental Information I and II.

RESULTS

The source study population was composed by an incident cohort of 8579 HD patients. Thirty-three patients were excluded because of no information about time to death/censoring or missing dialysate temperature. Thus, 8546 HD patients (age 67 ± 14 years; 65% males) treated in 103 dialysis clinics in Spain ($n = 4950$ patients from 59 clinics) and in Portugal ($n = 3596$ patients from 44 clinics). All patients included in the EuCliD5 database were assessed for eligibility. Among these, 475 patients were excluded because they did not display a constant value of the dialysate temperature during the 12 HD sessions preceding the enrolment (Fig. 1). Thus, 8071

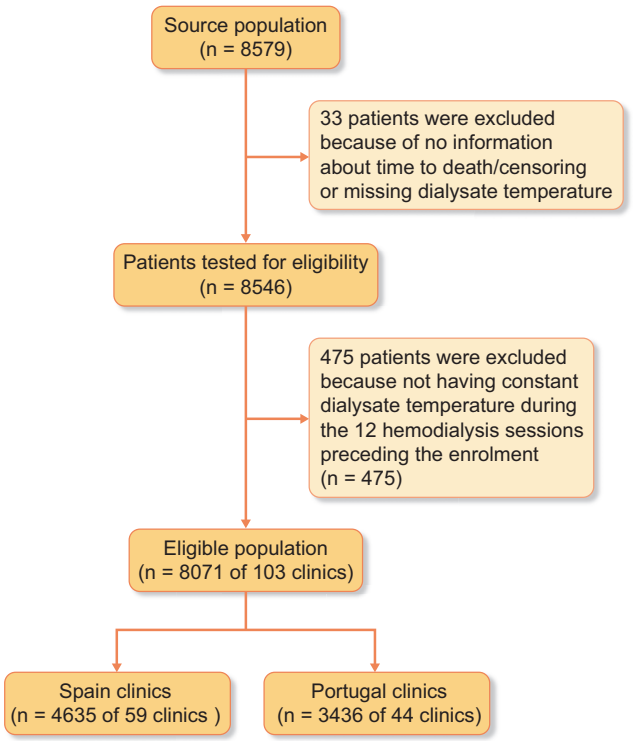

Figure 1: Flowchart of patients throughout the study.

patients (94% of the source population) were available for the present analysis. The characteristics of patients included into the analysis ($n = 8071$, Table 1) did not materially differ from those who were excluded because variable dialysate temperature ($n = 475$) (see Supplementary data, Tables I and II).

Eligible patients had a mean age of 67 ± 14 years and a median dialysis vintage of 1.4 months [interquartile range (IQR) 1.1–2.9 months]. Sixty five percent were males and 42% were diabetics. Average pre-dialysis body mass index, and pre- and post-dialysis BPs were 27.2 ± 6.2 kg/m^2, 143 ± 20/68±12 mmHg and 151 ± 22/72±13 mmHg, respectively. Fractional urea clearance (Kt/V) was on average 1.50 ± 0.40. Pre- and post-dialysis fluid overload were 1.84 ± 2.33 L and 0.38 ± 2.12 L, respectively. The large majority of patients ($n = 6474$, 80%) were treated with various anti-hypertensive drugs (Table 1) and 6410 (79%) had one or more comorbidities (Table 2). The remaining demographic, clinical and biochemical characteristics of the study population are detailed in Table 1.

Dialysate temperature

At baseline, i.e. during the 12 dialysis sessions preceding the study, the temperature of the dialysate was 35°C in 42 cases (0.5%), 35.5°C in 2145 cases (26.6%), 36°C in 5145 cases (63.7%), 36.5°C in 714 cases (8.8%) and 37°C in the remaining 25 cases (0.3%). Across the follow-up period, dialysate temperature was not changed in 6964 patients (86%) whereas it was in 1107 patients (14%), during a total of 111 079 dialysis sessions. In detail, the dialysate temperature was lowered in 55 654 dialysis sessions (50%) [≤0.5°C in 47 407 dialysis sessions (43%); >0.5°C to ≤1°C in 7938 (7%); and >1°C in the remaining 319 dialysis sessions (0.3%)] and increased in the other 55 425 sessions (50%) [≤0.5°C in 49 099 dialysis sessions (44%); >0.5°C to ≤1°C in 5847 (5%); and >1°C in the remaining 469 dialysis sessions (0.4%)]. Patients in whom changes of dialysate temperature were applied had been on dialysis for a shorter time, had less frequently atrial fibrillation and more frequently congestive heart failure or hemiplegia,

Table 1: Demographic and clinical characteristics of the study population.

Patients	$n = 8071$
Average dialysate temperature, °C	35.9 ± 0.34
Demographic, somatometric and hemodynamic data	
Age, years	67 ± 14
Dialysis vintage, months	1.4(1.1–2.9)
Males, %	65
Height, cm	164 ± 10
Weight post, kg	71.6 ± 15.6
Weight pre, kg	73.1 ± 15.8
Body mass index pre, kg/m^2	27.2 ± 6.2
Systolic BP pre, mmHg	143 ± 20
Systolic BP post, mmHg	151 ± 22
Diastolic BP pre, mmHg	68 ± 12
Diastolic BP post, mmHg	72 ± 13
Heart rate pre, beats/min	71 ± 12
Heart rate post, beats/min	72 ± 12
Treatment time, min	227 ± 20
Biochemical profiles	
Hemoglobin, g/dL	10.3 ± 2.1
Albumin, g/dL	3.7 ± 0.6
Calcium, mg/dL	8.8 ± 1.5
Phosphate, mg/dL	4.5 ± 1.5
Glucose, mg/dL	137 ± 69
Anti-hypertensive treatment	
ACE inhibitors and/or angiotensin antagonists, *n* (%)	2624 (32.5)
Alpha- and/or beta-blockers, *n* (%)	3179 (39.4)
Calcium channel blockers, *n* (%)	3472 (43.0)
Diuretics, *n* (%)	323 (39.9)
Peripheral vasodilators, *n* (%)	374 (4.6)
Other anti-hypertensive drugs, *n* (%)	1744 (21.6)

Data are mean and standard deviation, median and interquartile range, or as absolute number and % frequency, as appropriate.

Table 2: Patients' comorbidities.

Comorbidity	*n* (%)
Hypertension	4239 (52.5)
Diabetes mellitus	3428 (42.5)
Congestive heart failure	2107 (26.1)
Coronary artery disease/ischemic heart disease	1729 (21.4)
Atrial fibrillation	631 (7.8)
Other forms of heart disease	1945 (24.1)
Cerebrovascular disease	906 (11.2)
Peripheral vascular disease	781 (9.7)
Chronic pulmonary disease	784 (9.7)
Pulmonary hypertension	96 (1.2)
Dementia	163 (2.0)
Hemiplegia	40 (0.5)
Tumor without metastasis	1038 (12.9)
Metastatic solid tumor	77 (1.0)
Mild liver disease	405 (5.0)
Moderate/severe liver disease	112 (1.4)
Peptic ulcer disease	237 (2.9)
Chronic rheumatic disease	66 (0.8)
AIDS	55 (0.7)

Data are given as absolute number and % frequency.

Table 3: Generalized estimating equation of hypotension episodes.

Patient-level analysis		
Unadjusted analysis		
	Units of change	OR (95% CI), *P*-value Crude
Dialysate temperature (continuous variable)	0.5°C decrease	0.98 (0.96–0.99), $P = .013$
Adjusted facility-level analysis		
	Units of change	OR (95% CI), *P*-value
Case-mix adjusted dialysate temperature (continuous variable)[a]	0.5°C decrease	0.67 (0.63–0.72), $P < .001$
Case-mix adjusted dialysate temperature (binary variable)[a]	0 ≥ 36°C 1 < 36°C	0.71 (0.68–0.75), $P < .001$
Case-mix adjusted facility percentage of patients prescribed a dialysate temperature <36°C[a]	30%	0.82 (0.80–0.85), $P < .001$

The inclusion of post-dialysis fluid overload instead of pre-dialysis fluid over for calculating case-mix-adjusted dialysis temperature and case-mix-adjusted facility percentage of patients prescribed a dialysate temperature <36°C provided almost identical results.

[a]Variables applied for adjusting for case mix are age, gender, comorbidities (i.e. presence/absence of AIDS, cerebrovascular disease, chronic pulmonary disease, congestive heart failure, coronary artery disease, diabetes, dementia, hemiplegia, metastatic solid tumor, mild/moderate liver disease, peptic ulcer disease, peripheral vascular disease, tumor without metastasis, atrial fibrillation, chronic rheumatic heart disease, hypertensive disease, ischemic heart disease, other forms of heart disease, pulmonary heart disease, other unspecified disorder of circulatory system), dialysis vintage, pre-dialysis body mass index, pre-dialysis systolic and diastolic BPs, pre-dialysis heart rate, pre-dialysis fluid overload, fractional urea clearance (Kt/V), treatment effective time, hemoglobin, albumin, calcium, phosphate and anti-hypertensive therapy, i.e. use of ACE inhibitors and/or angiotensin antagonists, alpha- and/or beta-blockers, calcium channel blockers, diuretics, peripheral vasodilators and other anti-hypertensive drugs.

and showed higher pre-dialysis systolic BP, hemoglobin, calcium and Kt/V, and were more frequently being treated with angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin antagonists, alpha- and/or beta-blockers, calcium channel blockers and diuretics as compared with remaining patients (all $P < .05$). In a multiple logistic regression model including all these correlates of dialysate temperature change, only Kt/V [odds ratio (OR) (1 unit increase) 1.40, 95% confidence interval (CI) 1.18–1.64, $P < .001$] hemiplegia (OR 2.50, 95% CI 1.22–5.10, $P = .012$), use of calcium channel blockers (OR 1.20, 95% CI 1.04–1.38, $P = 0.012$), congestive heart failure (OR 1.17, 95% CI 1.01–1.37, $P = .04$) and dialysis vintage [OR (12 months) 0.977, 95% CI 0.957–0.997, $P = .02$] maintained an independent relationship with the change in temperature. Furthermore, in a separate analysis investigating the relationship between repeated episodes of hypotension (i.e. at least one episode in >50% of dialysis sessions) and cold dialysate temperature (<36°C, case mix), cold dialysate temperature reduced by 32% the frequency of repeated episodes of hypotension over time (OR 0.68, 95% CI 0.56–0.82, $P < .001$).

Dialysate temperature and incidence of IDH

Over a median follow-up of 13.6 months (IQR 5.2–26.1 months), a total of 1 688 243 dialysis sessions were analyzed in 8071 patients. The incidence rate of hypotension episodes over time was 16.8 events per person-year (95% CI 16.7–16.9). In an unadjusted patient-level generalized estimating equation model, a 0.5°C reduction of the dialysate temperature was associated with 2.4% reduction of the OR of hypotension episodes over time [OR (0.5°C decrease) 0.98, 95% CI 0.96–0.99, $P = .013$] (Table 3). Since bias by indication and confounding are a serious threat to data interpretation in studies about dialysis temperature we approached the problem by applying two instrumental variables that may remove such a bias: the case-mix-adjusted dialysate temperature by facility and the case-mix-adjusted facility percentage of patients prescribed a dialysate temperature <36°C. The partial F-statistics of these instrumental variables were 88.5 ($P < .001$) and 108 ($P < .001$), respectively. Such high F-values (see Materials and methods) indicate that the two instrumental variables adequately reflected the policies of facilities as for the prescription of dialysate temperature. Because of at least partial removal of bias by indication and cofounding, the effect of a reduction of the dialysate temperature on hypotension episodes over time resulted to be much stronger when investigated by a facility-level analysis adjusting for confounding by indication. Indeed, a 0.5°C decrease in the case-mix-adjusted dialysate temperature (continuous variable) was associated with 33% decrease of the OR of hypotension episodes over time [OR (0.5°C decrease) 0.67, 95% CI 0.63–0.72, $P < .001$], (Table 3). The same analysis carried out by dividing the study population according to the median value of case-mix-adjusted dialysate temperature showed that patients treated in centers with a value of this variable <36°C had an OR of hypotension episodes that was 28.9% lower than in those treated in centres with the same variable above this cut-off (OR 0.71, 95% CI 0.68–0.75, $P < .001$) (Table 3). A further instrumental variable analysis considering the case-mix-adjusted facility percentage of patients prescribed a dialysate temperature <36°C (see Table 3) showed that a 30% increase in the percentage of patients treated with a dialysate temperature <36°C at facility level associated with a 18% decrease of the OR of hypotension episodes over time (OR 0.82, 95% CI 0.80–0.85, $P < .001$). The inclusion of post-dialysis fluid overload instead of pre-dialysis fluid overload for calculating the case-mix-adjusted dialysis temperature and the case-mix-adjusted facility percentage of patients prescribed a dialysate temperature <36°C provided similar results (data not shown). The relationship between dialysate temperature and the incidence rate of IDH is presented in Supplemental Information II.

Table 4: Cox regression analyses for the risk of death.

Patient-level, country level stratified, unadjusted analysis		
	Units of change	HR[a] (95% CI), *P*-value Crude
Dialysate temperature (continuous variable)	0.5°C decrease	1.07 (0.97–1.19), $P = .16$
Adjusted facility-level analysis		
	Units of change	HR[a] (95% CI), *P*-value
Case-mix adjusted dialysate temperature (continuous variable)	0.5°C decrease	1.01 (0.88–1.16), $P = .84$
Case-mix adjusted dialysate temperature (binary variable)	0 ≥ 36°C 1 < 36°C	1.07 (0.95–1.21), $P = .26$
Case-mix adjusted facility percentage of patients prescribed a dialysate temperature <36°C (continuous variable)	30%	0.99 (0.94–1.06), $P = .96$

The case-mix-adjusted dialysate temperature and the case-mix-adjusted facility percentage of patients prescribed a dialysate temperature <36°C (the median value) were calculated using two separate linear regression models having patient dialysate temperature [as continuous variable or as binary (below/above 36°C) variable] as dependent variables. The independent variables were the facility indicator (N-1 dummy variables) together with the set of covariates listed in the Materials and methods, Statistical analysis section. [a]Country stratified. Variables applied for adjusting for case mix are listed in Table 3.

Survival analysis

During the follow-up period (median 13.6 months, IQR 5.2–26.1 months), 1155 patients died (incidence rate:10.4 deaths per 100 persons-year, 95% CI 9.8–11.0). In patient level analyses, dialysate temperature was unrelated to the incidence rate of all-cause mortality [HR (0.5°C decrease) 1.07, 95% CI 0.97–1.19, $P = .16$] (Table 4). The instrumental variable approach considering the case-mix-adjusted dialysate temperature at facility level as continuous variable [HR (0.5°C decrease) 1.01, 95% CI 0.88–1.16, P = 0.84] or as dichotomized according to the corresponding median value [HR (<36°C versus ≥36°C) 1.07, 95% CI 0.95–1.2, $P = .26$] confirmed no association between dialysate temperature and death (Table 4), and this was also true in a further instrumental variable analysis considering the case-mix-adjusted facility percentage of patients prescribed a dialysate temperature <36°C [HR (30%) 0.99, 95% CI 0.94–1.06, $P = .96$] (Table 4).

DISCUSSION

In this observational study based on the analysis of 1 688 243 HD sessions in 8071 patients in 103 HD clinics in Portugal and Spain, the use of cold dialysis was weakly associated with a reduced risk for incident IDH (risk reduction 2.4% for a 0.5°C lower dialysate temperature) but this association became substantially more pronounced (risk reduction 32%) in analyses adjusting for case mix at facility level. The prevention of IDH was confirmed in additional facility-level case-mix-adjusted analyses where dialysate temperature was categorized as below or above 36°C or considering the facility percentage of patients prescribed a dialysate temperature <36°C. However, cold HD bore no relationship to mortality in unadjusted and adjusted analyses.

In the largest trial that tested the effect of reduced dialysis temperature the frequency of IDH decreased was halved [6] and this treatment was tolerated without adverse effects. Modern dialysis monitors allow isothermal and cool HD but these treatments are generally applied only in severe cases. Overall in most dialysis centers no established policy exists for IDH prevention and these techniques are generally applied less than needed [15]. In the meta-analysis by Mustafa *et al.* [7] collating trials performed until April 2015 among the 26 trials performed by that date, 11 could be included in a quantitative synthesis (261 patients). The trials were small (number of patients ranging from 9 to 99) and of short duration (from 1 to 24 HD sessions with the majority of trials considering ≤6 HD sessions). Disparate definitions of IDH were applied and patients included in this meta-analysis had wide-ranging differences in background HD hypotension frequency. While these trials established the short-term efficacy of cold dialysis in selected patients, the long term effects of these interventions for the prevention of IDH and mortality in the dialysis population at large remain undefined.

The conventional modelling approach to eliminate selection bias in observational studies, i.e. adjustment for all known confounders and their potential interactions, is unlike to completely remove bias by indication. The instrumental variable method, the method we applied in the present study, aims at mimicking the randomized trial [11]. In brief, this method is based on a variable, the instrumental variable, which is related to the actual treatment, but at the same time can be considered to be allocated randomly to patients, i.e. independent of the prognostic profile of the individual patient [11]. The random allocation of this variable is a sort of "natural experiment." In this approach it is crucial that patients are analyzed according to the instrumental variable rather than to the actual treatment received, thereby mimicking the intention-to-treat analysis [11]. Because patients attend treatment facilities in the neighbourhood of their residence, in principle the facility's treatment strategy, in our case dialysate temperature, can be considered to be allocated (at least partially) at random to a patient and may therefore be utilized as an instrumental variable. A similar strategy was used to minimize bias by indication in a study by the Dialysis Outcomes and Practice Patterns Study (DOPPS) comparing outcomes of catheters/grafts vs native arteriovenous (AV) fistula in HD patients [16]. In about 23% of clinics in Spain and Portugal,

temperatures ≤35.5°C—i.e. temperatures whose efficacy for the prevention of IDH was established in clinical trials [7]—were systematically applied over the timeframe of this cohort study. Our analysis provides an estimate of the effect of the systematic application of cool HD for the prevention of IDH in the whole dialysis population and in selected patients with recurrent IDH. In our study instrumental variable analysis removed substantial bias by indication. Indeed the unadjusted OR of IDH episodes indicated a 2.4% risk reduction for each 0.5°C decrease in dialysate temperature while the corresponding case-mix-adjusted facility-level analysis registered a substantially larger effect, i.e. a 32.6% risk reduction for each 0.5°C decrease.

Notwithstanding our analyses mitigated bias by indication and other confounders and confirmed on a large scale the preventive effect of cold HD for IDH, we found no effect of this treatment on mortality in case-mix-adjusted analyses at facility level. This finding is apparently counterintuitive with the beneficial effect by cold dialysis on myocardial stunning in the landmark study by the McIntyre group [2] and the relationship of HD hypotension with mortality described in a study based on the occurrence of this complication in a single dialysis session [17]. However, the implication of repeated, reversible small ischemic events during dialysis for major cardiovascular outcomes is complex [18–21]. In adjusted analyses in the HEMO study the link of IDH with mortality was significant only with the "nadir BP < 90 mmHg" definition and only when this complication occurred in >50% of HD sessions, while other definitions failed to predict mortality [13]. Furthermore, no association between IDH and mortality was registered in adjusted analyses in another study that tested both patients with occasional or frequent IDH [22]. An additional study in a large dialysis network in the USA showed that the risk of BP during dialysis is U-shaped with a risk rise below 90 mmHg and above 140 mmHg [23].

This study has several limitations. The study population was almost entirely composed by Caucasian patients and therefore our findings cannot be generalized to other ethnicities. We could not include information on patients tolerance to cold HD. Given the observational nature of our findings, residual confounding by bias by indication and other factors cannot be excluded. The instrumental variable analysis we applied in this study, i.e a case-mix-adjusted facility-level analysis including 40 variables, can mitigate bias by indication and other confounders but it does not guarantee complete elimination of these factors. Such an approach led to the emergence of a strong association between cold dialysis and incident IDH which was not apparent in the crude, unadjusted analysis but did not modify the relationship between cold dialysate temperature and mortality. However robust, our observational findings remain just exploratory rather than hypothesis testing. The fact that we have no information on the effect of cold dialysate temperature on the patients feeling of coldness is another limitation that needs to be addressed in future trials. Whether in addition to reducing the incidence of HD hypotension cold HD may prevent mortality in the dialysis population is an issue that will be resolved by the MyTemp trial.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

FUNDING

None declared.

AUTHORS' CONTRIBUTIONS

C.Z. and S.S. conceived the idea of this study. C.Z. and G.T. designed the analytical plan. The data analysis was done by G.T. and L.N., and M.S. helped the data analysis. M.S. was responsible for the building of the analytical database. M.E.B.S. and P.P. are Country Medical Directors of Spain and Portugal, respectively, at Fresenius Medical Care and were responsible for the quality of data collection. F.Mallamaci contributed to the design of this study and to the writing of the manuscript. J.H. and F.Maddux provided significant intellectual contribution to the study by interacting with C.Z. and S.S. C.Z., G.T. and F.Mallamaci wrote the first draft of the paper, and C.Z. prepared the final draft. The paper was critically reviewed by all authors and finally approved by all authors.

DATA AVAILABILITY STATEMENT

The database of the study will be made available to interested investigators six months after the publication of this study. Interested investigators should ask the data to Dr Stefano Stuard, Fresenius Vice-President, E-mail: stefano.stuard@fmc-ag.com

CONFLICT OF INTEREST STATEMENT

L.N., M.S., M.E.B.S., P.P., J.H., F.Maddux and S.S. are Fresenius Medical Care employees. C.Z. and G.T. are scientific consultants to Fresenius Medical Care. F.Mallamaci declares no conflict of interest.

(See related article by Combe and Rubin. Cold haemodialysis: the instrumental power of large cohorts. *Nephrol Dial Transplant* 2023; 38: 1577–1579)

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