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Isonatric Dialysis Biofeedback in Hemodiafiltration with Online Regeneration of Ultrafiltrate in Hypertensive Hemodialysis Patients: A Randomized Controlled Study

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Key Words
Dialysis · Sodium · Biofeedback · Hemodialysis · Hypertension

Abstract
Dialysis biofeedback in hemodiafiltration with online regeneration of ultrafiltrate (HFR) could help to improve arterial hypertension. We evaluated the impact of isonatric HFR (HFR-iso) on hypertension control compared to conventional HFR. Forty-seven hemodialysis patients were included and randomized (ratio 2/1) HFR-iso versus HFR during 24 dialysis sessions. In the HFR-iso group (32 patients, 768 dialysis sessions), the predialytic systolic blood pressure (BP) decreased from S1 to S24 of 9 ± 20 mm Hg and increased of 5 ± 24 mm Hg in the HFR group (15 patients, 360 dialysis sessions), variation that differed between the 2 groups (ΔS1–S24, p = 0.035; interaction group*time, p = 0.012). The diastolic BP (HFR-iso –3 ± 14 mm Hg vs. HFR 5 ± 13 mm Hg; p = 0.088), the DDD of antihypertensive treatment and the dry weight did not vary significantly during the study. Number of sessions complicated by symptomatic hypotension was similar in the 2 groups. HFR-iso improved BP control without increasing dialysis hypotension episodes. ***Short Summary:*** In this multicenter, open-label, controlled, randomized study, we evaluated the impact of dialysis biofeedback in HFR on arterial hypertension compared to conventional HFR. We observed that HFR-iso improved arterial BP control without increasing dialysis hypotension episodes.

Introduction

Hypertension is a common cardiovascular complication in hemodialysis patients and its treatment is challenging. The meta-analysis on antihypertensive treatment in hemodialysis patients evidenced that its control

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is associated with an all cause 20% and cardiovascular 29% survival improvement [1]. There is a dilemma between assuring a correct blood pressure (BP) control and avoiding dialysis hemodynamic intolerance. Antihypertensive drugs, salt restricted regimen and specific dialysis approaches take part in the therapy. Reduction of the dry weight is commonly used to reduce BP in hemodialysis patients but can be limited in some patients by dialysis hemodynamic intolerance [2]. Longer dialysis session time periods or more frequent dialysis is the first approach but both increase treatment time, and therefore, they are not always well accepted by patients. Long time dialysis sessions, 8 h 3 times a week compared to 4 h 3 times a week showed significant improvement in arterial hypertension [3]. Several biofeedback studies have been proposed to limit the risk of per dialytic hypotension. These were primarily related to biofeedback of plasma volume, but some also focused on biofeedback on plasma conductivity both to lessen dialytic hypotension, however without improving arterial BP or survival [4].

Dialysate sodium prescription has major implications for hemodialysis tolerance and for arterial BP control. Biofeedback systems have been developed to drive dialysate conductivity in order to reach a prescribed plasma sodium concentration, indirectly evaluated by the calculations of ionic dialysance and plasma conductivity or by the direct measurement of ultrafiltrate conductivity. In the studies using this biofeedback, the plasma conductivity target was equal to the mean of the plasma conductivity values measured just before the 6 last dialysis sessions. The biofeedback permits less dispersion of the plasma conductivity at the end of the session and to decrease the number of per-dialytic hypotensive episodes [5–7]. Biofeedback based on plasma conductivity in the isonatric mode uses the same algorithm but aims to reach a target at the end of the session equal to the value measured at the beginning of the session. A biofeedback system using hemodiafiltration with online regeneration of ultrafiltrate (HFR) has been specially developed with an isonatric mode based on profiles derived from conductivity of the pure ultrafiltrate. The plasma sodium of a hemodialysis population evaluated in observational studies is currently equal to 136–138 mmol/l, and the sodium dialysate is frequently above this range [8–10]. The sodium patient dialysate gradient is well correlated with interdialytic weight gain as increasing natremia is a potent mechanism to induce thirst, induces water shift from intracellular to the extracellular compartment [11] and lessens the sodium mass transfer that mostly occurs via convection [6]. Systematic reduction of the dialysate to plasma gradient has been evaluated using plasma sodium measurement or online biofeedback [12–14]. A better control of arterial BP and a decrease of the interdialytic weight gain were obtained. As a mode that also decreases the sodium dialysate patient gradient, our hypothesis was that the use of biofeedback in an isonatric mode would help to improve hypertension control with fewer dialysis intolerance symptoms. We evaluated the impact of isonatric HFR (HFR-iso) on arterial hypertension compared to conventional HFR.

Subjects and Methods

Study Design

The Isodial study is a prospective multicenter, open-label, controlled and randomized study [15]. Patients from ten French and Belgian dialysis centers were included. After a run-in period of 1 week, patients having an arterial BP >140/90 mm Hg were randomized either to conventional HFR (control treatment) or to HFR-iso (intervention treatment) with a 1:2 allocation ratio. Patients had 24 dialysis sessions during 8 weeks in their treatment group. The randomization was centrally carried out according to a randomization list. This study received approval from the local ethics committee (CPP Ile de France VI), and all the patients gave written informed consent to participate.

End Points

The primary end point was the variation between the first and the last dialysis session of the predialytic mean systolic BP (SBP) measured 3 times at each session before any connection to the hemodialysis circuit.

Secondary end points were the change in predialytic mean diastolic BP (DBP) and heart rate, the intradialytic variations for SBP and DBP, the number of sessions complicated by hypotension and intradialytic symptoms, the total defined daily dose by the World Health Organization of the antihypertensive treatment [16] and the change in dry weight during the study period. Thirst was evaluated on a 0–10 scale at the end of dialysis sessions, and so the cumulative score on the 24 dialysis sessions ranged from 0 to 240.

Inclusion and Exclusion Criteria

Patients were included in the study if they met the following criteria: age >18 years, dialyzed for >3 months, treated 3 times a week for 3.5–5 h, having an arterial SBP >140 mm Hg or a DBP >90 mm Hg evaluated at dialysis start for at least 2 of the 3 dialysis sessions in the week of the run-in period, absence of acute adverse medical events during the 3 last months and having signed the informed consent. Pregnant women, patients with a life-threatening disease, those with an acute illness during the 3 last months, those included in another study protocol and those with a psychiatric disease were not included.

Hemodialysis Treatment

Hemodialysis treatment was performed according to the following guidelines: 3.5–5 h, prescribed blood flow rate, dialysate temperature <37°C and ultrafiltration rate to reach the dry weight

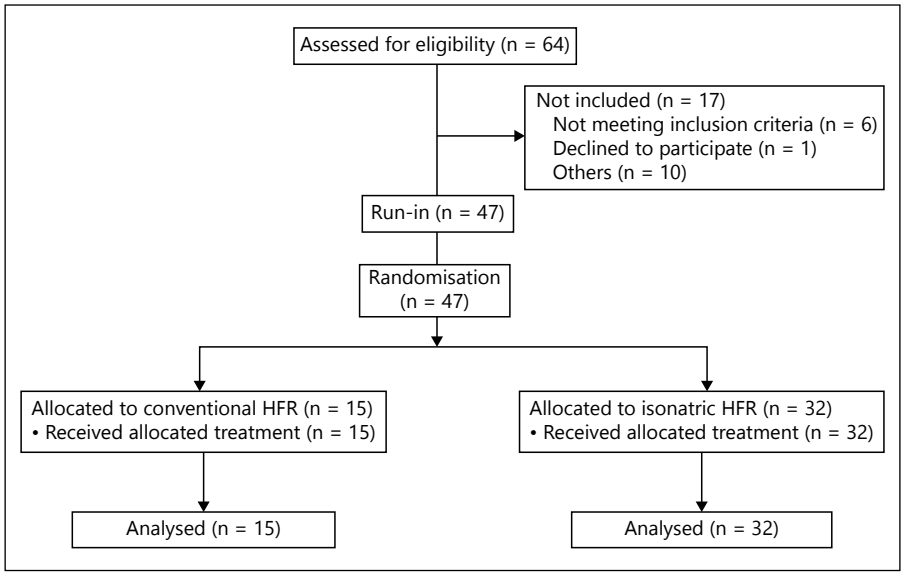

Fig. 1. Flowchart.

in the 2 groups of treatment. Dialysate conductivity was set during the run-in period for the conventional HFR arm (control group) and was not modified during the study protocol. In HFR-iso (treatment group), the dialysate conductivity was automated and driven by the monitor to reach a patient conductivity equal to the value measured at 15 min of dialysis and using ultrafiltration and sodium profiles.

Sample Size Calculation

For a standard deviation of 15 mm Hg in arterial BP, the possibility to demonstrate a difference of 10 mm Hg of the predialytic SBP between the 2 therapies with a power of 80% was reached with 28 patients per group. Considering a dropout rate of 10%, we planned to include 70 patients, 23 in the control group and 47 in the isonatric group.

Statistics

Data were expressed as mean (±standard deviation) for quantitative variables and frequency (%) for qualitative variables.

For normally distributed quantitative variables, the t test was used, while for the non-normally distributed variables (variation of the defined daily dose of antihypertensive drugs, number of sessions with at least one hypotension and/or intolerance criteria), the Wilcoxon signed-rank test was performed to compare the variation in parameters between the first and the last dialysis session. Fisher's exact test was used to assess differences in frequency of qualitative variables.

The course of the arterial SBP during follow-up was analyzed using linear mixed models with time as both a fixed and random effect (degree of freedom estimated using Satterthwaite approximation) and the treatment effect characterized by a group*time interaction.

To identify factors that influence the BP, a covariance analysis was conducted with arterial SBP as dependent variable and gender, age, dry weight, presence of diabetes or comorbidities and total defined daily dose of antihypertensive treatment at baseline as independent variables. Influence of these variables on the evolution was tested via interactions between the given factor and the time variable. Independent factors that were significant in the univariate analysis were included in a multivariable model, including the interactions with backward selection. Estimates derived from the model are given as mean ± SE.

Statistical analyses were performed with the SAS 9.3 software (SAS Institute, Cary, N.C., USA). All tests were 2-sided. Test results were considered significant at the 0.05 level. Statistical analyses were conducted using intention-to-treat analyses.

Results

Patients and Dialysis Session Characteristics

Between September 2011 and June 2013, 64 patients were selected of whom 17 patients were not included: 8 patients had incomplete files, 6 patients did not meet inclusion criteria, 1 patient declined to participate, 1 patient was transferred and 1 patient underwent renal transplantation. Fifteen patients were allocated to the control group and 32 to the HFR-iso group. All 47 patients completed the study (fig. 1). In the isonatric group, 768 dialysis sessions were available for statistical analyses and 360 in the conventional group.

Patients and dialysis sessions characteristics at baseline are shown in table 1. Baseline predialytic SBP was 147 ± 18 mm Hg in the conventional HFR group and 161 ± 20 mm Hg in the HFR-iso group. Baseline postdialysis weight was 73 ± 17 kg in the conventional HFR group and 72 ± 19 kg in the HFR-iso group. Interdialytic weight gain averaged 2.2 ± 1 kg in both isonatric and con-

Table 1. Baseline clinical and dialysis characteristics according the randomized treatment

Characteristics	HFR-iso	Conventional HFR
Number of patients	32	15
Men, n (%)	16 (50)	10 (67)
Age, years	71 (16)	64 (14)
Mean SBP, mm Hg	161 (20)	147 (18)
Mean DBP, mm Hg	82 (15)	77 (11)
Mean heart rate, beats/min	75 (13)	76 (14)
Weight before session, kg	74 (20)	75 (17)
Weight after session, kg	72 (19)	73 (17)
Interdialytic weight gain, kg	2.2 (1.2)	2.2 (1.0)
Biochemistry		
Albumin, g/l	38 (4)	38 (5)
Hemoglobin, g/dl	11 (1)	11 (1)
C-reactive protein, mg/l	7 (8)	9 (20)
Plasma sodium, mmol/l	138 (4)	138 (2)
Antihypertensive drugs, n (%)		
Beta- blockers	14 (44)	5 (33)
Angiotensin converting enzyme inhibitors	8 (25)	2 (13)
Angiotensin receptor blockers	2 (6)	1 (7)
Calcium channel blockers	8 (25)	6 (40)
Diuretics	10 (31)	4 (27)
Others	4 (13)	4 (27)
Total defined daily dose of antihypertensive treatment	3.2 (3.4)	2.8 (2.7)
Kidney disease, n (%)		
Nephroangiosclerosis	16 (50)	4 (27)
Diabetes	7 (22)	4 (27)
Glomerulonephritis	2 (6)	1 (7)
Interstitial nephritis	0 (0)	1 (7)
Renal cancer	1 (3)	0 (0)
Other	3 (9)	1 (7)
Unknown/not available	3 (9)	4 (27)
Comorbidities		
(at least 1 comorbidity), n (%)	10 (31)	6 (40)
Diabetes	8 (25)	5 (33)
Heart failure	2 (6)	1 (7)
History of myocardial infarction	2 (6)	3 (20)
History of angina	0 (0)	2 (13)
Arteritis stage 3 or 4	4 (13)	1 (7)
History of cerebrovascular accident	2 (6)	1 (7)
Other comorbidities, n (%)	10 (31)	5 (33)
Number of sessions studied	768	360
Dialysate conductivity at onset, mS/cm	14.1 (0.3)	14.0 (0.2)

Values are mean (SD) or n (%) unless otherwise mentioned.

ventional HFR groups. Total defined daily dose was 2.8 ± 2.7 in the conventional HFR group and 3.2 ± 3.4 in the HFR-iso group at baseline. In both groups, the main causes of kidney disease were nephroangiosclerosis, diabetes and glomerulonephritis.

Variation of SBP and DBP, Heart Rate, Weight and Total Defined Daily Dose of Antihypertensive Treatment from Baseline to the End of the Study

In the HFR-iso group, the predialytic SBP decreased significantly from baseline to the end of the study of 9 ± 20 mm Hg and non-significantly increased by 5 ± 24 mm Hg in the conventional HFR group. The change in predialytic SBP differed between the 2 groups (p = 0.035; table 2). The changes during the study in predialytic DBP, heart rate, interdialytic weight gain and dry weight did not significantly differ between the 2 groups. The total defined daily dose of antihypertensive drugs changed by 0.3 in the HFR-iso group and 0.1 in the conventional HFR group (p = 0.7).

Predialytic SBP Time Course

A linear mixed model was used to evaluate the response to treatment according to the group. The course of the predialytic SBP over time is shown in figure 2.

We confirmed that the intercept and the course of the predialytic SBP differed between the 2 treatment groups (interaction time*group, p = 0.012). The mean predialytic SBP in the HFR-iso group was 157.5 ± 3.8 mm Hg on the first day of dialysis and decreased by 0.12 ± 0.08 mm Hg every day. In the conventional HFR group, the mean predialytic SBP was 147.7 ± 2.6 mm Hg on the first day of dialysis and increased by 0.13 ± 0.05 mm Hg every day.

Older age at inclusion (0.01 ± 0.00 per additional year, p = 0.053) was associated with slower evolution of the predialytic SBP. We did not find any influence of the initial SBP, gender, dry weight, presence of diabetes or comorbidities and total defined daily dose of antihypertensive drugs at baseline on the evolution of the SBP.

Tolerance

The table 3 shows the symptoms of intolerance according to the groups during the course of the trial. In both HFR groups, patients had on an average 2 sessions that were complicated by a symptomatic hypotension. One patient in both groups had >30% of the sessions complicated by hypotension. Patients in the HFR-iso group had significantly more sessions with thirst as compared with patients in the conventional HFR group (9.3 vs. 3.0 sessions complicated with thirst, p = 0.0029) with a cumulative mean thirst score of 12 ± 26 in the HFR group versus 49 ± 51 in the HFR-iso group (p = 0.01). The number of sessions stopped and complicated by at least one symptom of intolerance, nausea, cramps, vomiting were very similar between the groups.

Table 2. Changes in SBP and DBP, heart rate, dry weight and interdialytic weight gain and defined daily dose of antihypertensive treatment during the study

Change in	HFR-iso	Conventional HFR	p value
Pre-dialytic SBP, mm Hg	–9 (20)	5 (24)	0.0351
Pre-dialytic DBP, mm Hg	–3 (14)	5 (13)	0.0883
Pre-dialytic heart rate, bpm	1 (7)	1 (15)	0.9832
Interdialytic weight gain, kg	–0.2 (1.5)	–0.2 (1.0)	0.9386
Weight at the end of the session, kg	–1.6 (4.3)	0.9 (4.7)	0.1637
Defined daily dose of antihypertensive treatment	0.3 (1.1)	0.1 (0.9)	0.7031

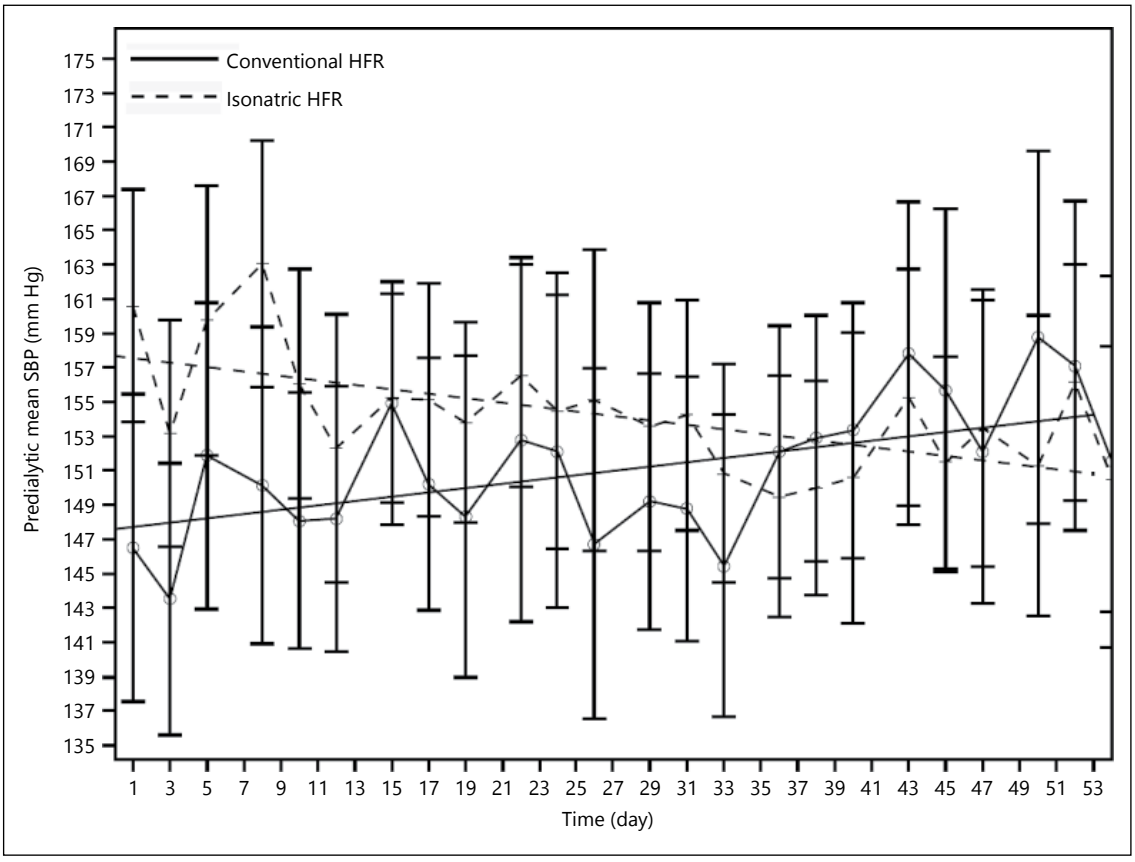

Fig. 2. Course of the predialytic SBP according to the treatment group (for a mean age of 69 years). In the HFR-iso group, the intercept was 157.5 ± 3.8 mm Hg and the slope was –0.12 ± 0.08 mm Hg per day (p = 0.021). In the conventional HFR group, the intercept was 147.7 ± 2.6 mm Hg and the slope was 13 ± 0.05 mm Hg per day (p = 0.121). The conventional HFR group being the reference, the estimates were 9.9 ± 4.7 (p = 0.041) for the group, 0.3 ± 0.2 (p = 0.207) for the day, 0.1 ± 0.1 (p = 0.476) for the age, –0.3 ± 0.1 (p = 0.012) for the interaction time*group and –0.01 ± 0.00 (p = 0.053) for the interaction time*age.

Discussion

This study provides an analysis of the effect of isonatric dialysis on arterial hypertension and tolerance symptoms. This modality of hemodialysis was performed for the first time with a totally automated monitor using a biofeedback system. Predialytic SBP decreased more in HFR-iso group than in conventional HFR group during the 8 weeks of the study. We observed a similar trend to a lesser extent for DBP, where-

Table 3. Intolerance episodes per patient evaluated on 768 sessions in HFR-iso and 360 sessions in conventional HFR

	HFR-iso	Conventional HFR	p value
Symptomatic hypotension	1.5 (2.9)	2.2 (3.0)	0.17
Hypotension >30% of the sessions, n (%)	1 (3)	1 (7)	0.5
At least one symptom	2.8 (2.7)	2.8 (3.6)	0.7
Sessions with thirst	9.3 (7.5)	3.0 (5.5)	0.002
Cumulative score of thirst (0–240)	49 (51)	12 (26)	0.01
Vomiting	0.1 (0.4)	0.2 (0.4)	0.3
Cramps	1.5 (2.1)	1.7 (2.7)	0.8
Nausea	0.5 (1.0)	0.5 (0.5)	0.3
Sessions prematurely stopped	1.3 (1.8)	1.1 (1.4)	0.9
Fill in	1.1 (2.0)	1.2 (2.9)	0.2
Dialysate conductivity variation	0.3 (1.0)	0.2 (1.0)	0.3
Trendelenburg position	2.6 (5.1)	1.4 (2.7)	0.2
Ultrafiltration stop	0.7 (1.5)	1.5 (2.8)	0.05

Values are mean (SD) or n (%).

as heart rate, dry weight, interdialytic weight gain and defined daily dose of antihypertensive treatment remained stable in both groups.

The number of intolerance symptoms during the sessions was very similar in both groups except for thirst, which appeared significantly more in HFR-iso than in conventional HFR. This problem was resolved by decreasing the upper value of sodium during the first part of the profile. The maximum of dialysate conductivity allowed was set to 15.0 mS/cm and can be further decreased in patients not suffering from intradialytic hypotension episodes. Ultrafiltration and sodium profiles were combined to avoid hypotension and should not counteract the effect of isonatric dialysis for the control of arterial BP by generating thirst in the first part of dialysis. The maximum dialysate conductivity reached in the first part of the dialysate conductivity profile should be carefully set in this goal. This side effect may explain why we did not experience a decrease in the interdialytic weight gain as evidenced in another study on isonatric dialysis and not using sodium profile [12].

The main limitation of our study is the small sample size that precludes any generalizability. Despite randomization, the SBP at baseline differed between the 2 groups. During the study, SBP of the 2 groups converged to a similar level that needed statistical treatment to eliminate a regression phenomenon toward the mean. After adjustment for baseline SBP, the model confirmed that SBP changes during the study differed between the 2 groups. The second limitation is that the study was not blinded. We verified that the antihypertensive treatment was modified similarly in both groups. Of notice, the dry weight decreased in the HFR-iso group and increased in the HFR group; however, the difference was not statistically different. The impact of these changes on arterial pressure was analyzed by a model taking into account the per-study changes in dry weight and still found a different arterial pressure course between groups. Secondarily, the sodium transfer was not evaluated and should be included in upcoming studies to confirm the difference between the sessions with and without isonatric biofeedback. The mean natremia was equal to 138 mmol/l and the dialysate conductivity to 14.0 mS/cm at baseline. The hyponatremic patients benefited obviously from a decrease of the dialysate conductivity in the isonatric mode associated with an increase in the sodium transfer. One can argue that it was not the case for the patients having hypernatremia who could have been dialyzed with a higher dialysate conductivity in the isonatric mode. In our experience, these patients could more easily benefit from a reduction in dry weight in isonatric mode because of less intradialytic hypotension. The small effective did not permit to differentiate the arterial pressure course in hypo- vs. hypernatremic patients, and this point should be further studied in trial with a larger population. Finally, we used a standardized BP measurement repeated 3 times before dialysis and not the interdialytic ambulatory BP monitoring.

Our conclusions suggest that HFR-iso could help to decrease SBP in hemodialysis patients without increasing intolerance symptoms.

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Authors Contributions

Study design and statistical analysis written by L.M., statistical analysis done by L.C. and S.T. and results discussed by all coauthors.

Statement of Financial Interest

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