Acetate-Free Biofiltration Reduces Intradialytic Hypotension: A European Multicenter Randomized Controlled Trial

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Key Words

Bicarbonate hemodialysis · Acetate-free biofiltration · Hemodiafiltration · Intradialytic hypotension · Systolic blood pressure · Cardiovascular morbidity · Cardiovascular mortality

Abstract

Background: Intradialytic hypotension (IH) is a common complication of bicarbonate hemodialysis (BD) and contributes to the intolerance of dialysis and the high cardiovascular morbidity and mortality among dialysis patients, the risk of which can be contained by convective therapies. **Aims/Methods:** To assess whether acetate-free biofiltration (AFB), a hemodiafiltration technique found to improve intradialytic cardiovascular stability in short-term studies, can influence long-term IH rates, predialysis systolic blood pressure (SBP), cardiovascular morbidity and mortality by comparison with BD, we analyzed data from a randomized controlled trial enrolling 371 new-to-dialysis patients, 194 on BD and 177 on AFB. **Results:** During a 3-year follow-up, AFB carried a significantly lower risk of IH (incidence rate ratio 0.60 (95% CI

0.53–0.68), $p < 0.0001$). SBP dropped on AFB ($p = 0.01$), while it did not change on BD. Cardiovascular morbidity and mortality were similar between AFB and BD. **Conclusion:** AFB carries a lower long-term IH rate and reduces SBP by comparison with BD.

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Introduction

Various factors make hemodialysis (HD) patients sensitive to cardiovascular events and death [1–9]. Conventional short, intermittent HD treatments themselves may contribute to the high rate of cardiac events in HD patients as a result of intradialytic hypotension (IH) [10], the most frequent complication of the standard HD procedure [11], which not only contributes to reducing the tolerability of dialysis but also causes a drop in coronary blood flow, which would lead to a left ventricular dysfunction that may persist even after a return to normal perfusion (myocardial stunning) [12, 13]. Such repeated, HD-induced ischemic events may raise the mortality rate

[14–17], cause sudden death [18], and have a role in the onset of heart failure [3, 19] and inability to reach the required dry weight, leading to fluid overload and its untoward effects, hypertension and left ventricular hypertrophy [20]. The HD procedure may also carry the risk of a reduced perfusion to other vascular beds in vulnerable organ systems [21, 22], such as the brain, and therefore contribute to the higher risk of cerebrovascular events in dialysis patients [23].

Modified dialysis procedures (such as biofeedback-controlled and cooled dialysis, or online hemofiltration and hemodiafiltration) has been shown to improve the hemodynamic tolerability of dialysis and to reduce the risk of IH [24, 25], resulting in a lower likelihood of cardiac injury [26, 27]. Another strategy for containing the risk of IH may be acetate-free biofiltration (AFB), a low-volume hemodiafiltration technique based on buffer-free dialysate, a biocompatible high-flux membrane, and sterile bicarbonate infusion in postdilution mode [28], which has been shown to improve systemic hemodynamics during dialysis in short-term studies [29], although this remains controversial [30].

To establish whether AFB improves long-term cardiovascular stability during dialysis, we analyzed the data collected in the open controlled randomized European multicenter study on the morbidity and mortality relating to AFB and bicarbonate hemodialysis (BD) [31], which had IH as the preset endpoint and enrolled patients at high risk of dialysis-related adverse events because they were elderly, diabetic and/or hypotension-prone on BD. Secondary aims of the study were to evaluate the influence of AFB on blood pressure, left ventricular mass index (LVMI), and cardiovascular morbidity and mortality, as compared with BD.

Methods

Study Design

The design of the trial has been described elsewhere [31]. The trial recruited patients from 92 European HD centers between March 1998 and December 2002 and ended in December 2006. All study procedures complied with the principles of the Helsinki Declaration. The study was approved by the local Ethics Committee of the Malpighi Hospital, Bologna, Italy, and registered under the Current Controlled Trials No. ISRCTN37257308.

Incident HD patients 18–78 years of age who started on conventional three times weekly BD were assessed for eligibility at the end of a 6- to 8-month stabilization period to identify their dry weight (on clinical grounds) and ensure the maturity of their vascular access, plus an extra 2-month run-in period to assess their intradialytic cardiovascular stability. Patients were eligible for the

study if they were considered ‘critical’, i.e. at high risk of dialysis-related adverse cardiovascular events because they were elderly (>60 years of age), diabetic and hypotension-prone (i.e. experiencing IH episodes in >20% of the dialysis sessions during the 2-month run-in period on BD). The exclusion criteria are reported elsewhere [31]. Eligible patients were enrolled after providing their informed consent and were randomly assigned to receive AFB or to continue on BD. Randomization was done centrally (with a computerized random-number generator) using the balanced block randomization technique with a 1:1 ratio, stratification according to the clinical center concerned and a block size of eight. After randomization, baseline Charlson comorbidity index [32], IH rate, pre- and postdialysis blood pressures (averaged over six consecutive dialysis treatments), cardiovascular data (including two-dimensional, M-mode and Doppler echocardiographic evaluation approximately 24 h after a mid-week dialysis session), dialysis prescription, biochemical data, outpatient medications (including classes of antihypertensive drugs and phosphate binders, nitrates, and antiplatelet agents) were recorded during an additional 2-week period on BD.

Dialysis prescriptions were at the discretion of the attending nephrologists and adjusted so that dialysis machine ultrafiltration control system, dialysate temperature, composition and flow, dialysis time, Q_b , ultrafiltration rate, and target $\text{spKt/V} > 1.2$ [33] were comparable for the two dialysis techniques at a given center. For the BD group, low- or high-flux synthetic membranes and dialysate with bicarbonate and acetate concentrations of 30–34 and 4–6 mM, respectively, were used according to each center practice patterns. AFB was conducted using the AN69 membrane, infusing a 145–167 mM sodium bicarbonate solution usually warmed to a temperature similar to that of the dialysate, at a rate targeting for a postdialysis plasma bicarbonate levels of 27–30 mEq/l. Water and dialysate quality were not ultrapure and complied with the criteria specified in the European Pharmacopoeia of 1997.

The study lasted 3 years during which time the number of IH episodes (occurring over a fortnight) was recorded every 6 months. All IH episodes occurring during each 6-month interval were also recorded. IH was defined as (i) a symptomatic drop of systolic blood pressure (SBP) of at least 25 mm Hg, requiring nursing intervention (any fluid administration or transient withdrawal of ultrafiltration), or premature termination of the session, (ii) a SBP <90 mm Hg even in the absence of symptoms in patients with predialysis SBP >100 mm Hg, or (iii) a symptomatic drop in SBP by at least 10% of the predialysis value for chronically hypotensive patients with a predialysis SBP ≤ 100 mm Hg.

In addition, adherence to the protocol, dialysis parameters, pre- and postdialysis body weight and SBP (averaged over six consecutive dialysis treatments), biochemical data, and outpatient medications were assessed every 6 months. LVMI [34] was evaluated every 6 months in the first year of follow-up and then yearly. To identify any carryover effect of the intradialytic events on clinical outcomes, all clinical events (including deaths, hospital admissions and their causes) were collected by the attending nephrologists up to 4 years of follow-up based on the EDTA codes, and were assessed independently by two of the three principal investigators of the study (A.S., G.O.P., N.T.). Dropouts and deaths due to noncardiovascular causes were included in the survival analysis and censored at the time of premature termination.

Fig. 1. Flow diagram of the Controlled Randomized European Study on Mortality and Morbidity [30].

Outcomes

The main outcome was the change in IH rate. Secondary outcomes were changes in predialysis SBP and LVMI, and cardiovascular mortality, morbidity and case fatality rates (i.e. the risk of cardiovascular death after a cardiovascular event). Cardiovascular mortality was defined as death due to cardiac causes (cardiac arrest, acute myocardial infarction or heart failure), or stroke (ischemic or hemorrhagic). A major cardiovascular event (MCE) was defined as a fatal or nonfatal cardiac event (cardiac arrest, heart failure, myocardial infarction, prolonged angina, the need for coronary angioplasty or bypass surgery) or stroke. The early cardiovascular case fatality rate was defined as the percentage of patients with an MCE that proved fatal. The long-term case fatality rate described the number of cardiovascular deaths among patients who had an MCE and survived 28 days or more afterwards [35].

Statistical Analysis

Data are reported as means $\pm$ SD, $\pm$ SE or (95% confidence interval (CI)), medians, percentages and rates, as appropriate. Categorical variables are compared with the χ^2 test and continuous variable with Student's *t* test or the Mann-Whitney *U* test. Poisson's analysis was used to estimate differences in rates. The relative effect of treatment on IH rate was assessed by the incidence rate ratio (IRR), derived by the IH incidence rate (the total number of events divided by the sum of person-years of follow-up) for AFB divided by the IH incidence rate for BD [36]. Cardiovascular survival was defined as the time from randomization to cardiovascular death and estimated using the Kaplan-Meier method. A generalized linear model was used to identify the determinants of the follow-up IH rates, and a Cox's multivariate proportional hazards model to pinpoint predictors of cardiovascular mortality. Differences were considered significant at $p \leq 0.05$.

Results

The flow diagram of the Controlled Randomized European Study on Mortality and Morbidity [31] is shown in figure 1. The median number of participants (range) per center was 2 (1–4) on BD and 2 (1–4) on AFB.

Table 1 shows the patients' baseline characteristics. The two groups were well matched, except for the proportion of hypotension-prone patients. Table 2 shows the baseline dialysis prescriptions and ultrafiltration rates.

The proportion of patients dropping out during the follow-up and the reasons for doing so were comparable in the two treatment groups (fig. 1).

Primary Outcome

Figures 2 and 3 show the baseline and follow-up IH rates and the changes in IH rates during the follow-up, respectively. The cumulative drop in IH rate during follow-up was 0.468 (95% CI 0.088–0.847) episode/patient-month for BD (from 3.154 (95% CI 2.936–3.544) at run-in to 2.686 (95% CI 2.529–2.829)) and 2.000 (95% CI 1.613–2.386) for AFB (from 4.154 (95% CI 3.717–4.627) to 2.154 (95% CI 2.003–2.313)) ($p < 0.0001$). The IH rate for AFB was significantly higher than for BD at run-in, and significantly lower at follow-up ($p < 0.0001$). The reasons for the unbalanced baseline IH rate are not readily apparent, but this unbalance may be due to the fact that no blinding was used in our study and/or to a more ag-

Table 1. Patients' baseline characteristics

	BD (n = 194)	AFB (n = 177)	p
Male/female	112/82	106/71	0.75
Age, years	67.1±8.8	66.9±8.8	0.88
Proportion of patients aged 65 years or more, %	66.0	68.4	0.88
BMI	25.2±4.6	25.0±4.6	0.71
Vascular access, AVF/PTFE/permanent CVC	177/5/12	157/8/12	0.49
Charlson comorbidity index	5.9±1.8	5.9±1.6	0.9
Comorbidities, %			0.45
Diabetes	41.1	37.1	
Ischemic heart disease	27.6	30.6	
Congestive heart failure	8.9	12.2	
Cerebrovascular disease	16.7	17.1	
Peripheral vascular disease	24.5	31.2	
Predialysis SBP, mm Hg	145.7±19.2	144.9±19.1	0.70
Pre-/postdialysis difference in SBP, mm Hg	7.2±14.2	8.6±17.0	0.41
Proportion not taking antihypertensive therapy, %	35.0	34.2	0.64
Proportion of hypotension-prone patients ¹ , %	26.6	39.4	0.01
Left ventricular mass/body surface area (LVMI), g/m ²	137.1±42.0	142.5±48.7	0.29

¹ Patients with ≥20% dialysis sessions with hypotensive episodes over the 2-month run-in period.

Table 2. Dialysis prescriptions

	BD (n = 194)	AFB (n = 177)	p
Dialysis time, min	234±25	230±28	0.90
Ultrafiltration rate, l/session	2.27±0.85	2.28±0.98	0.85
Blood pump flow rate, ml/min	284±34	290±35	0.77
Median dialysate sodium, mEq/l	140	140	0.94
Infusion rate, l/h	–	2.0±0.2	–
Median infusate bicarbonate, mEq/l	–	145	–
Dialysis membranes, %			
AN69	14.4	100	
Other high-flux	19.6	–	
Low-flux	66.0	–	

Table 3. Determinants of IH rate during the follow-up at multivariate analysis

Variable	IH rate at 6 months			Cumulative IH rate		
	β	95% CI	p	β	95% CI	p
Treatment (AFB/BD)	–0.76	–1.35 to –0.17	0.011	–2.57	–5.00 to –0.14	0.038
Centered baseline IH rate (episodes/patient over 2 weeks)	0.15	0.00–0.30	0.050	1.00	0.35–1.66	0.003
Membrane flux	0.44	–0.19 to 1.06	0.171	0.86	–1.68 to 3.41	0.504
Diabetes	0.39	–0.07 to 0.85	0.100	1.77	–0.14 to 3.67	0.070
Female/male	0.38	–0.06 to 0.03	0.092	1.33	–0.51 to 3.18	0.155
Age, years	0.003	–0.02 to 0.03	0.788	0.04	–0.07 to 0.15	0.451
Interaction variable ¹	–0.03	–0.12 to 0.06	0.564	–0.22	–0.64 to 0.20	0.307

¹ The interaction variable was obtained by combining the centered baseline IH rate and the treatment modality.

Fig. 2. IH rate on BD and AFB at baseline and during follow-up. Data are expressed as mean (95% CI). The IH rate for AFB was significantly higher than for BD at baseline ($p = 0.0007$) and significantly lower after 6 and 24 months ($p < 0.01$).

Fig. 3. Drop in IH rate during follow-up on BD and AFB. Data are expressed as mean (95% CI). The drop was significantly higher for AFB than for BD at any given time point ($p < 0.0001$).

gressive dehydration before randomization for AFB patients (this hypothesis cannot be tested, however, because no data were available on the changes in dry weight from the initiation of dialysis to randomization). Given the significant difference in the baseline IH rate between BD and AFB, a test of interaction was performed by centering baseline IH rate [37] and an interaction variable was included in the generalized linear model used to identify the determinants of follow-up IH rate (table 3). At multivariate analysis, the only significant, independent determinants of the IH rate during the follow-up were treatment (AFB being associated with a lower IH rate) and the baseline IH rate (the higher the baseline, the higher the IH rate during the follow-up). AFB and baseline IH rate remained the only significant determinants of the IH rate during the follow-up when age and diabetes were substituted by the Charlson comorbidity index, and when the country of origin was added as variable in the model (data not shown). Figure 4 shows the IRR at run-in and follow-up.

There were no significant differences within and between the two groups in terms of baseline and follow-up intradialytic ultrafiltration and dry weight (fig. 5).

Secondary Outcomes

Figure 6 shows the changes in mean predialysis SBP. The proportion of individuals not requiring antihypertensive therapy during the follow-up increased on AFB (from 34 to 39%, $p = 0.01$) and remained stable on BD (35%, $p = 1.00$). The mean (95% CI) number of antihy-

Fig. 4. Unadjusted IH IRR and associated 95% CIs at run-in and follow-up. The IRR for AFB was significantly higher than for BD at the baseline ($p < 0.0001$) and significantly lower at the follow-up ($p < 0.0001$). The same pattern was observed during the follow-up when AFB was compared with subgroups of BD patients on high-flux (BD HF) ($p < 0.0001$) and low-flux membranes (BD LF) ($p = 0.0001$), with no difference between the latter.

pertensives classes did not change significantly in both groups (from 0.889 (0.717–1.061) to 0.954 (0.779–1.129) for BD, $p = 0.456$, and from 0.992 (0.728–1.116) to 0.740 (0.576–0.904) for AFB, $p = 0.080$), with no significant differences between groups at baseline ($p = 0.092$) and during the follow-up ($p = 0.070$). Figure 7 shows the changes in mean LVMI.

Fig. 5. Mean (95% CI) intradialytic ultrafiltration rate (ml/h·kg) (a) and dry weight (kg) (b) at the baseline and during follow-up on BD and AFB. There were no differences within or between groups for either parameter.

Fig. 6. Mean predialysis SBP values at baseline and during follow-up on BD and AFB. Mean predialysis SBP did not change in BD patients (from 146 ± 19 to 144 ± 22 mm Hg, $p = 0.13$ for linear trend), while it dropped significantly in AFB patients (from 145 ± 19 to 138 ± 18 mm Hg, $p = 0.004$ for linear trend). Predialysis SBP for AFB was significantly lower than for BD after 12, 18, and 36 months ($p < 0.04$).

Fig. 7. Mean LVMI values at baseline and during follow-up on BD and AFB. The within- and between-group differences were not significant. Median LVMI tended to increase in cases on BD (4.76 (IQ range -1.15 to 13.26) g/m²), and to decrease in those on AFB (-2.36 (IQ range -13.92 to 7.44) g/m²) ($p = 0.14$).

84 patients died of cardiovascular causes, 48 on BD (11 myocardial infarctions, 14 heart failures, 11 cardiac arrests, and 12 strokes) and 36 on AFB (7 myocardial infarctions, 9 heart failures, 12 cardiac arrests, and 8 strokes) ($p = 0.31$). Figure 8 shows the unadjusted cardiovascular-death-free survival, showing no difference between BD and AFB patients ($p = 0.56$).

In the Cox's multivariate analysis (adjusting for gender, country of origin, type of HD, baseline IH rate, Charl-

son comorbidity index, predialysis SBP, LVMI, serum albumin, total cholesterol and phosphate, and spKt/V) the only significant predictor of a higher cardiovascular mortality was the Charlson comorbidity index (HR 1.291 (95% CI 1.128–1.479), $p < 0.001$).

MCEs occurred in 116 patients, 31.4% on BD and 31.1% on AFB ($p = 0.96$). The proportion of patients who had a fatal MCE (i.e. the early case fatality rate) was similar for the two treatment groups, whereas the long-term

Table 4. Case fatality rates of MCEs

	BD	AFB	RR AFB vs. BD	p
Number of subjects who had MCE	61	55	–	–
Cardiac events	38	34		
Stroke	23	21		
Early case fatality rate, % (n)	52.5 (32/61)	52.7 (29/55)	1.01 (0.71–1.43)	0.90
Long-term case fatality rate, % (n)	55.2 (16/29)	26.9 (7/26)	0.49 (0.40–0.99)	0.04

Table 5. Baseline and follow-up predialysis biochemical parameters and dose of dialysis

	Baseline					Follow-up				
	BD		AFB		p	BD		AFB		p
	mean	95% CI	mean	95% CI		mean	95% CI	mean	95% CI	
Hemoglobin, g/dl	10.7	10.4–11.0	10.4	10.2–10.6	0.11	11.1*	10.9–11.3	11.3*	11.0–11.6	0.72
Albumin, g/l	3.88	3.80–3.96	3.90	3.79–4.00	0.68	3.81	3.74–3.88	3.80	3.72–3.88	0.76
Calcium, mg/dl	9.33	9.16–9.49	9.33	9.15–9.51	0.87	9.45	9.33–9.57	9.53	9.39–9.66	0.43
Phosphate, mg/dl	5.2	5.0–5.4	5.2	4.9–5.5	0.90	5.2	5.0–5.4	5.1	4.8–5.3	0.45
Total cholesterol, mg/dl	204	196–212	198	191–205	0.25	199	190–208	194	185–203	0.81
Triglyceride, mg/dl	209	192–226	207	188–226	0.84	194	174–214	181	162–200	0.39
Bicarbonate, mEq/l	20.6	20.2–21.0	21.1	20.7–21.5	0.11	20.9	20.4–21.4	21.7	21.1–22.3	0.11
spKt/V	1.31	1.28–1.34	1.32	1.28–1.36	0.67	1.41*	1.36–1.45	1.46*	1.41–1.51	0.09

* $p < 0.02$ vs. baseline.

Fig. 8. Unadjusted cardiovascular mortality-free survival rate. Survival was similar in AFB and in BD patients ($p = 0.23$).

case fatality rate (i.e. the proportion of cardiovascular deaths among patients who had an MCE and survived 28 days or more afterwards) was significantly lower for patients on AFB (table 4).

There were no significant differences between the two groups in terms of their baseline and follow-up predialysis hemoglobin, total cholesterol, triglycerides, albumin, calcium, phosphate and bicarbonate, and dose of dialysis. Hemoglobin levels and spKt/V rose significantly in both groups ($p < 0.02$) (table 5).

Discussion

The main finding of our randomized controlled trial is that AFB improves long-term cardiovascular stability during dialysis in comparison with conventional BD, leading to a 40% reduction in the risk of IH (IRR 0.60 (95% CI 0.53–0.68), $p < 0.0001$). This effect of AFB was evident after the first 6 months of treatment (in agreement with the findings of previous short-term nonrandomized studies [29, 38]) and persisted over the 36-month follow-up.

The better intradialytic cardiovascular stability associated with AFB may conceivably be related to several factors: those peculiar to the hemodiafiltration techniques (which combine an enhanced removal of the higher molecular weight solutes with a more biocompatible system) [39]), though this may be questionable because the small substitution volume should only marginally affect middle molecule removal; the use of high-flux membrane (though in our study AFB coincided with a lower IH rate than BD regardless of membrane flux); the (albeit small) convective component (consistent with the results of a recent randomized controlled study [26] showing that online hemofiltration and hemodiafiltration reduce symptomatic IH in the long term); the absence of acetate in the bath and the infusate (since it has been demonstrated that even small amounts of this solute in the dialysate may impair cardiovascular reactivity [39]), and/or a thermal effect induced by the bicarbonate solution infused in the postdilution mode [39] since it is well known that a cold dialysate and/or infusate reduces the frequency of IH [40] (though this should not be a major contributor in our study since the infusate for AFB was usually warmed to a temperature similar to that of the dialysate and its infusion rate was always <15% of the prescribed Q_b). Moreover, our study strongly suggests that the beneficial effects by AFB are unrelated to changes in intradialytic ultrafiltration and dry weight, since these parameters did not vary within or between the two groups.

The lower IH rate seen in our study with AFB was associated with a drop in predialysis SBP, similar to the situation seen with frequent HD [41] and unlike the one seen in online hemofiltration and hemodiafiltration [26], for which a lower rate of IH was associated with no change in predialysis SBP in the former and its increase in the latter (which could become clinically relevant in the long term [42]).

The two conditions may be related, since the reduction in IH may contribute to reducing the risk of long-term volume overload and interdialytic hypertension by lowering the need of intradialytic sodium loading and allowing a more consistent attainment of dry weight [43, 44]. We also cannot exclude the possibility that a lag time phenomenon [45] (due to a more aggressive dehydration before randomization for AFB patients) contributing to different time course of predialysis SBP between BD and AFB; this is unlikely in our study, however, because the difference in SBP between BD and AFB only became evident as of the 12th month of follow-up (i.e. 20–22 months after starting dialysis), whereas the lag time phenomenon has been described only up to 10–12 months after attaining the target

weight [45, 46]. On the other hand, a lag time phenomenon may explain the time course of the changes in predialysis SBP for AFB versus BD, as a result of AFB being more successful in attaining a better extracellular volume control already in the first 6 months of this treatment.

We are aware that predialysis SBP is not the ideal way to assess blood pressure control and its prognostic value in HD patients [47] and it is probably just a marker of extracellular volume status [46], but the different blood pressure profile (and possibly volume status) in patients on BD and AFB may also contribute to the different trend in LVMI changes observed during the study, which were of potential clinical (though not statistical) significance, suggesting that AFB may also improve cardiovascular outcomes by preventing any gradual increase in LVMI, which proved to be a strong predictor of cardiovascular mortality in dialysis patients [48].

All the above findings suggest that patients who develop frequent IH when they start conventional BD (once their optimal dry weight has been identified) may be preferentially placed on AFB to minimize many dialysis-related cardiovascular adverse events.

In spite of its favorable effects, AFB did not influence the overall cardiovascular morbidity and mortality, possibly because our study recruited patients at much lower risk than we had originally expected, making it underpowered for the purpose of detecting any significant differences between the two treatment modalities due to the lower than expected cardiovascular event rate.

We confirmed that MCEs carry a high mortality among HD patients [49, 50] and showed that AFB reduces the risk of cardiovascular death for initial survivors of MCEs, indicating that this dialysis technique does not alter the severity of MCEs (or the efficacy of specific treatment for these conditions), but it can favorably affect the outcome of less severe, nonfatal MCE by comparison with standard BD, possibly by reducing the burden of the repeatedly damaging ischemic effects of HD-related hypotension on the heart and the brain. Given the post hoc nature of our analysis however, these results should be considered only as food for thought and should be tested formally in further randomized clinical trials.

Moreover, any beneficial effect by AFB should be balanced against an increase in costs of dialysis. To give an example based on the Azienda Ospedaliera Universitaria Integrata Verona financial data system as at 2011, AFB is associated to an estimated extra cost for consumables of EUR 30–40 per session by comparison with BD.

We are aware that our study has several weaknesses. For a start, it was not blinded, since this would have been

impossible in a clinical setting given the use of an infusate for AFB but not for BD. Secondly, our randomization was only partially successful, since the baseline IH rates in the AFB group were higher than in the BD group, meaning that our findings might have been prone to bias by regression to the mean. To take this bias into account, we performed a test of interaction by creating a baseline interaction variable, which proved not to be a significant determinant of IH rate during follow-up – unlike AFB. Thirdly, our findings are only applicable to patients on dialysis for a short time (8–10 months). Finally, our results may be biased by the fact that dry weight was assessed on clinical grounds (raising the possibility of the dialysis-related hypotensive episodes being difficult to separate from an inappropriate estimation of the target weight), the echocardiographic LVMI assessment was not performed at a centralized laboratory, and patients were recruited from many different centers and over a lengthy period of time; on the other hand, the impact of these confounders should be minimized by our study design enrolling both AFB and BD patients at any given center.

In conclusion, our randomized controlled trial shows that AFB lowers the long-term IH rate and the predialysis SBP by comparison with conventional BD. While AFB did not affect the incidence of cardiovascular events and deaths in our sample, it may reduce the cardiovascular mortality after a nonfatal major cardiac and cerebrovascular event, possibly thanks to the better intradialytic cardiovascular stability.

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Supplementary Appendix

The following dialysis centers took part in the study: *Czech Republic*: Plzen; *France*: Fleury and Saint Briec. *Germany*: Augsburg, Bad Nauheim, Bad Windsheim Berlin, Chemnitz, Detmold, Donaueschingen, Dresden, Eisenhüttenstadt, Gelsenkirchen, Giessen, Göttingen; Herne, Magdeburg, Mannheim, Mühlhausen, Neuruppin, Plauen, Rostock, Schwandorf, Simmern, Tübingen, Unna, and Wiesbaden; *Italy*: Altamura, Arezzo, Ascoli Piceno/Pagliare, Bergamo, Bologna/Imola, Bolzano, Brescia/Montichiari, Cagliari, Cerignola, Chiari, Cinisello Balsamo, Como, Cremona, Crotone, Firenze, Gorizia, Ivrea, Lauria, Leno/Manerbio, Manduria, Martina Franca, Matera, Melegnano, Milano Policlinico, Milano Sacco, Milano San Carlo, Monza, Nuoro, Pesaro, Pontremoli, Ravenna, Rimini, Roma, Ruvo/Andria, San Giovanni Rotondo, San Miniato, San Severo, Scorrano/Corsano, Taranto, Torino Maurizioano, Trento, Treviso, Tricase, Trieste Cattinara, Verona Ospedale Civile Maggiore, Verona Borgo Roma, and Viterbo. *Spain*: Acoruna, Galdakao, Gandia, Leon, Madrid Del Aire, Madrid Maranon, Madrid La Paz, Ourense, Toledo, Valladolid Rio-Ortega, and Valladolid Hospital Universitario.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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