ANTE 2023 Dialisi e Tecnologia

“LE SCELTE TERAPEUTICHE IN SALA DIALISI”

Moderatori: L. Morrone, A. Zucchelli

Terapia dialitica nel paziente cronico senza anticoagulanti: Quali possibilità

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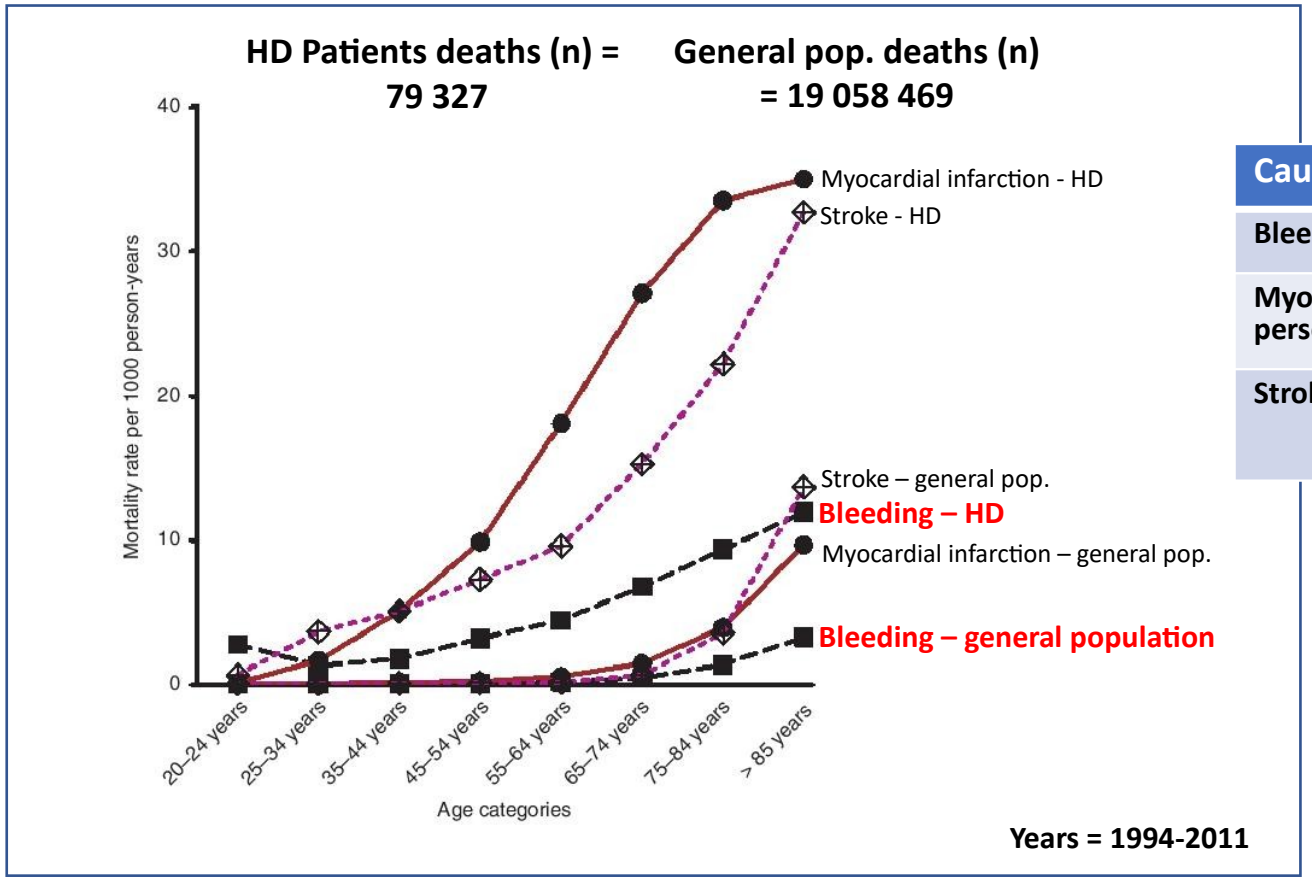
Policlinico

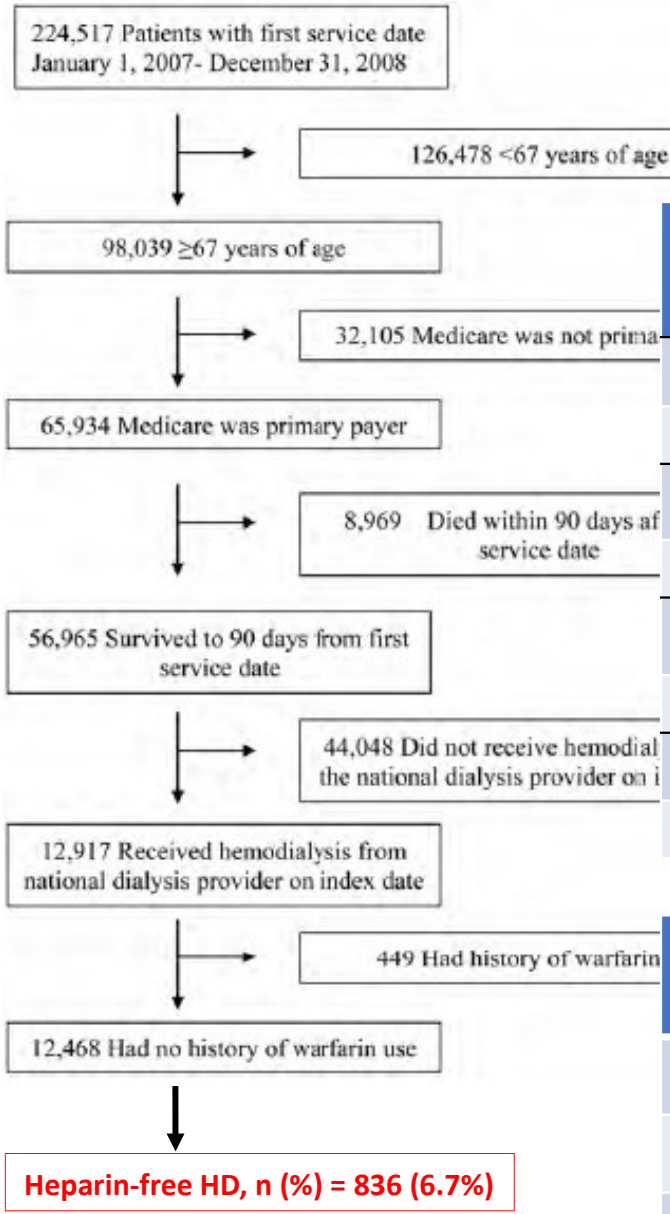
Mortality due to Bleeding in Dialysis Patients



Cause specific mortality	Dialysis patients	General population
Bleeding (x 1000 person-years)	6.2	0.3
Myocardial infarction (x 1000 person-years)	22.5	0.9
Stroke (x 1000 person-years)	14.3	0.7

Ocak, G. et al. Journal of Thrombosis and Haemostasis. Volume 16, Issue 10, October 2018, Pages 1953-1963

Use and safety of heparin-free maintenance hemodialysis in the USA



Outcome	Exposure group	Number of events	Follow-up (yrs)	Incidence rate (x 100 person-year)	Hazard Ratio (95% CI)
All bleeding events	Heparin-free	75	1.14±0.76	9.1	1.15 (0.83-1.60)
	Heparin	67	1.18±0.77	7.8	
Atherotrombosis	Heparin-free	228	1.08±0.76	28.9	1.09 (0.90-1.13)
	Heparin	217	1.13±0.77	26.5	
Venous thrombosis	Heparin-free	102	1.08±0.76	12.9	1.23 (0.93-1.64)
	Heparin	87	1.15±0.77	10.4	
All-cause mortality	Heparin-free	360	1.19±0.77	41.5	1.08 (0.94-1.26)
	Heparin	342	1.23±0.77	38.1	

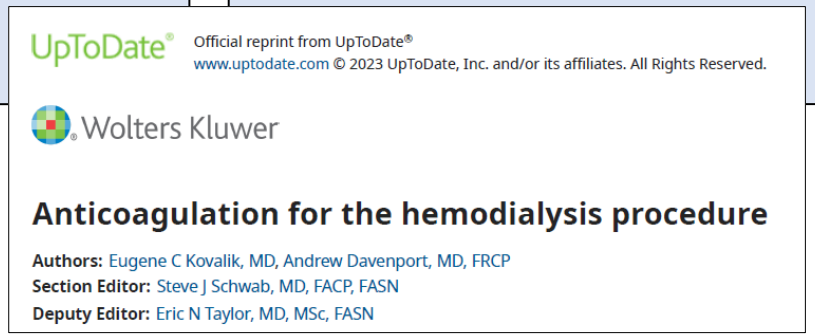
Variable	Heparin-free dialysis patients	Heparin dialysis patients
Patients, n	728	728
Age (years)	77±6	77±7
Males, n (%)	374 (51)	370 (51)

Shen JI et al. Nephrol Dial Transplant, 2013; 28 . 1589-1602

Rischio SANGUINAMENTO >> Rischio COAGULAZIONE

- Piastrinopenia grave (<20.000/microL)
- Sanguinamento attivo durante la dialisi
  - tratto gastrointestinale
  - intra-addominale
  - ferite chirurgiche
  - cateteri arteriosi o venosi
- Interventi chirurgici maggiori, intraoculari e spinali nelle 72 ore precedenti

- Emorragia intracranica o extradurale attiva
- Uso di anticoagulanti sistemici
- Pericardite uremica
- Deficit del fattore VII o VIII della coagulazione



Dialisi senza eparina: Opzioni

A) ↓ Rischio coagulativo

1. Boli di fisiologica
2. HDF in prediluizione
3. Anticoagulazione regionale con citrato
4. Dialisato con citrato

B) ↓ Attivazione da contatto

1. Membrane rivestite
2. Struttura della membrana

C) A + B

Evaluation of Three Different Methods to Prevent Dialyzer Clotting Without Causing Systemic Anticoagulation Effect

Pavlina Richtrova, Kamila Rulcova, Jan Mares, and Tomas Reischig
Department of Internal Medicine I, Charles University, Medical School and Teaching Hospital Plzen, Czech Republic

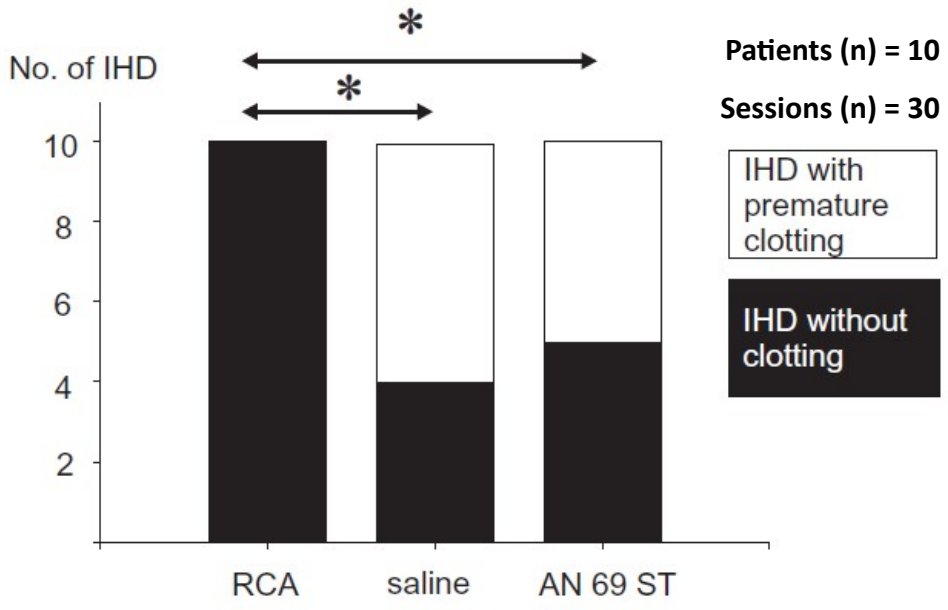


FIG. 1. Successful completion of hemodialysis procedures. *$P < 0.05$.

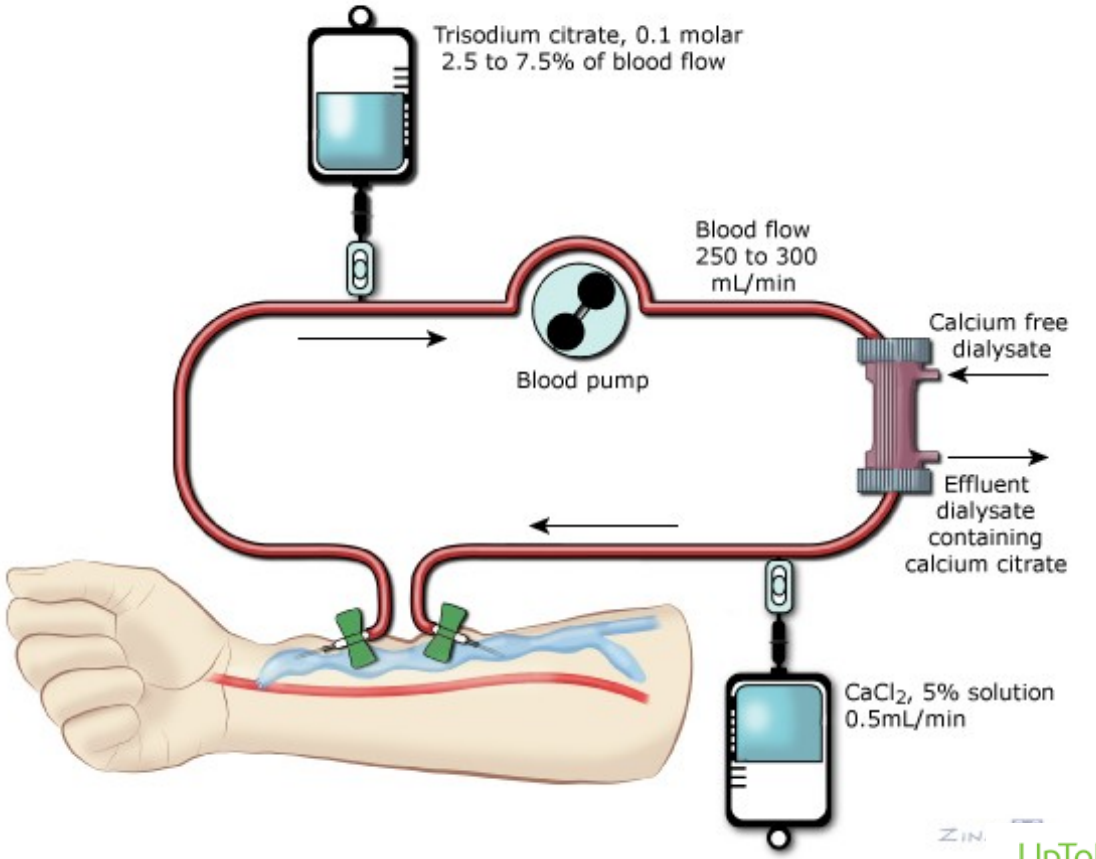
Anticoagulation methods

1 Regular saline flushes of ECC. A polysulfone hemodialyzer F60(S) (Fresenius Medical Care, Bad Homburg, Germany) was used. During IHD, saline flushes with 250 mL were carried out every 20 min and the BF was 250 mL/min.

2 RCA. The same F60(S) dialyzer was used. The acid citrate dextrose-A (ACD-A) solution with 2.2% trisodium citrate was infused at the beginning of the ECC at a rate of 300 mL/h (36 mmol/h). After 20 min and then every 60 min, this flow rate was adjusted based on ionized calcium (iCa^{2+}) values at the dialyzer outlet with a target range of 0.25–0.35 mmol/L. The effect of citrate was reversed by infusion of calcium gluconicum 10% before returning the blood to the systemic circulation. The flow rate of calcium was set according to the baseline value of systemic iCa^{2+} (median 9 mmol/h). The BF was 250 mL/min and the dialysis solution contained no calcium (Mg concentration was 0.5 mmol/L).

3 AN69 ST. A Nephral ST 300 dialyzer (Gambro Hospal Industrie, Meyzieu, France) with AN69 ST membrane was used. The ECC was primed according to the manufacturer's recommendations with heparinized saline. The BF was 250 mL/min and the dialysis solution was identical as for saline flushes.

Anticoagulazione regionale con Citrato-Calcio



Anticoagulation for the hemodialysis procedure

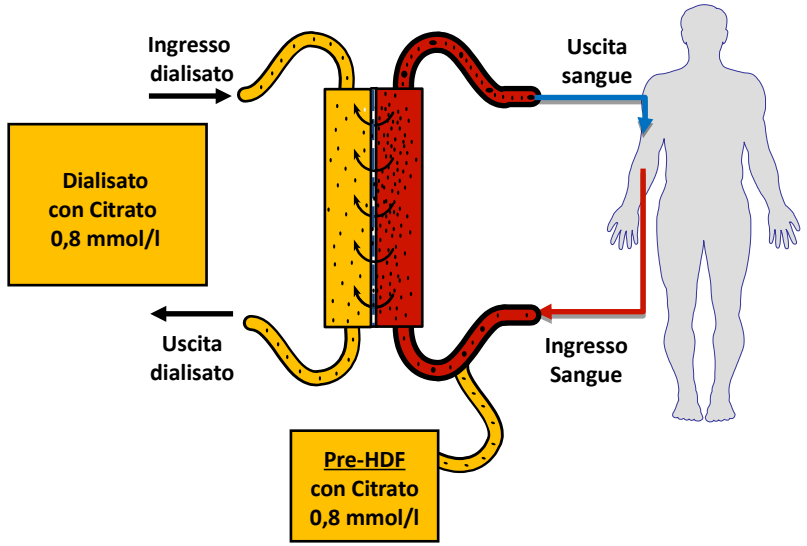
Pre-HDF con Citrato e Anticoagulazione

Artificial Organs

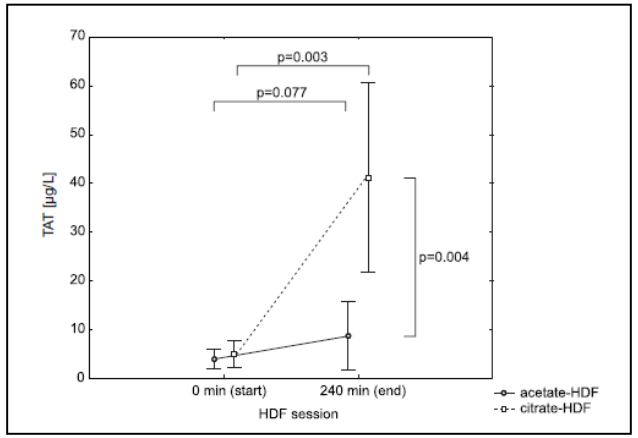
TABLE 1. *Compositions of acetate- (SW127/286) and citrate-based (Citrasate) dialysis solutions*

Solution*	Na^+ (mmol/L)	K^+ (mmol/L)	Ca^{++} (mmol/L)	Mg^{++} (mmol/L)	Cl^- (mmol/L)	Bicarbonate (mmol/L)	Acetate (mmol/L)	Citrate (mmol/L)
SW127/286	138	2/4	1.25	0.5	109	32	3	0
Citrasate	140	2/4	1.25	0.5	110	33	0.3	0.8

*Electrolyte and organic buffer concentrations within the ready-to-use, online mixed dialysis solutions.



	Citrate-preHDF	Acetate-preHDF	p
Sessions, n	10	10	
Clotting score	3.4±0.65	1.8±0.79	0.002
Kt/V	1.48±0.16	1.58±0.17	0.006



Richtrova P et al. Artif Organs 2017: 41(8): 759-766

Effects of Citrate Acid Concentrate (Citrasate®) on Heparin N Requirements and Hemodialysis Adequacy: A Multicenter, Prospective Noninferiority Trial

Jeffrey J. Sands[a] Peter Kotanko[b, c] Jonathan H. Segal[d] Chiang-Hong Ho[a]
Len Usvat[b] Amy Young[e] Mary Carter[b] Olga Sergeyeva[a, b] Lisa Korth[e]
Eileen Maunsell[a] Yueping Zhu[a] Mahesh Krishnan[e] Jose A. Diaz-Buxo[a]

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[e]DaVita Clinical Research, Minneapolis, Minn., USA

Blood Purif 2012;33:199–204

Citrate vs. acetate dialysate on intradialytic heparin dose: A double blind randomized crossover study

Kelvin C. W. LEUNG,[1] Davina J. TAI,[2] Pietro RAVANI,[1] Rob R. QUINN,[1]
Nairne SCOTT-DOUGLAS,[1] Jennifer M. MACRAE[1,3]

[1]Cumming School of Medicine, University of Calgary; [2]Cumming School of Medicine, University of Saskatchewan; [3]Department of Cardiac Sciences, University of Calgary

Hemodialysis International 2016; 20:537–547

The use of dialysate with citrate allows the reduction of the dose of heparin per treatment but *not* allows heparin free dialysis

Citrate-Buffered Dialysis Solution (Citrasate) Allows Avoidance of Anticoagulation During Intermittent Hemodiafiltration—At the Cost of Decreased Performance and Systemic Biocompatibility

*†Pavlina Richtrova, *†Jan Mares, *†Lukas Kielberger, †‡Ladislav Trefil,
*†Jaromir Eiselt, and *†Tomas Reischig

Artificial Organs 2017, 41(8):759–766

clinical trial http://www.kidney-international.org

see commentary on page 1084

Results of the HepZero study comparing heparin-grafted membrane and standard care show that heparin-grafted dialyzer is safe and easy to use for heparin-free dialysis

Maurice Laville[1], Marc Dorval[2], Joan Fort Ros[3], Renaud Fay[4], Joëlle Cridlig[5], Joëlle L. Nortier[6], Laurent Juillard[7], Alicja Dębska-Ślizień[8], Loreto Fernández Lorente[9], Damien Thibaudin[10], Casper Franssen[11], Michael Schulz[12], Frédérique Moureau[13], Nathalie Loughraieb[13] and Patrick Rossignol[4]

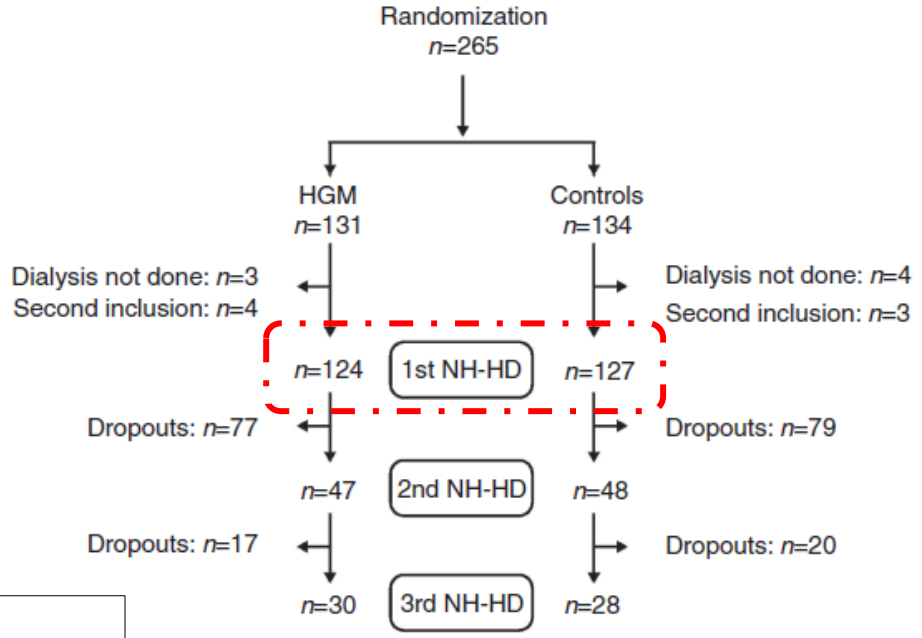


Table 4 | Efficacy according to the usual practice of the center

Usual practice	Treatment	Success	Success rate (95% CI)	*P*-value
Predilution	Evodial	36/63	57.1 (44.1–67.9)	
	Controls	26/65	40.0 (28.3–51.4)	0.078
	Difference E-C[a]		17.1 (2.6–30.7)	
Saline flushes	Evodial	49/61	80.3 (67.8–87.7)	
	Controls	38/62	61.3 (48.0–71.7)	0.034
	Difference E-C[a]		19.0 (5.4–32.0)	
Interaction[b]			− 1.9 (− 24.9; + 20.9)	0.64[c]

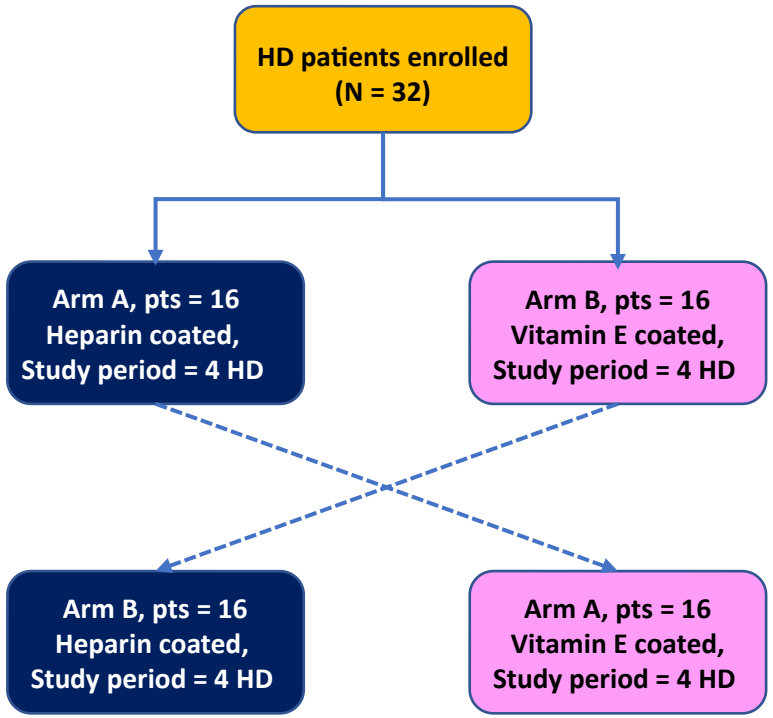
[a]Difference E-C: Evodial-controls. CI, confidence interval. The 95% CIs are 2-tailed for intragroup success rates (in agreement with *P*-value), 1-tailed for the intergroup difference (in agreement with the noninferiority/superiority analysis).
[b]Interaction: between usual practice and treatment, i.e., difference between differences Evodial–controls.
[c]*P*-value of the Breslow-Days test of homogeneity of odds ratios.

1st No-Heparin Hemodialysis

AJKD
Original Investigation

Vitamin E–Coated and Heparin-Coated Dialyzer Membranes for Heparin-Free Hemodialysis: A Multicenter, Randomized, Crossover Trial

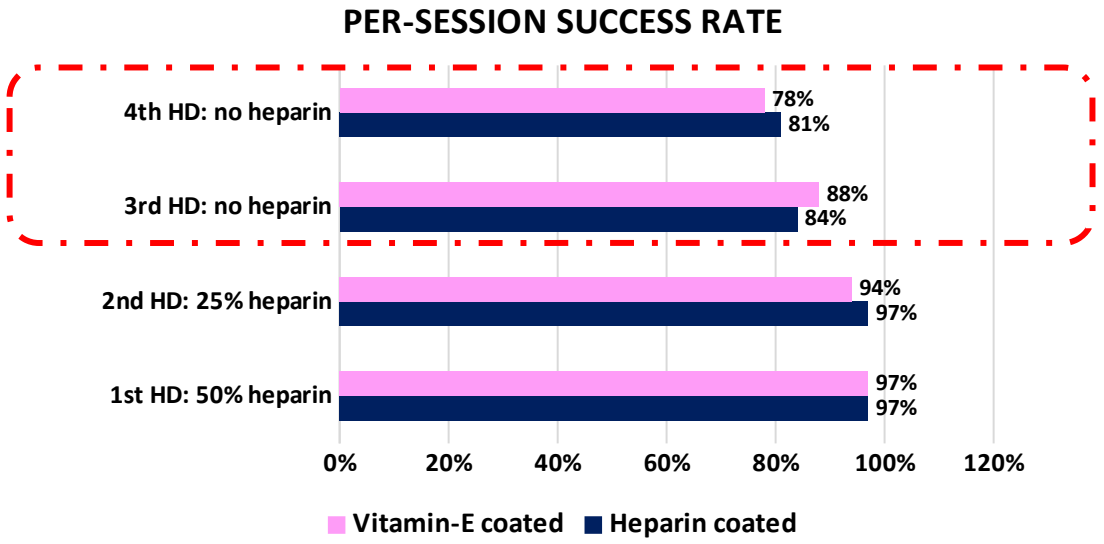
Mohamed Shariful Islam, MBBS,[1] Zarih Alcheikh Hassan, MD,[2] Florence Chalmin, MD,[1] Sandor Vido, MD,[1] Mohamed Berrada, MD,[1] David Verhelst, MD,[2] Patrick Donnadieu, MD,[2] Olivier Moranne, MD, PhD,[1] and Vincent L.M. Esnault, MD, PhD[1,3]



Study period =
1st HD 50% heparin + 2nd HD 25% heparin + 3rd HD no heparin + 4th HD no heparin

	Vitamin E coated pts = 16	Heparin coated pts = 16
N° of successful study period	25/32 (78%)	26/32 (81%)
N° of sessions without clotting	114/128 (89%)	115/128 (90%)
N° of patients who needed saline flushes	19 (59%)	20 (63%)
Mean transmembrane pressure, mmHg	23.5±20	24.2±21
Mean blood flow rate, mL/min	340±26	344±23

Successful study period = no circuit-clotting event leading to premature interruption of any of the 4 dialysis sessions



Nephrol Dial Transplant (2017) 32: 707–714
doi: 10.1093/ndt/gfw461

A noninferiority trial comparing a heparin-grafted membrane plus citrate-containing dialysate versus regional citrate anticoagulation: results of the CiTED study

Björn Meijers[1,2], Christoph Metalidis[2,3], Thomas Vanhove[1], Ruben Poesen[1], Dirk Kuypers[1,2] and Pieter Evenepoel[1,2]

[1]Department of Microbiology and Immunology, KU Leuven, Leuven, Belgium, [2]Division of Nephrology, UZ Leuven, Leuven, Belgium and [3]Nephrology Unit, ZOL, Genk, Belgium

Randomized Cross Over Trial

25 Patients

1284 HD sessions

636 CiTED arm

648 RCA arm

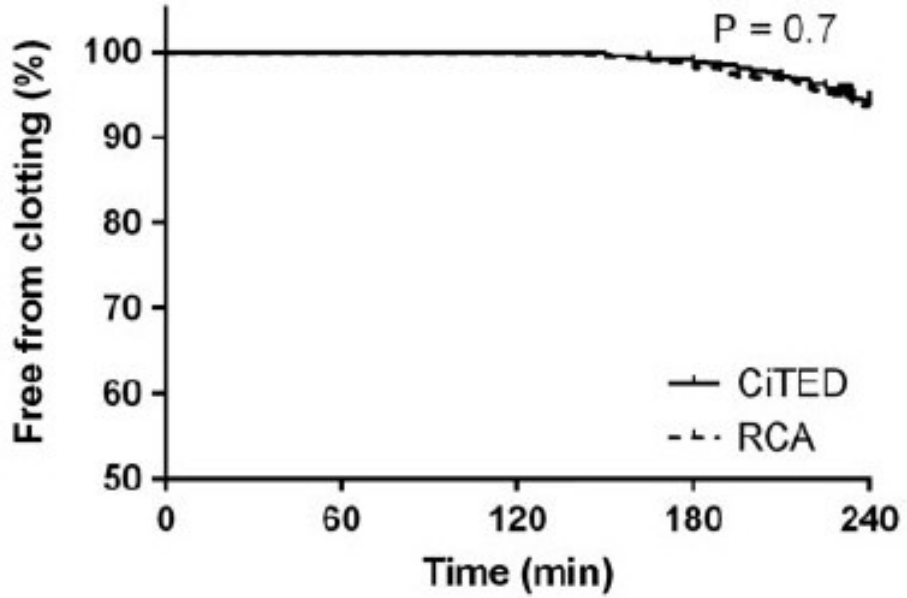
The combination of heparin grafted membrane and citrate containing dialysate

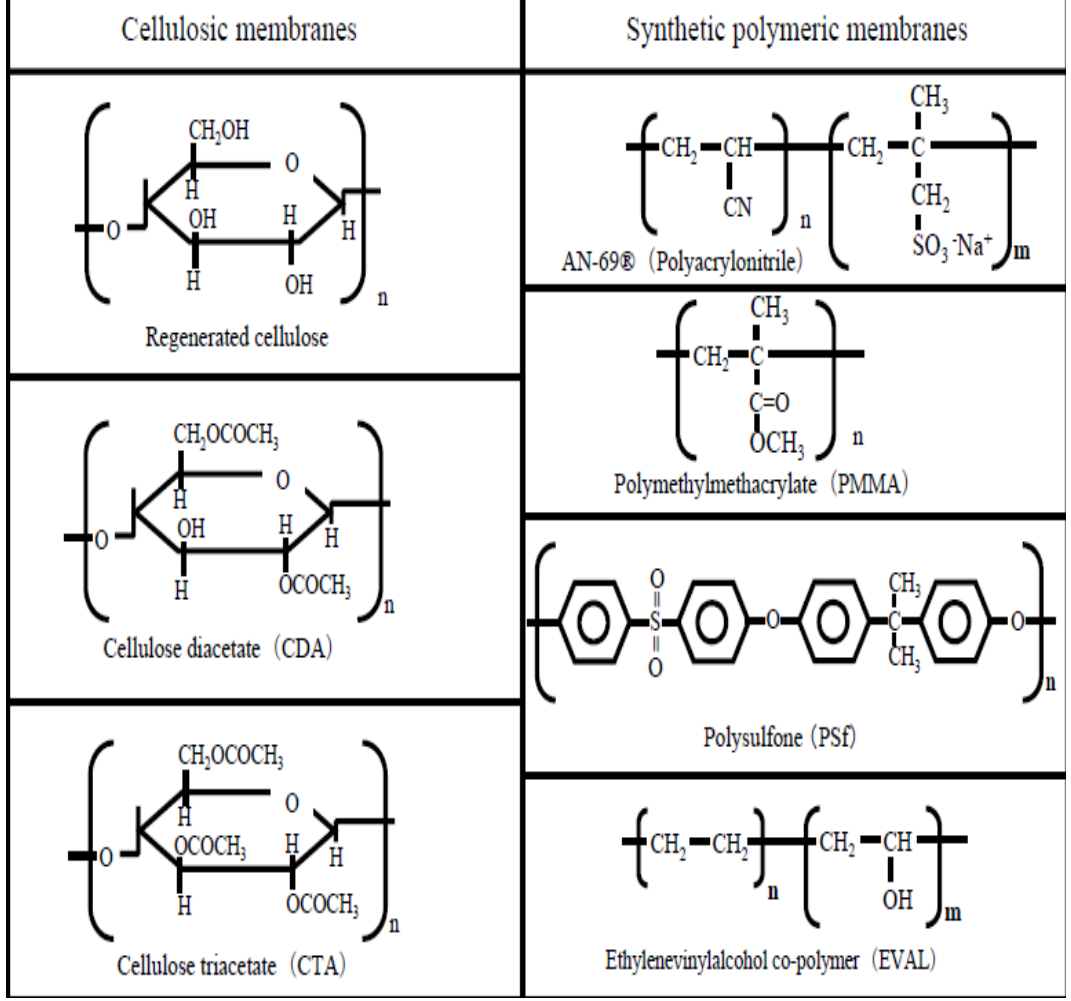
versus

Regional citrate anticoagulation

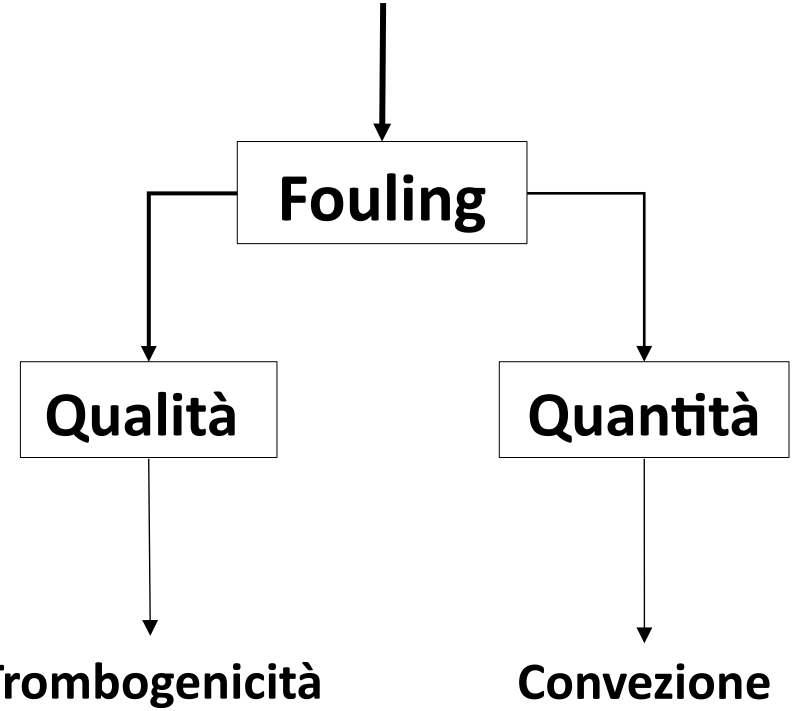
Citrate-containing dialysate was produced using Selectbag® Citrate 1/200 A concentrate (Gambro Dasco, Sondalo, Italy). We used the **E**vo**d**ial 1.6 (Gambro Industries) with an effective membrane surface area of 1.65 m². This device is a precoated heparin-grafted membrane.

A hypertonic sterile solution of trisodium citrate dihydrate was infused into the afferent blood line at a rate 60mL/h using a separate infusion pump. The anticoagulant effect of citrate was neutralized using calcium-containing dialysate with a calcium concentration of 1.5 mmol/L.
In all sessions, a polyarylethersulfone dialyser (Polyflux® 170H, Gambro Dialysatoren, Hechingen, Germany) was used, with an effective membrane surface area of 1.7 m²

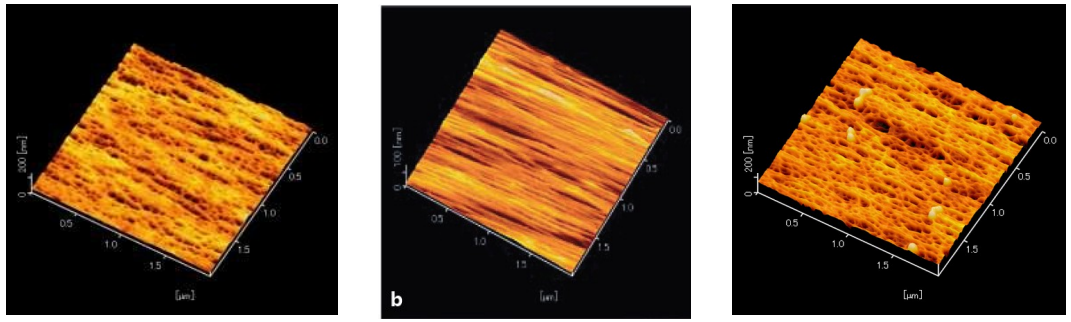




Chimica e Rugosità delle Membrane



Helixone® **ATA ™** **Rexebrane™**

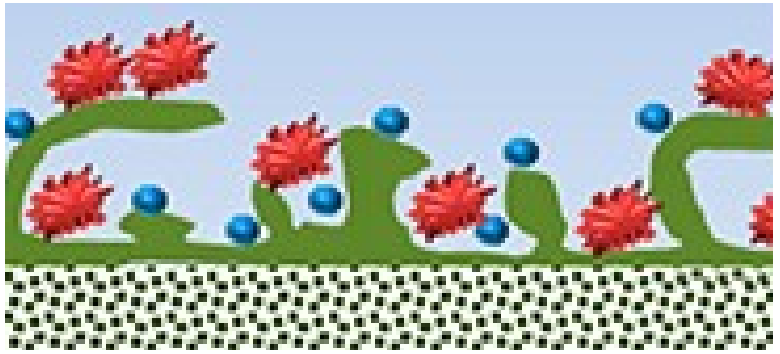


Yamashita AC et al. Updates in Hemodialysis, 2015

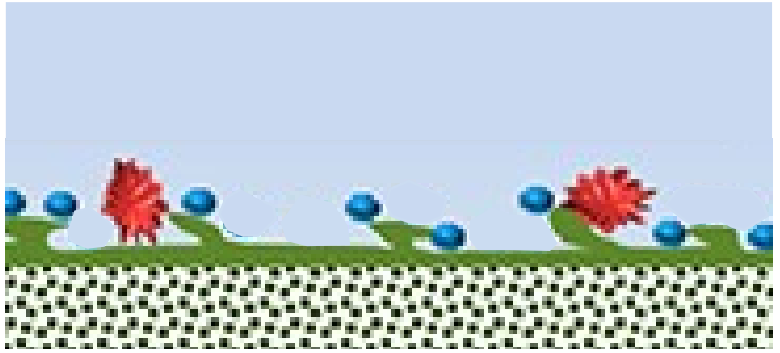
Sunohara T & Masuda T. Contrib Nephrol. 2017; 189: 215–221

Fouling e Rugosità delle Membrane per Emodialisi

Superficie rugosa



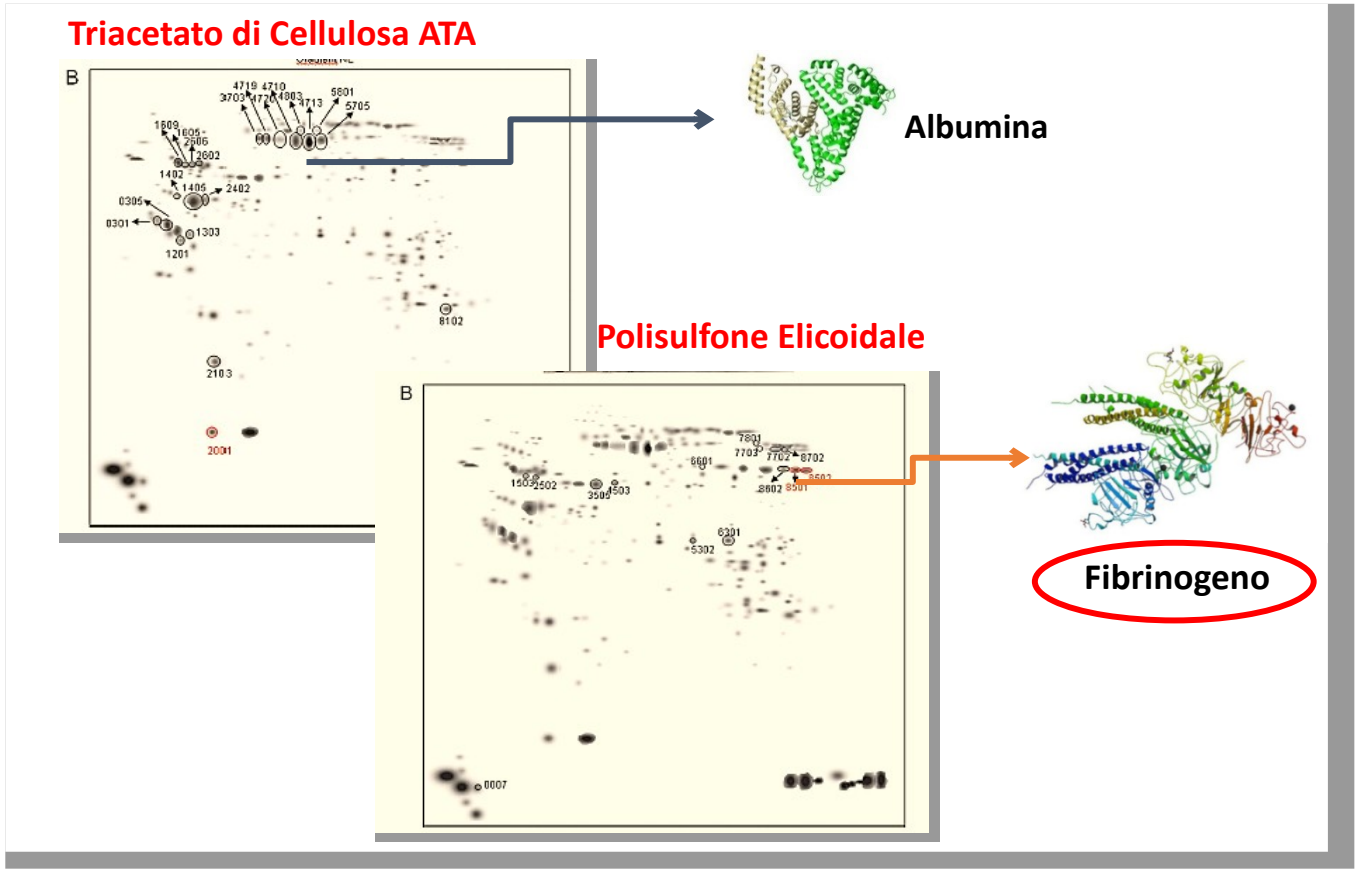
Superficie liscia



Membrana	Immagine 2D	Ra (nm)	RMS (nm)
PES-Polynephron™		5.5	7.0
PS Elicoidale®		11	15
Polyamix Polyarylethersulfone		7.5	11
CTA		5,5	7.0
ATA		4,5	5.5
PS / PVP		13	18

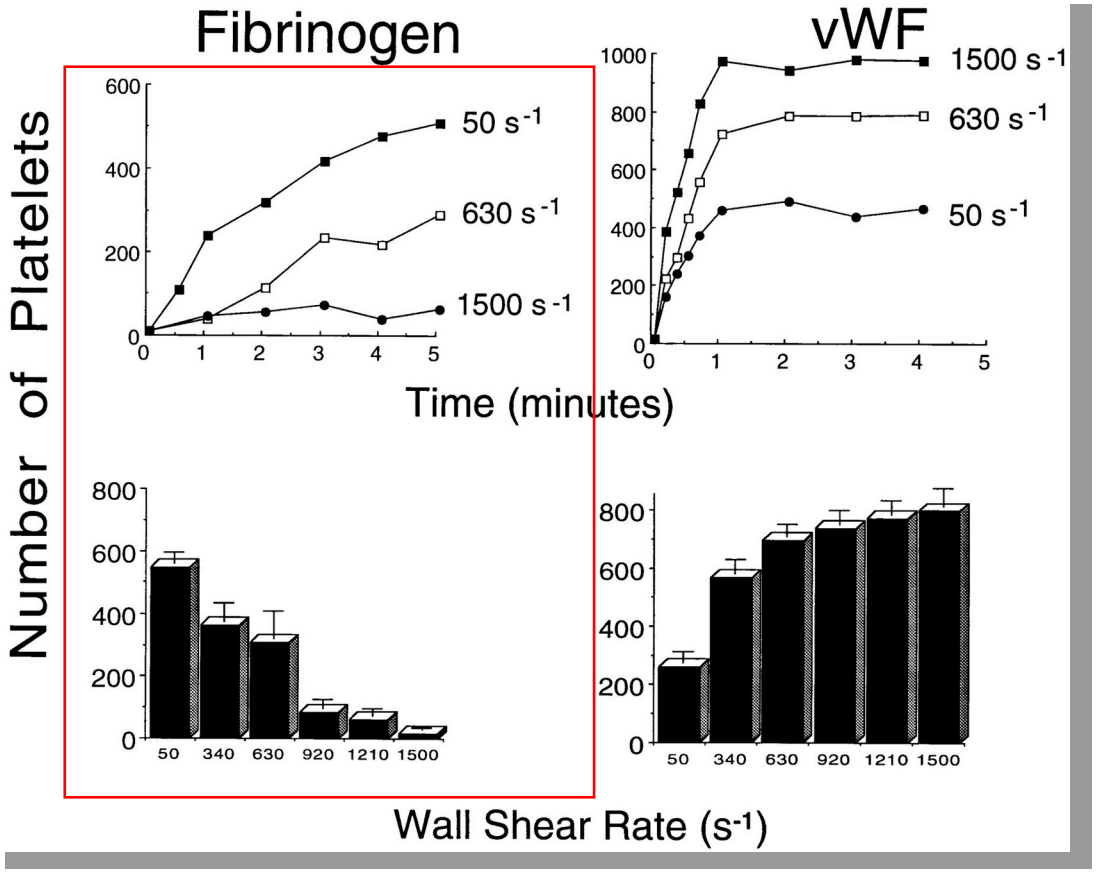
Sunohara T & Masuda T. Contrib Nephrol. 2017; 189: 215–221

Qualità delle Proteine del Fouling e Chimica della Membrana di dialisi



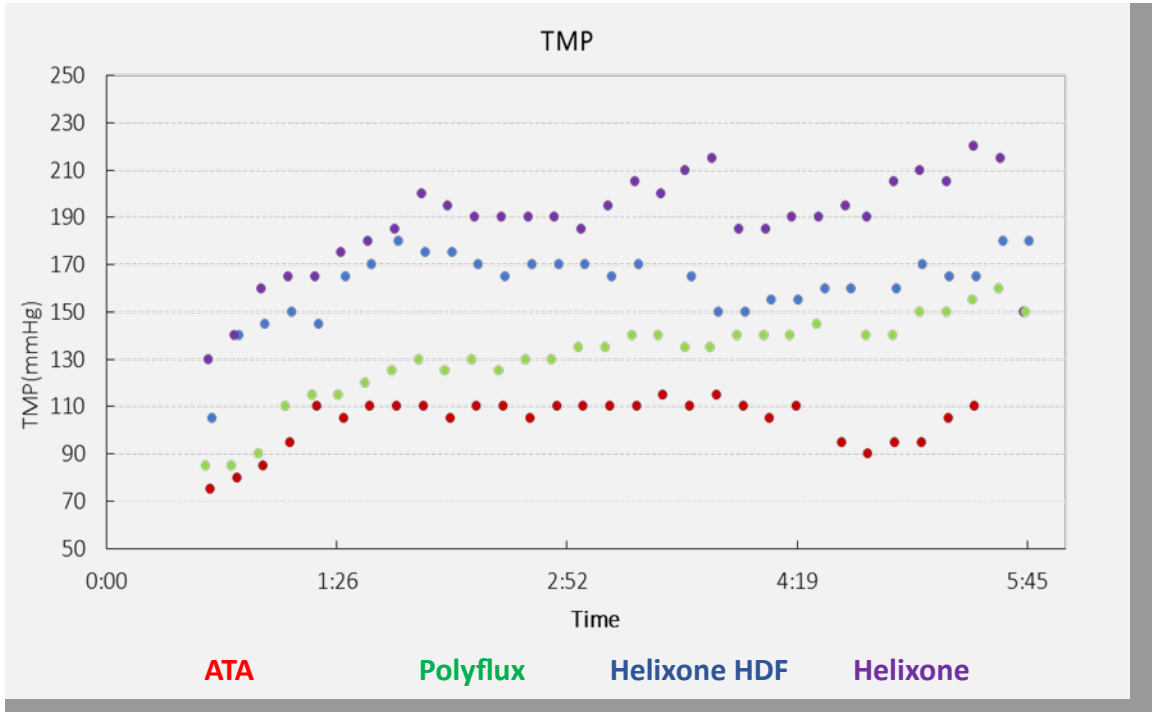
Urbani A, et al. Mol Biosyst 2012; 8(4):1029-39

Platelet Interaction with Fibrinogen: Wall Shear Rate



Savage B, et al. Cell 1996; 84(2):289-97

Fouling e Pressione di Transmembrana (TMP)



Dialyzers	Roughness average (nm)
ATA	4.5
Polyflux	7.5
Helixone HDF	15
Helixone	11

In vivo **(patients, n=5): Qb:350 ml/min, Qd:600 ml/min, Qs:85 ml/min**

BioArtProducts, Rostock, Germany, 2015

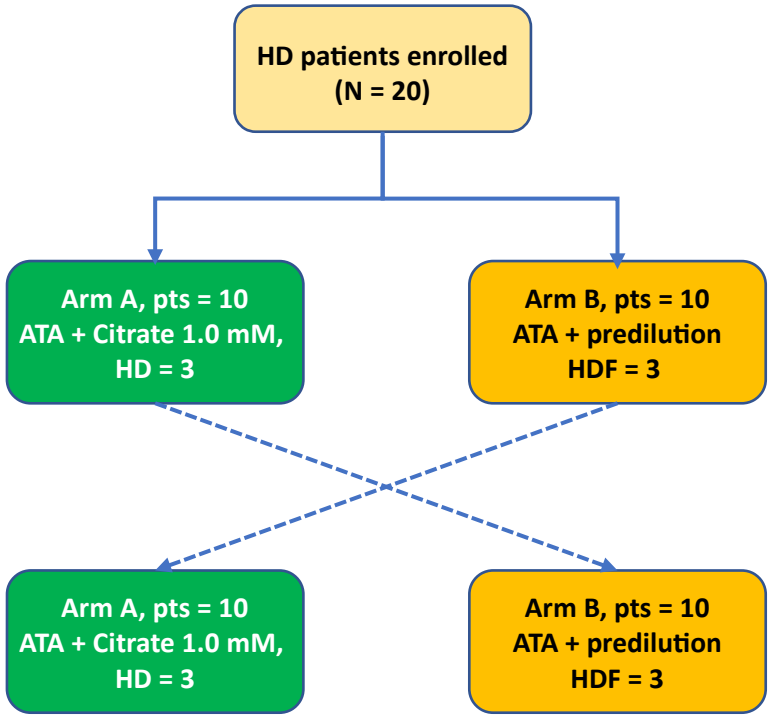
Clinical Kidney Journal, 2021, vol. 14, no. 8, 1901–1907

doi: 10.1093/ckj/sfaa228
Advance Access Publication Date: 28 November 2020
Original Article

ORIGINAL ARTICLE

Strategies for asymmetrical triacetate dialyser heparin-free effective haemodialysis: the SAFE study

Ines Vandenbosch[1,3], Sander Dejongh [2], Kathleen Claes[3,2], Bert Bammens[3,2], Katrien De Vusser[3,2], Amaryllis Van Craenenbroeck[3,2], Dirk Kuypers[3,2], Pieter Evenepoel [3,2] and Björn Meijers [3,2]



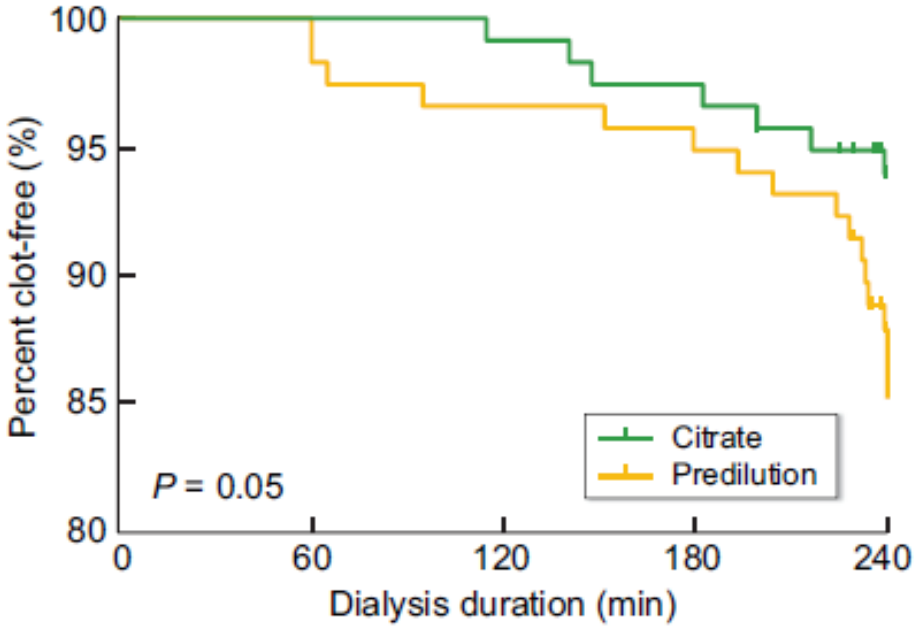


FIGURE 2: Kaplan–Meier curve of time to clotting. Time to clotting was not significantly different (P = 0.05).

Arm A: Asymmetric cellulose triacetate plus citrate containing dialysate 1mM/L

Arm B: Asymmetric cellulose triacetate with high volume predilution hemodiafiltration

Microtrombosi: ATA vs Helixone

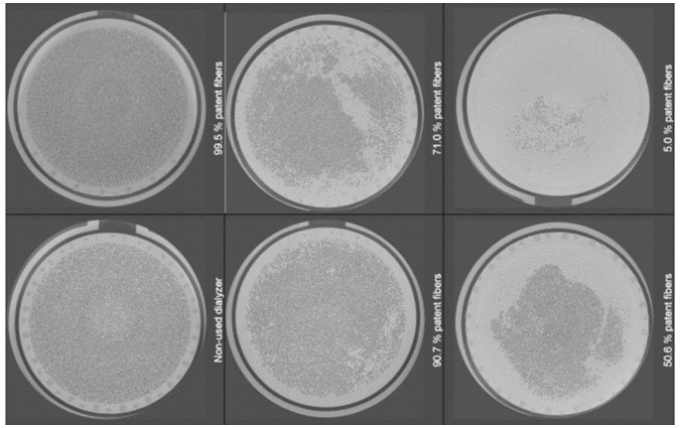
- HD patients (n)= 10
- Study: Randomized cross over
- Dialyzers: ATA vs. Helixone
- Dialysis at mid week
- Anticoagulation: ¼ dose LMWH

Post-dilution HDF:

1. Qb 300 mL/min
2. Qd 500 mL/min
3. Qf 75 mL/min

HDF length: 1) 60 min
2) 120 min
3) 240 min

Dialyzers Micro-CT scanning



OPEN FIBER AREA (%)	ATA_60 min median (25pct; 75pct)	ATA_120 min median (25pct; 75pct)	ATA_240 min median (25pct; 75pct)	Helixone_60 min median (25pct; 75pct)	Helixone_120 min median (25pct; 75pct)	Helixone_240 min median (25pct; 75pct)	P-Value
50	100 % (100;100)	100 % (100;100)	99 % (98;100)	90 % (81;98)	84 % (69;92)	32 % (27;43)	<0.001
70	100 % (99;100)	100 % (99;100)	99 % (97;99)	90 % (81;98)	83 % (68;92)	31 % (26;41)	<0.001
90	74 % (70;79)	74 % (67;88)	64 % (59;69)	63 % (56;65)	52 % (38;59)	14 % (9;17)	<0.001

Vanommeslaeghe F et al. Scientific Reports 2022; 12: 5717

Take home messages

1. **La dialisi senza eparina è un'opzione indispensabile nella gestione del paziente cronico in dialisi e in qualsiasi contesto clinico «acuto»**

2. **Le opzioni per la dialisi senza eparina sono molteplici**

3. **Le strategie più efficienti sembrano la combinazione di membrane speciali per caratteristiche o per funzionalizzazione con un dialisato a basso contenuto di citrato**

Diapositive di backup

Categorie di Rischio per Emorragia

Rischio Medio

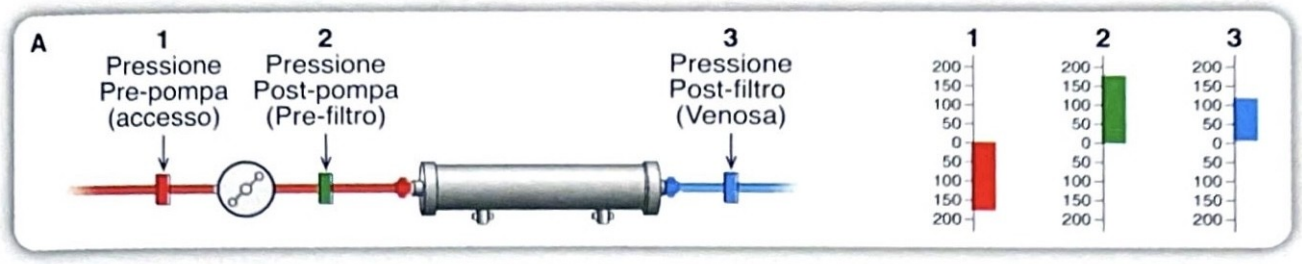
- **Pericardite**
- **Emorragia < 48 h**
- **Posizionamento CVC tunnellizzato < 24 h**
- **Chirurgia minore < 72 h**
- **Chirurgia maggiore o chirurgia oculistica 3-7 gg**

Rischio Alto

- **Sindrome emorragica**
- **Coagulopatia**
- **Emorragia cerebrale < 7 gg**
- **Ferita sanguinante**
- **Chirurgia maggiore o oculistica < 72 h**

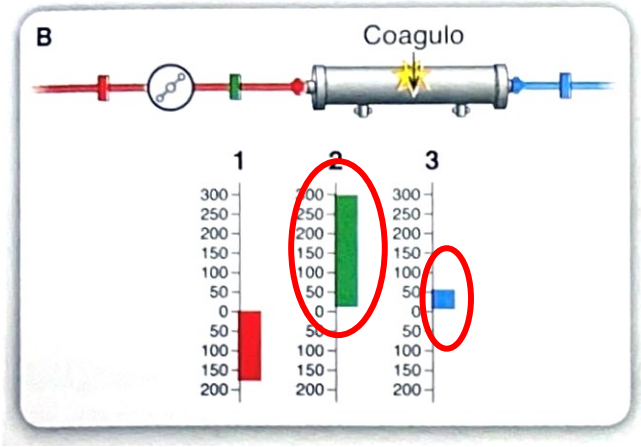
Nissenson AR & Fine RN, *Handbook of Dialysis Therapy, 4th edition, 2008*

Differenza fra Pressione Pre-filtro (post-pompa) e Post-filtro (venosa)



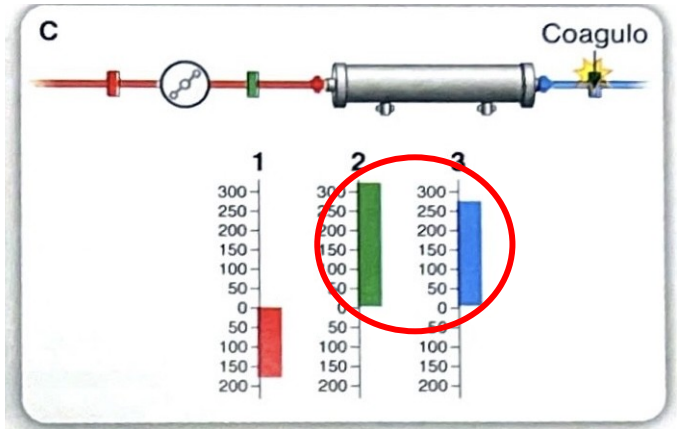
⬆ Pressione Pre-filtro >> Post-filtro

Coagulo nel Filtro



⬆ Pressione Pre-filtro = ⬆ Post-filtro

Coagulo nel Pozzetto venoso e/o linea



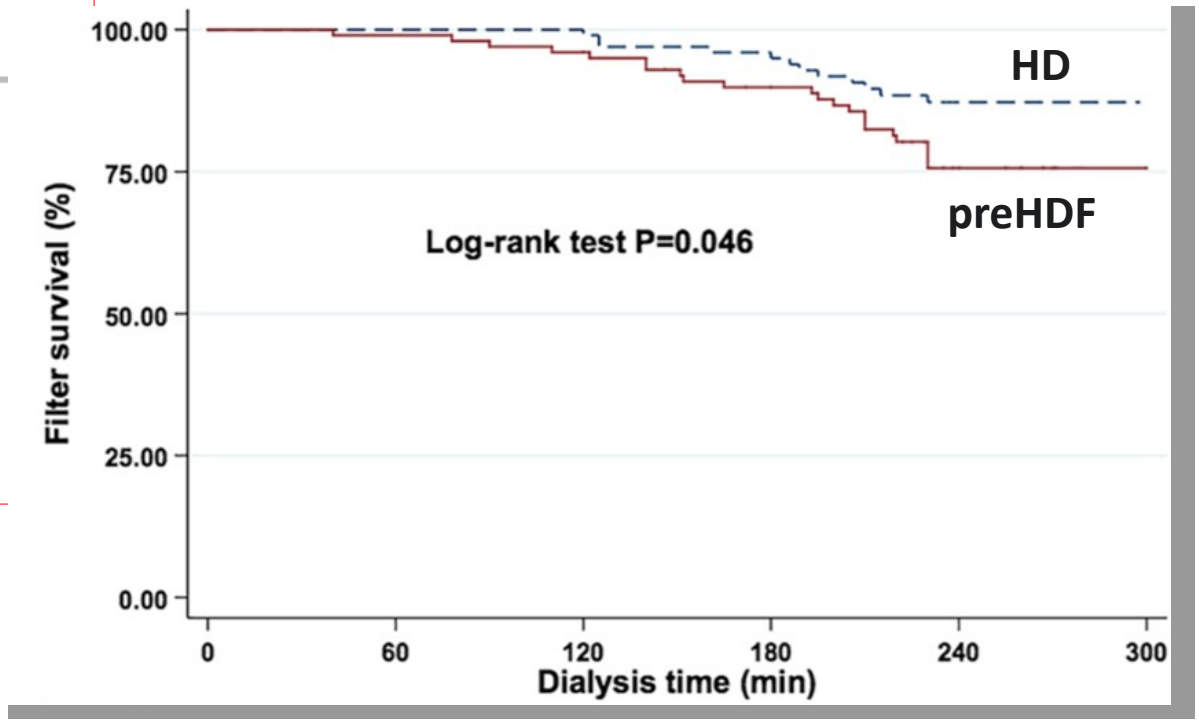
C. Ronco, 2022. In: *Emodialisi*, Ed. Piccin, Padova: pg 153-166

Hemodialysis International 2019

ORIGINAL ARTICLE

Hemodialysis without anticoagulation: Less clotting in conventional hemodialysis than in predilution hemodiafiltration

Thierry KRUMMEL,[1] Etienne CELLOT,[2] Alicia THIERY,[3] Géraldine DE GEYER,[1] Nicolas KELLER[1], Thierry HANNEDOUCHE[1]

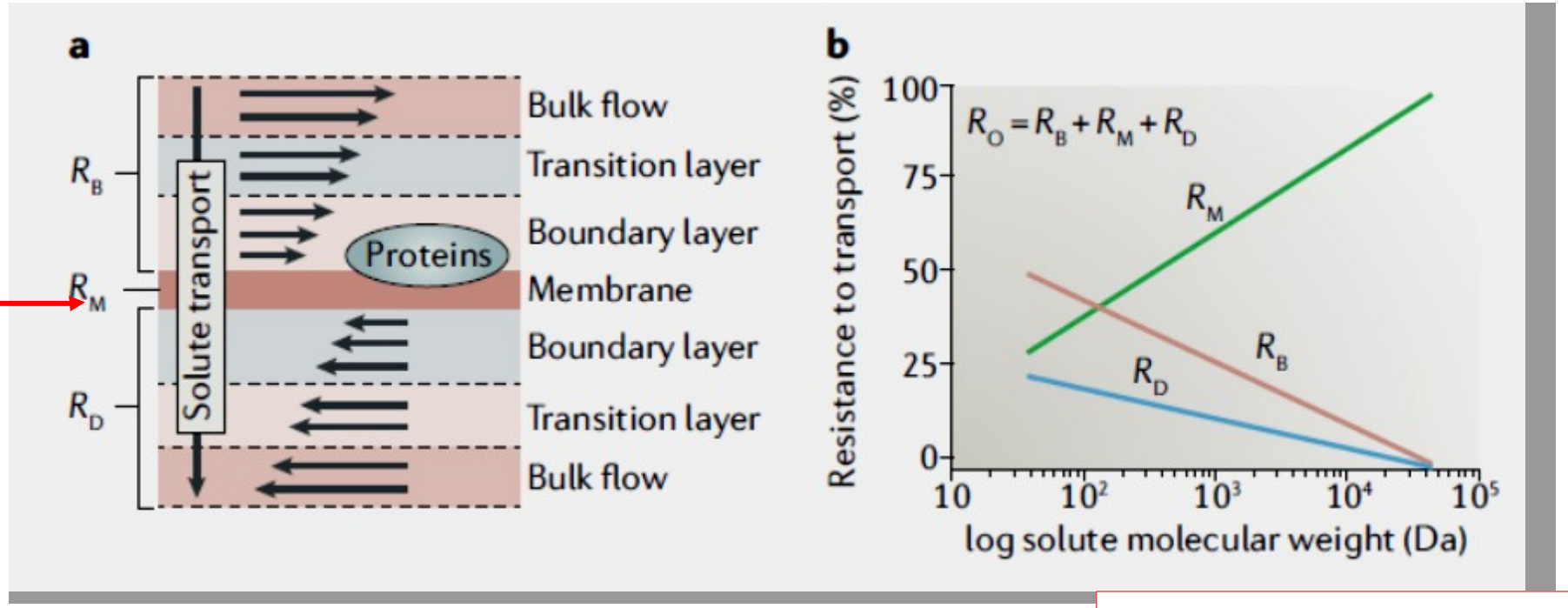


- Patients (n): 155
- Dialysate Citrate 0.80 mmol/L
- Dialyzer: FX 100
- HD vs Pre HDF
- Pre-dilution: 50 ml/min

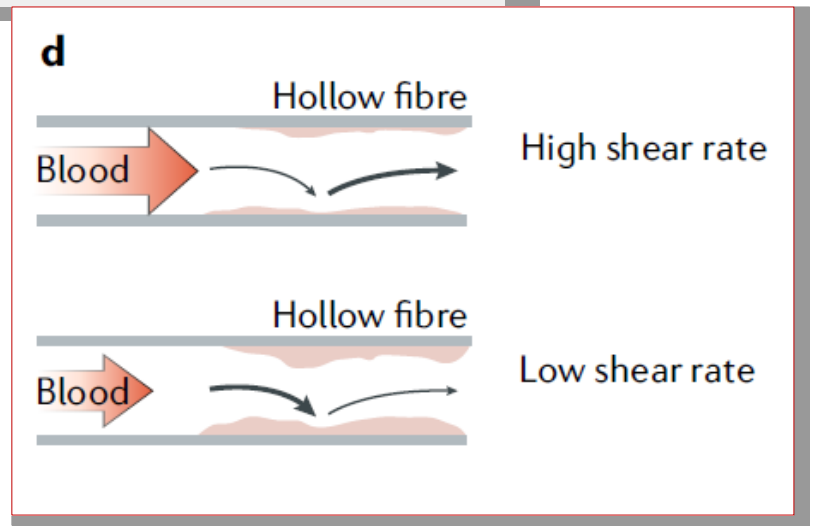
	HD (n = 100)	preHDF (n = 100)	P
Effective sessions duration, min	228 ± 31	221 ± 41	0.53
Sessions interrupted for coagulation, n (%)	12 (12.0)	23 (23.0)	0.04
Shortened dialysis time due to clotting, min	7.4 ± 2.4	15.5 ± 3.9	0.04
Time to clotting, min	178.4 ± 10.9	172.6 ± 11.5	0.83
Sessions interrupted for other reasons, n (%)	13 (13.0)	9 (9.0)	0.37
D-dimers at H3, µg/L	6991 ± 7052	6873 ± 6996	0.84
Doubling D-dimers, n (%)	35 (45.5)	34 (44.2)	0.87

HD = hemodialysis; H3 = third hour of hemodialysis; preHDF = predilution hemodiafiltration.

Resistenza al Trasporto

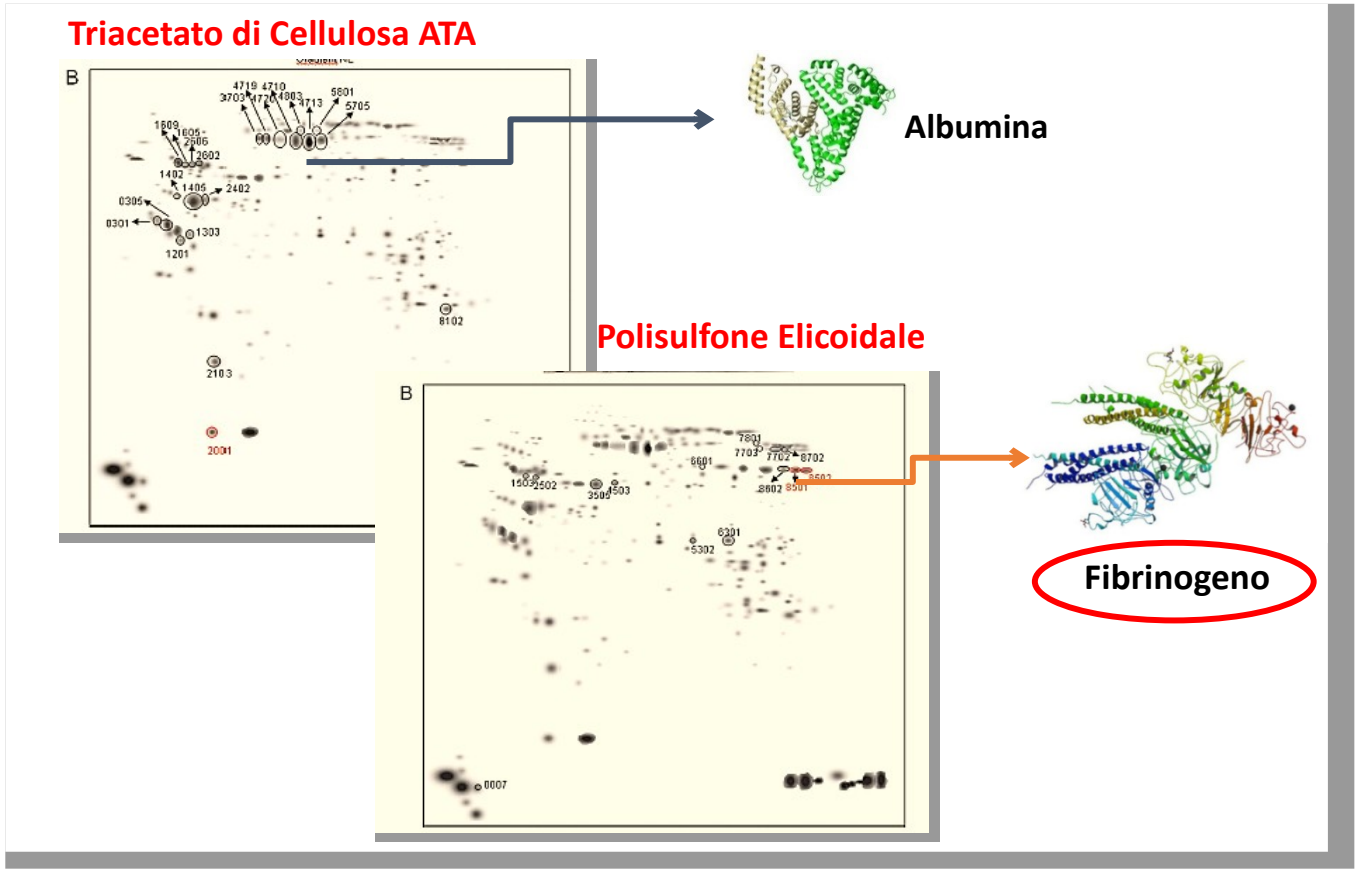


R_M è la Resistenza opposta dalle Caratteristiche della Membrana al Trasporto dei soluti



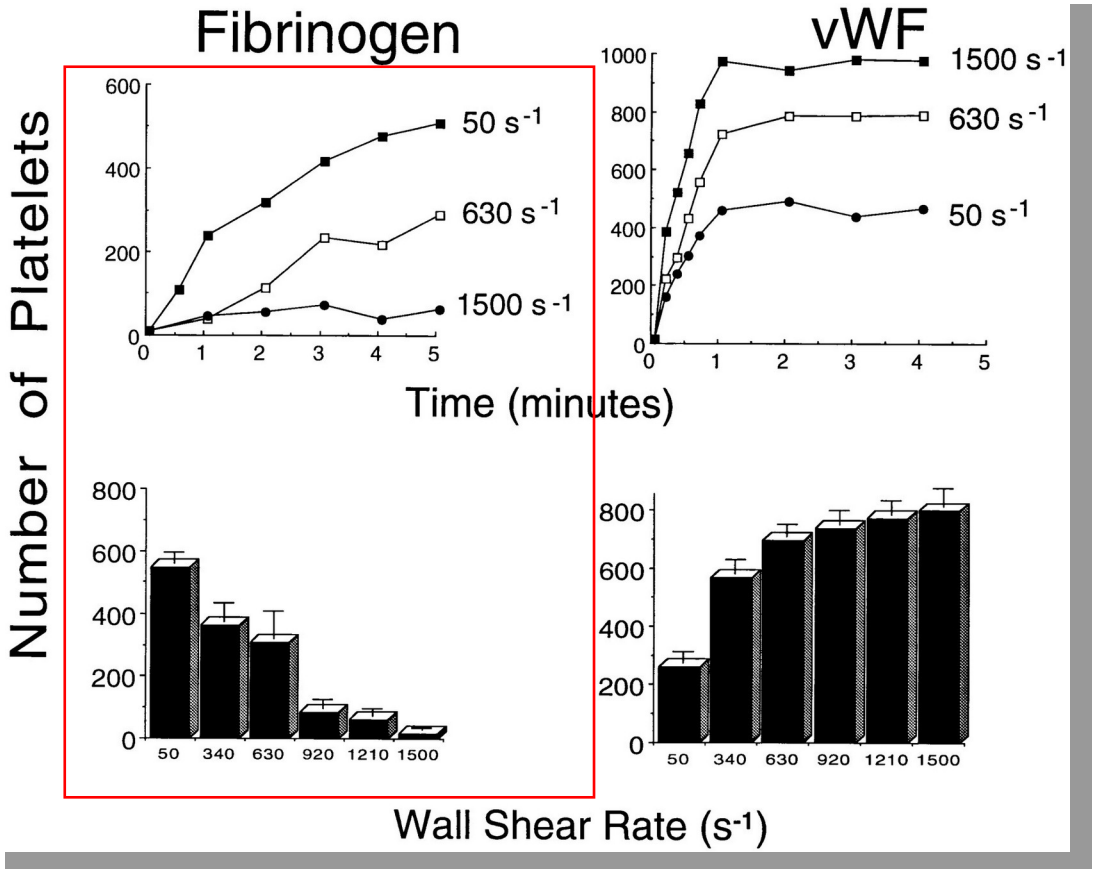
Ronco C & Clark WR. Nat Rev Nephrol. 2018;14(6):394-410

Qualità delle Proteine del Fouling e Chimica della Membrana di dialisi



Urbani A, et al. Mol Biosyst 2012; 8(4):1029-39

Platelet Interaction with Fibrinogen: Wall Shear Rate



Savage B, et al. Cell 1996; 84(2):289-97

Dialysis

Heparin-Coated Polyacrylonitrile Membrane Versus Regional Citrate Anticoagulation: A Prospective Randomized Study of 2 Anticoagulation Strategies in Patients at Risk of Bleeding

Pieter Evenepoel, MD, PhD,[1] Tom Dejagere, MD,[1] Peter Verhamme, MD, PhD,[2] Kathleen Claes, MD,[1] Dirk Kuypers, MD, PhD,[1] Bert Bammens, MD, PhD,[1] and Yves Vanrenterghem, MD, PhD[1]

33 patients

Patients were randomly allocated to :

1) RCA using a calcium-free dialysate (RCA-Ca0)

2) RCA using a calcium containing dialysate (RCA-Ca3.0)

3) Anticoagulant-free hemodialysis with AN69ST

Table 3. Clotting Phenomena

	AN69ST	RCA-Ca0	RCA-Ca3.0	*P*
No. of sessions	31	32	30	
Clotting events	14 (45)[a]	1 (3)[a]	5 (17)	<0.05
Clotting events necessitating early termination	12 (39)[a]	0 (0)[a]	4 (13)	<0.005
Time to clotting (min)	181 (135-235)	30	172 (18-223)	
Dialysis duration (min)	220 ± 32[a]	240 ± 0[a]	236 ± 12	<0.005
Clotting score dialyzer	2.7 ± 1.0[a,b]	1.1 ± 1.0[a]	1.5 ± 1.0[b]	<0.0001
Clean, white (%)	0	6.5	10.7	<0.0001
White, limited fibrin deposits, head of dialyzer (%)	16.7	77.4	42.9	
White, mild fibrin deposits, head and along body dialyzer (%)	20.0	12.9	32.1	
Completely clotted, rinse back successful (%)	43.3	3.2	10.7	
Completely clotted, rinse back unsuccessful (%)	20.0	0.0	3.6	
Clotting arterial expansion chamber (%)	76.7[a,b]	22.6[a]	14.3[b]	<0.0001
Clotting venous expansion chamber (%)	86.7[a]	12.9[a,b]	75.9[b]	<0.0001

Note: Values expressed as number (percent), mean (range), or mean ± SD.
[a,b]Parameters with same suffix differ significantly (analysis of variance).

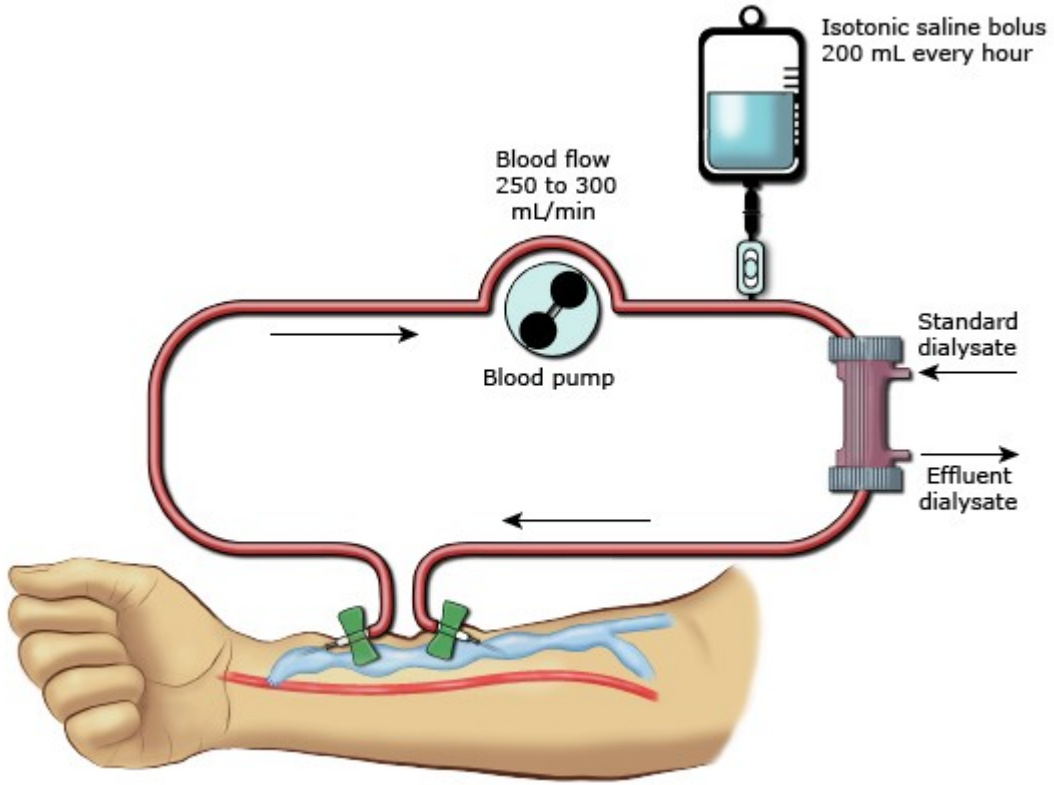
Table 2. Operational Characteristics

	AN69ST	RCA-Ca0	RCA-Ca3.0
Dialyzer	AN69ST	F60	F60
Access (AV fistula/catheter/both)	8/3/0	7/3/1	8/1/2
Dialysate sodium (mEq/L)	140	135	135
Dialysate bicarbonate (mEq/L)	34	25	25
Dialysate calcium (mEq/L)	3.0	0	3.0
Qblood (mL/min)	293.1 ± 25.6	300.1 ± 15.4	288.3 ± 32.4
Qdialysate (mL/min)	500	500	500
Qcalcium chloride (mL/h)	—	37.6 ± 5.1	—
Qcitrate (mL/h)	—	60	60
UF (L)	1.8 ± 1.0	1.8 ± 0.8	1.9 ± 1.2

Note: To convert sodium and bicarbonate in mEq/L to mmol/L, multiply by 1; calcium in mEq/L to mmol/L, multiply by 0.5.
Abbreviations: AV, arteriovenous; UF, ultrafiltration.

American Journal of Kidney Diseases, Vol 49, No 5 (May), 2007: pp 642-649

Meccanico: Boli di Fisiologica



Anticoagulation for the hemodialysis procedure