LA SCOAGULAZIONE DEL CIRCUITO PER EMODIALISI

Eparina sodica, eparina a basso peso molecolare, emodialisi senza eparina

Gabriele Donati, Giuseppe Di Chiaro
SC Nefrologia Dialisi e Trapianto renale

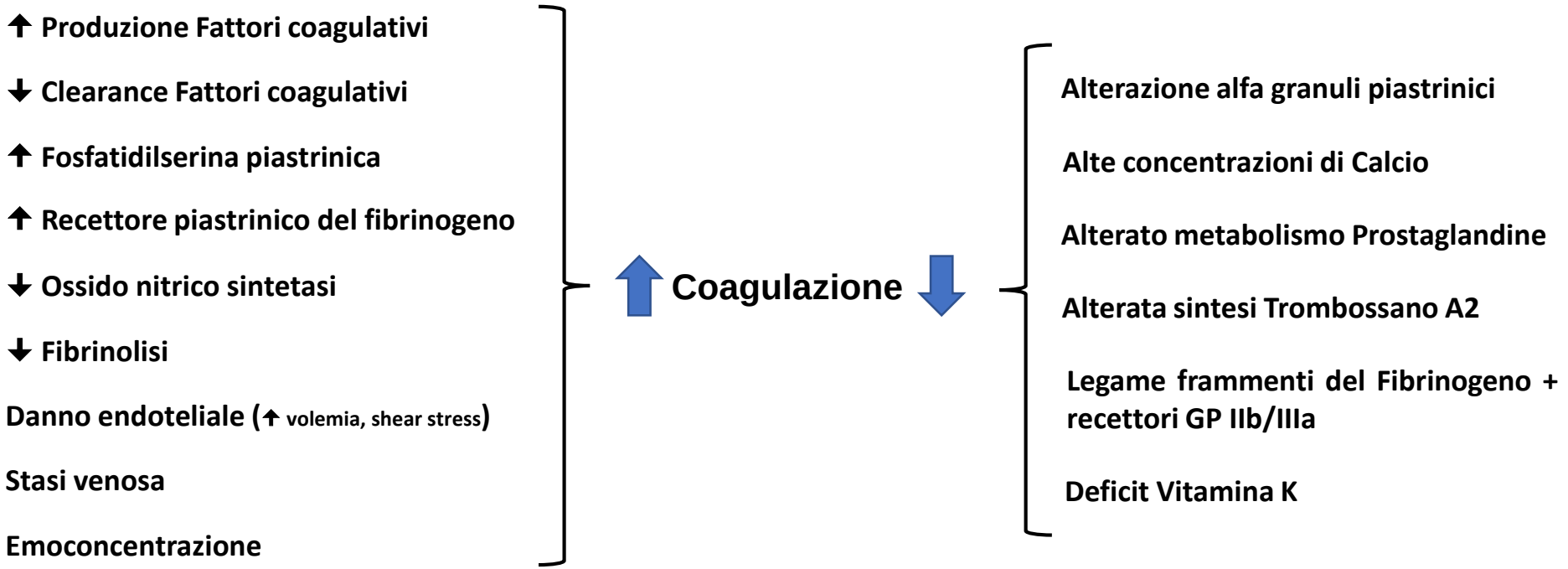
UNIMORE
UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero-Universitaria di Modena

Premesse

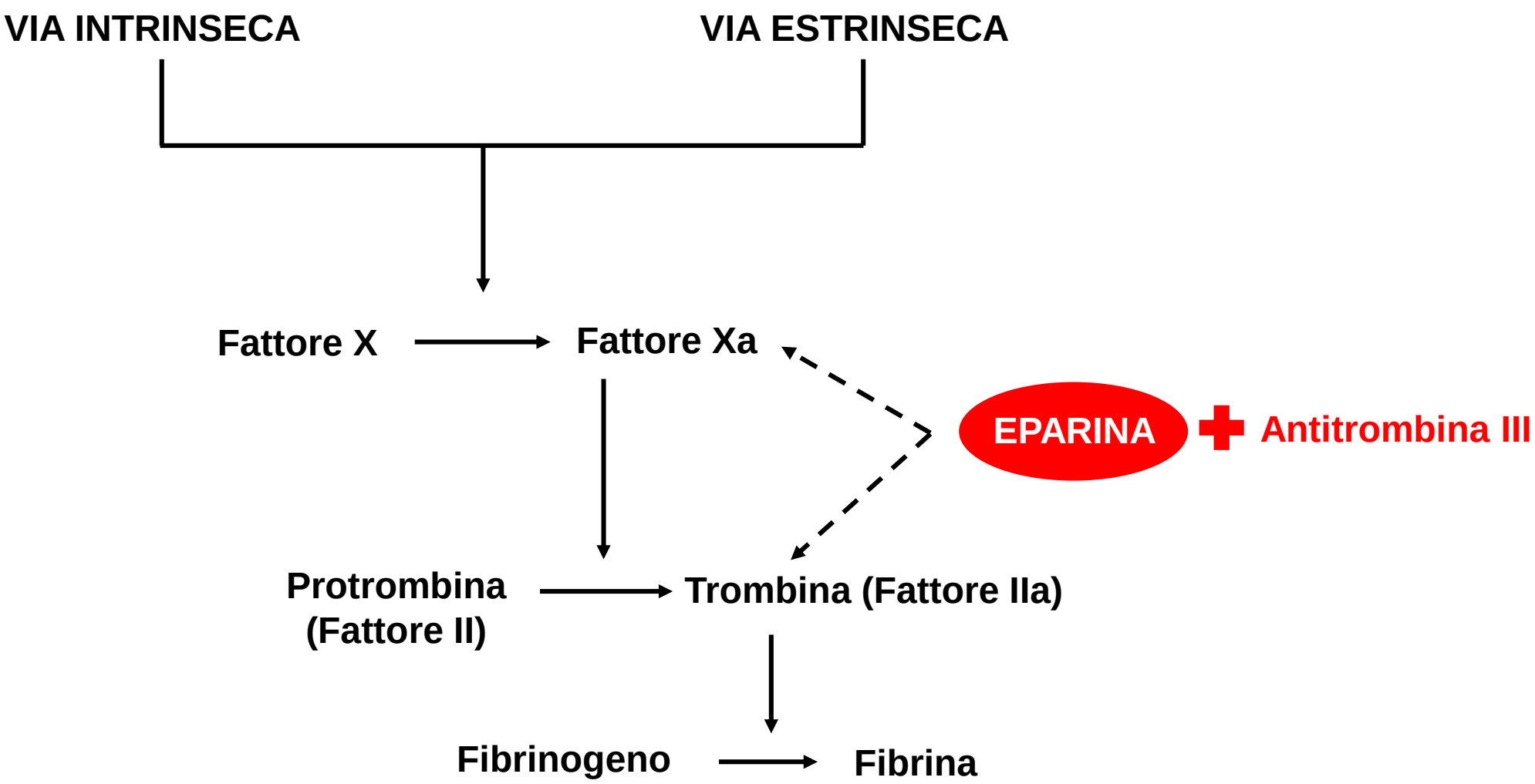
1. **Nessuno dei materiali artificiali che entra in contatto con il sangue possiede a tutt'oggi le proprietà antitrombotiche dell'endotelio vascolare**
2. **Il paziente uremico si trova in un equilibrio instabile tra l'emorragia e la trombosi**

Stato Coagulativo e ESRD

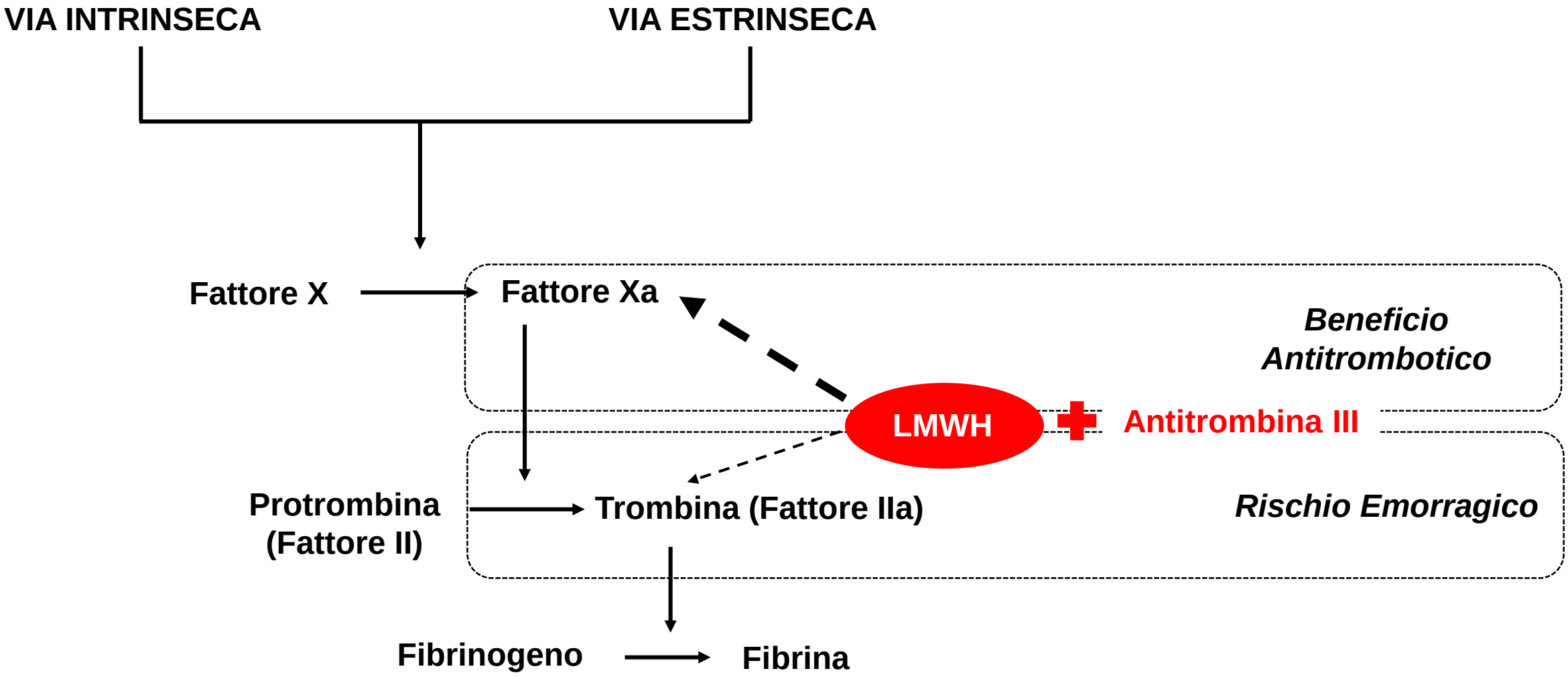


Jegatheswaran J, et al. Can J Cardiol 2019; 35: 1241-1255

FASE COAGULATIVA



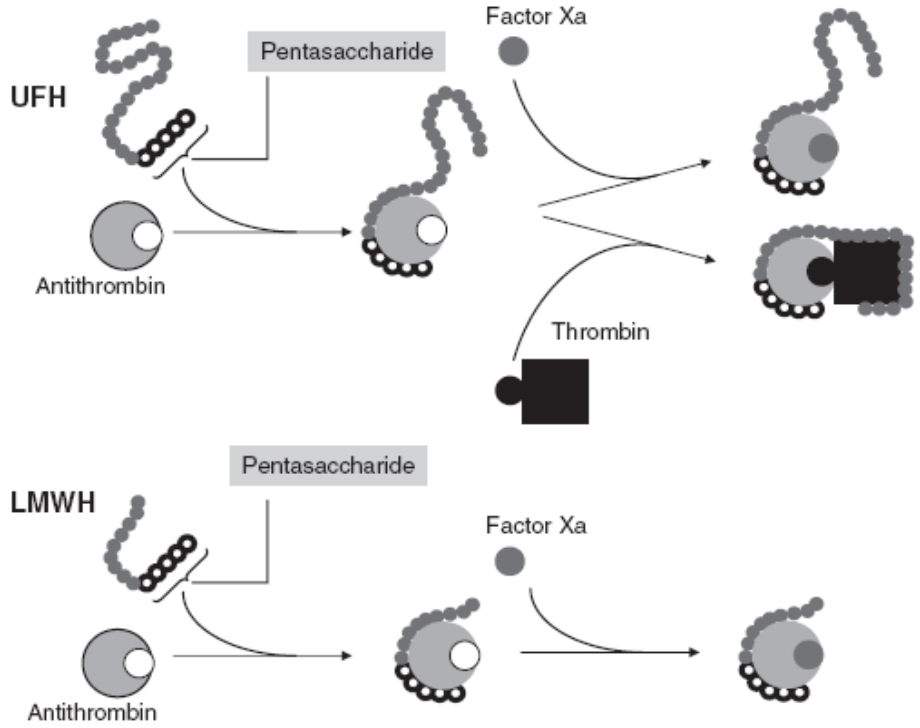
FASE COAGULATIVA

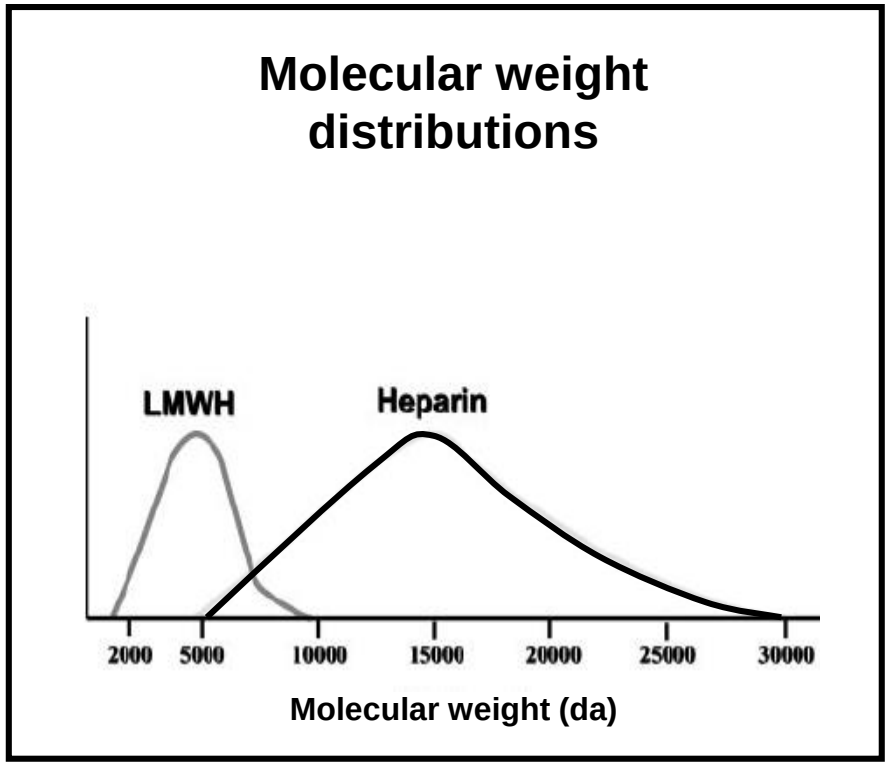


Capodicasa E, De Bellis F. Ars Medica, Edizioni CELI 1989

Struttura e Meccanismo d'azione

Eparina standard (UFH) vs Eparina a basso peso molecolare (LMWH)

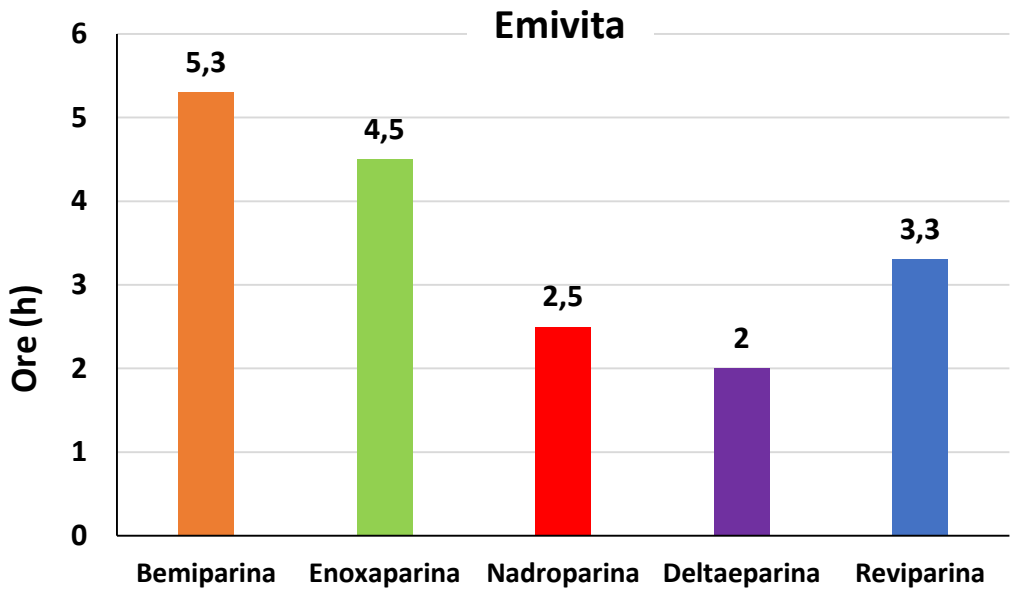


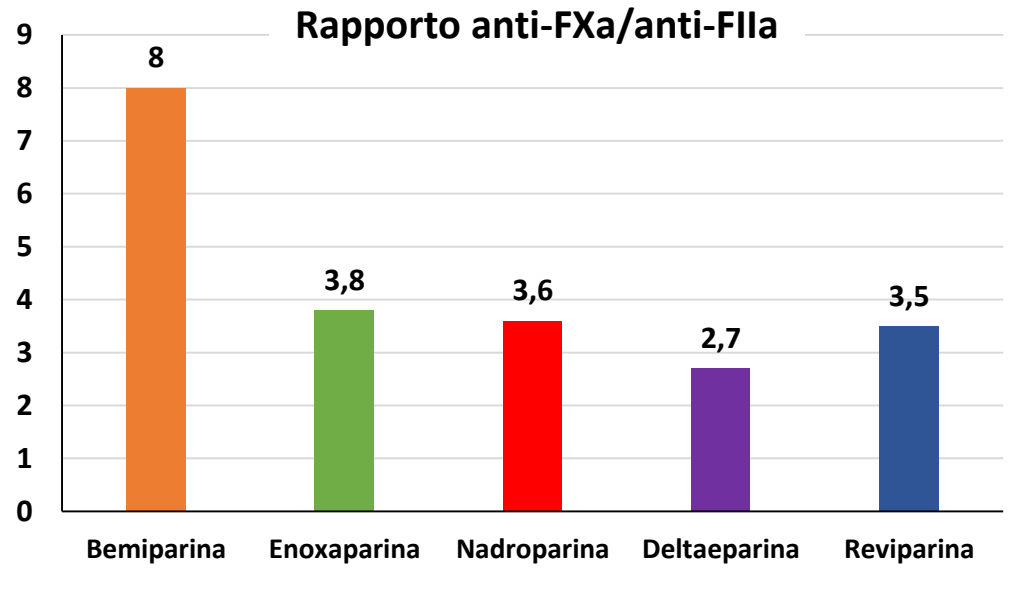


Hetzel GR, Sucker C. Nephrol Dial Transplant. 2005;20(10):2036-42

Hirsh J, Chest. 2008;133(6 Suppl):141S-159S

LMWH





Fernández Pavón A. Emergencias 2002; 14 (3): 38-47

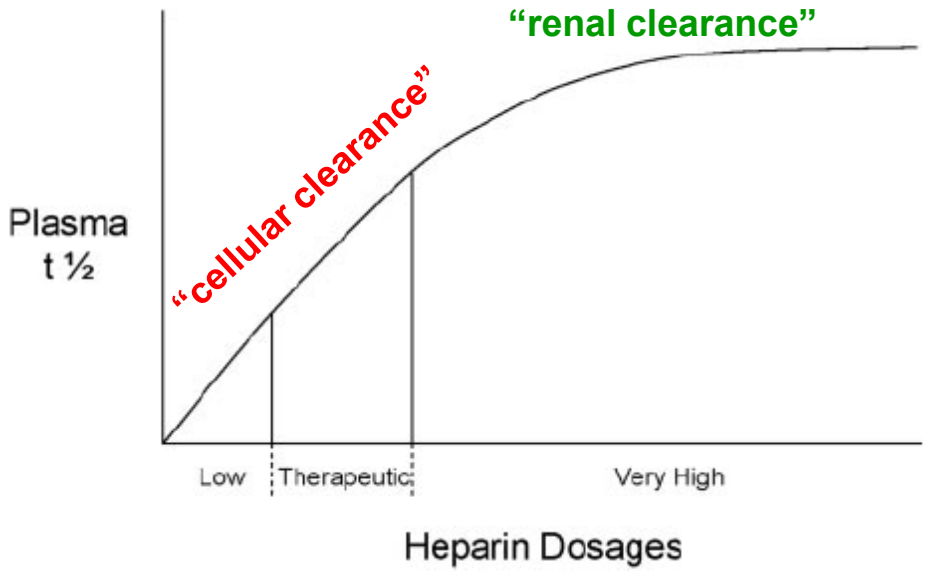
Davenport A et al. Nephrology 2009; 14: 455-461

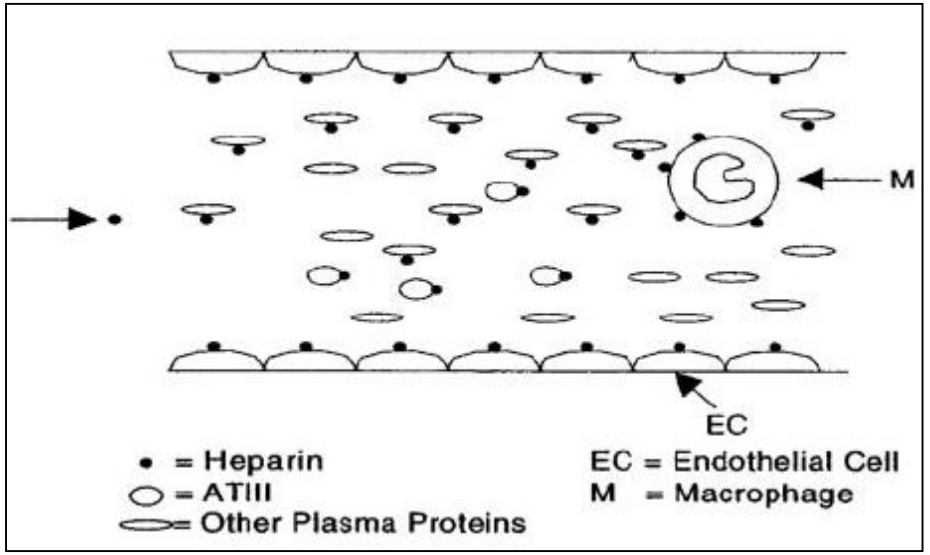
Le varie eparine a basso peso molecolare sono preparate in base a differenti metodi di depolimerizzazione, per cui differiscono nelle rispettive proprietà farmacocinetiche e anticoagulanti. Per questo motivo non sono interscambiabili clinicamente.

Hirsh J, Chest. 2008;133 (6 Suppl):141S-159S

Farmacocinetica (I): Clearance

1. **Basse dosi di UFH vengono metabolizzate rapidamente attraverso un meccanismo rapido cellulare saturabile**
2. **Alte dosi di eparina sono metabolizzate prevalentemente attraverso un meccanismo di clearance renale non saturabile**





Hirsh J, Chest. 2008;133(6 Suppl):141S-159S

Farmacocinetica (II)

Le eparine a basso peso molecolare, avendo una catena polisaccaridica di piccole dimensioni, interagiscono in misura ridotta con il sistema macrofagico e reticolo-endoteliale per cui la loro clearance è eminentemente renale

Anche le eparine standard, quando utilizzate a dosaggi elevati, saturando la "clearance cellulare", sono eliminate in maggior proporzione grazie alla "clearance renale" aumentando teoricamente il rischio di sovradosaggio nei pazienti con ridotta funzione renale

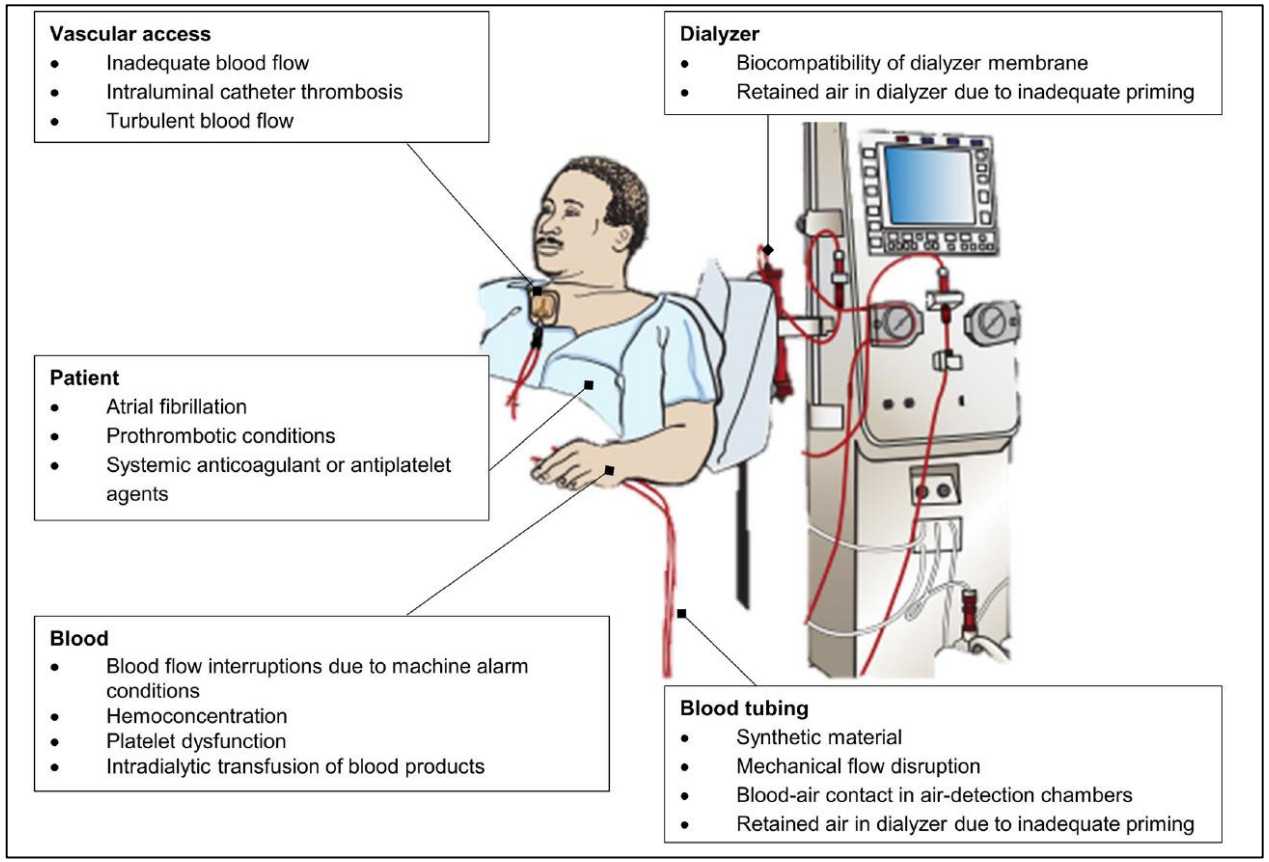
Hirsh J, Chest. 2008;133(6 Suppl):141S-159S

Variabili del Fabbisogno Eparinico

Circuito Extracorporeo

Paziente

Fabbisogno Eparina



Claudel SE et al. Semin Dial. 2021;34(2):103-115.

Anticoagulazione con Eparina non frazionata (UFH)

Standard

Loading Dose
(25-30 UI/kg)

↓

1500-2000 UI
(*infusione/bolo*)

Low-Dose

Loading Dose
(10-25 UI/kg)

↓

10-22 UI/kg
(*infusione/bolo*)

Ouseph R, Ward RA. Semin Dial 2000; 13:181

Anticoagulazione con Eparina non frazionata (UFH): Modifiche prescrizionali

Evento	Prescrizione
A. Coagulo nel pozzetto venoso e nella testata del filtro durante la prima metà della dialisi	• **AUMENTARE** il bolo di UFH con incrementi di 500 UI per trattamento, per un massimo di 4000 UI
B. Coagulo viene rilevato durante la seconda metà della dialisi	• **AUMENTARE** la velocità di infusione di UFH di 100 UI/h per ogni dialisi fino ad un massimo di 1000 UI/h
C. Coagulazione del filtro persiste nonostante un'appropriata titolazione dell'eparina	• **VALUTARE** l'accesso vascolare
D. Emorragia dai siti di puntura al termine della seduta dialitica	• **ALLUNGARE** il tempo di Pre-STOP dell'eparina con incrementi di 10 minuti fino a quando il tempo di emorragia si normalizza • **VALUTARE** l'accesso vascolare

Anticoagulation for the hemodialysis procedure

Target Clotting Time During Dialysis

			Routine Heparin		Tight Heparin	
Test	**Reagent**	**Baseline Value**	**During dialysis**	**Dialysis End**	**During dialysis**	**Dialysis End**
aPTT (ratio)		1.0	2.0-2.5	1.5-2.0	1.5-2.0	1.5-2.0
ACT (activated clotting time)	Siliceous earth	120-150 s	+80% (200-250s)	+40% (170-190s)	+40% (170-190s)	+40% (170-190s)

Davenport A, et al. Handbook of Dialysis
Eds: Daurgirdas J. et al, Fifth Edition. 2016

Anticoagulazione con Eparina a basso peso Molecolare (LMWH)

Enoxaparina

Peso (kg)	Enoxaparina (UI)
<50 kg	2000
50-90 Kg	4000
>90 Kg	6000

Nadroparina

Peso (kg)	Nadroparina (UI)
<50 kg	2000
50-90 Kg	4000
>90 Kg	6000

Deltaeparina

Peso (kg)	Deltaeparina (UI)
<60 kg	2500
>60 Kg	5000

LMWH	MWs (kDa)	Anti-Xa/ Anti-IIa	Dose for hemodialysis
Deltaeparin	6.0	2.7	5000 IU
Enoxaparin	4.2	3.8	1 mg/Kg
Nadroparin	4.5	3.6	70 IU/Kg
Reviparin	4.0	3.5	85 IU/Kg
Tinzaparin	4.0	1.9	4500 IU

Davenport A et al. Nephrology 2009; 14: 455-461

Comparison of the injection of low-molecular weight heparin in the arterial vs. venous blood line for preventing extracorporeal circuit clotting during hemodialysis

LMWH 40 mg (4000 IU)		OL-HDF (n=12)	MCO-HD (n=13)	HF-HD (=18)	p
Arterial line	Post dialysis AntiXa activity (IU/mL)	0.14 (0.1-0.35)	0.33 (0.1-0.6)	0.32 (0.15-0.49)	0.02
Venous line	Post dialysis AntiXa activity (IU/mL)	0.31 (0.20-0.55)	0.39 (0.21-1.3)	0.4 (0.32-0.67)	NS

LMWH 20 mg (2000 IU)		OL-HDF (n=12)	MCO-HD (n=13)	HF-HD (=18)	p
Arterial line	Post dialysis AntiXa activity (IU/mL)	0.1 (0.1-0.15)	0.1 (0.1-0.17)	0.1 (0.1-0.33)	NS
Venous line	Post dialysis AntiXa activity (IU/mL)	0.1 (0.1-0.14)	0.16 (0.14-0.24)	0.17 (0.1-0.47)	NS

LMWH 20 and 40 mg	Arterial line bolus	Venous line Bolus after 1 week	Venous line Bolus after 1 month	p
Ultrafiltration (L) (n=31)	2.7 (1.4-4)	2.6 (1.5-4)	2.5 (0.6-4)	NS
Substitution volume (L) (n= 12)	19.3 ± 4.5	22 ± 2.9	21 ± 3.5	NS
Compression time (min) (n = 12)	7 ± 4	9 ± 3	8 ± 2.9	NS

When LMWH were first introduced, anti-Xa activity targets were higher than 0.4–0.6 IU/mL,[12] although in current clinical practice lower targets are advisable, 0.2–0.4 IU/mL,[13] particularly in patients with increased risk for haemorrhage.

Davenport A et al. Nephrology 2009

Belmouaz M, et al. Hemodial Int. 2022;26(3):314-322.

LMWH e Protamina

	Enoxaparin	Tinzaparin
Average MWt (Da)	4200	4500
Clearance	Mostly renal some hepatic	Renal with additional endothelial
Half-life (h)	24	5
Dose	0.5–1.0 mg/kg	2500–4500 IU
Ratio Xa/IIa activity	3.8	1.9
Protamine reversal	0.5 mg per 1 mg <60% reversibility	1 mg per 100 anti-Xa IU 85% reversibility
Other options	rH-Factor VIIa	

Davenport A et al. Nephrology 2009

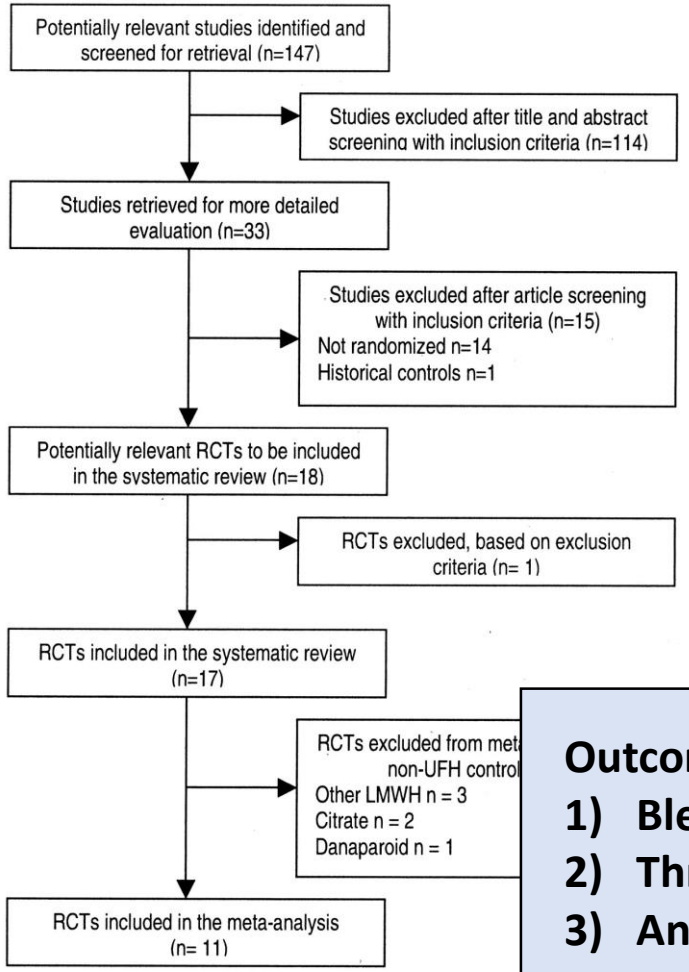
The following approach is recommended in clinical situations where the anticoagulant effect of LMWH needs to be neutralized. If LMWH was given within 8 h, protamine sulfate should be administered in a dose of 1mg per 100 anti-Xa units of LMWH (1 mg enoxaparin equals approximately 100 anti-Xa units). A second dose of 0.5 mg protamine sulfate per 100 anti-Xa units should be administered if bleeding continues. Smaller doses of protamine sulfate can be given if the time since LMWH administration is longer than 8 h.

Parenteral Anticoagulants*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

Safety and Efficacy of Low Molecular Weight Heparins for Hemodialysis in Patients with End-Stage Renal Failure: A Meta-analysis of Randomized Trials

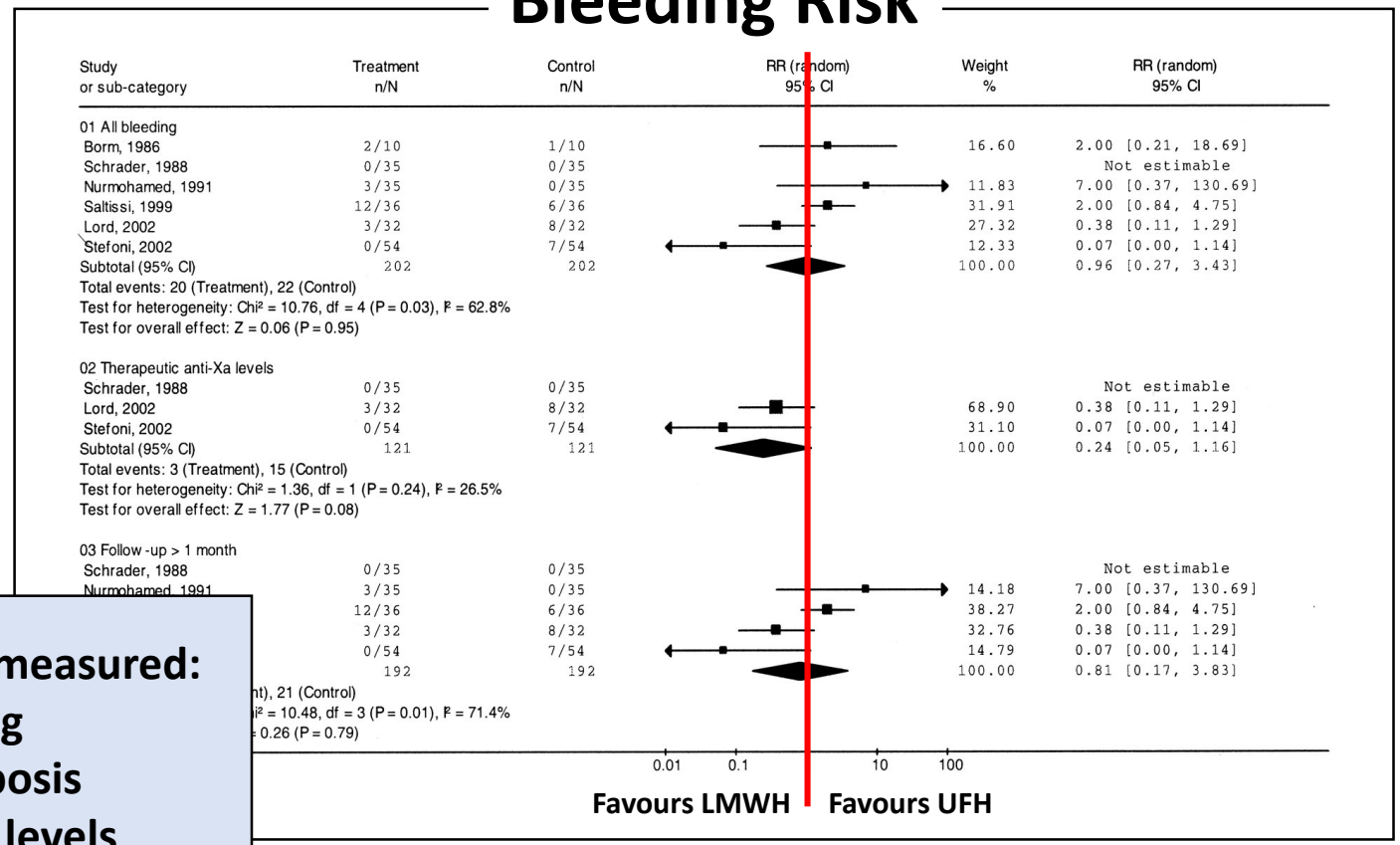
JASN



Outcomes measured:

1) **Bleeding**
2) **Thrombosis**
3) **Anti Xa levels**

Bleeding Risk



Lim W et al. J Am Soc Nephrol 2004: 3192-3206

Decreased Platelet Reactivity in Blood Anticoagulated with Bivalirudin or Enoxaparin Compared with Unfractionated Heparin: Implications for Coronary Intervention

- **Patients (n): 13 affected by coronary artery disease**
- **Platelet reactivity:**
  -Expression of P-selectin in response to adenosine diphosphate (ADP: 0.2 and 1 μM).

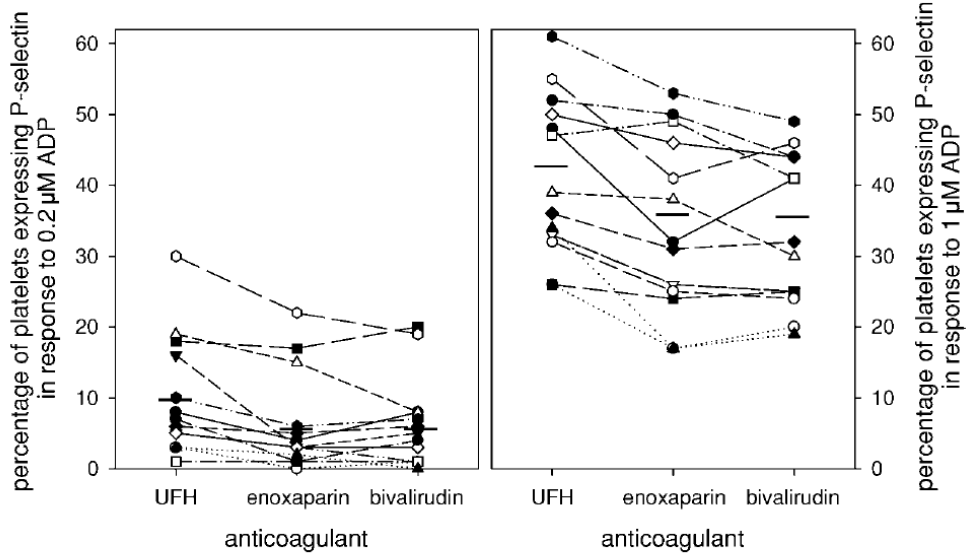


Fig. 1. *P-selectin expression in response to 0.2 µM ADP (left) and 1 µM ADP (right). Each group of three symbols connected by a line represents values obtained from each subject. The bar depicts the average percentage of platelets expressing P-selectin. Despite inter-individual variability, anticoagulation with enoxaparin and bivalirudin is associated with lower platelet reactivity than anticoagulation with UFH ($p \leq 0.01$ for either bivalirudin or enoxaparin compared with UFH). ADP = adenosine diphosphate, UFH=unfractionated heparin.*

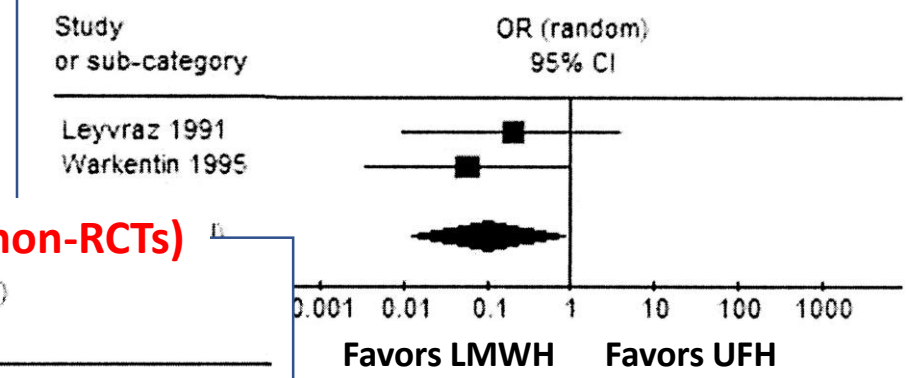
Aggarwal A, et al. J Thromb Thrombolysis. 2002;13(3):161-5.

Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis

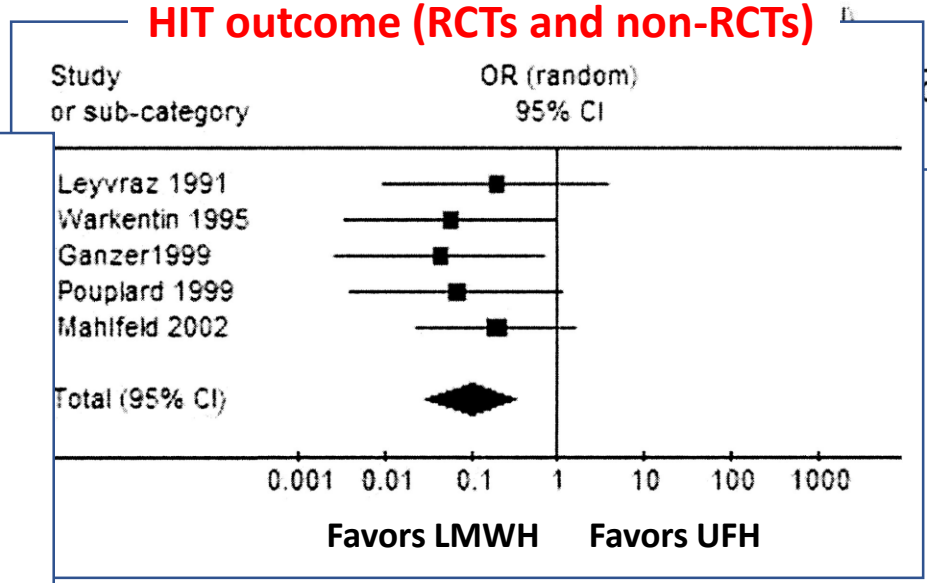
Reports included (n) = 15

- 2 RCTs measuring HIT, patients (n) = 1014
- 3 Non-RCTs measuring HIT, patients (n) = 1464
- 10 RCTs measuring thrombocytopenia but not HIT, patients (n) = 4809

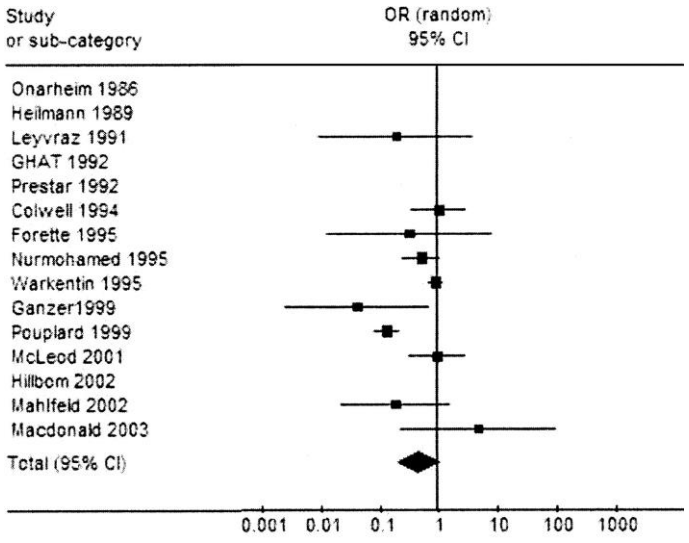
HIT outcome (RCTs)



HIT outcome (RCTs and non-RCTs)



Thombocytopenia



Martel N, et al. Blood. 2005;106(8):2710-5.

Anticoagulazione in Emodialisi

Guideline V.2.1:

Low-dose of UFH or LMWH

1. **UFH: loading dose ~ 50 IU/Kg followed by a continuous infusion 800-1500 IU/h.**
2. **LMWH: see I.F.U.; reduced dose if antiplatelets or antivitamin K**

Guideline V.2.2:

LMWHs over UFH due to Proven safety

1. **Equal efficacy**
2. **Easy handling**
3. **Other benefits of LMWHs:**
   a) **Improved lipid profile**
   b) **Less hyperkalaemia**
   c) **Less blood loss**

Guideline 7.1: UFH or LMWH

UFH = standard AC

a) **loading dose (unspecified) followed by a continuous infusion of 500-1500 IU/h**
b) **discontinued ~ 30 minutes before the end of the session**

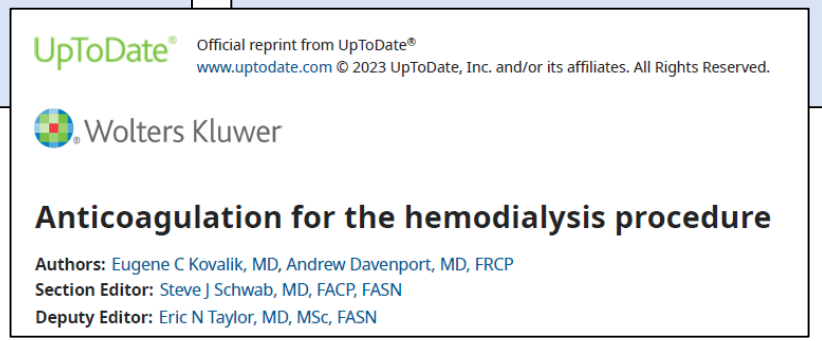
LMWH = alternative AC

a) **lower risk of bleeding**
b) **less frequent hyperkalaemia**
c) **improved lipid profile**

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

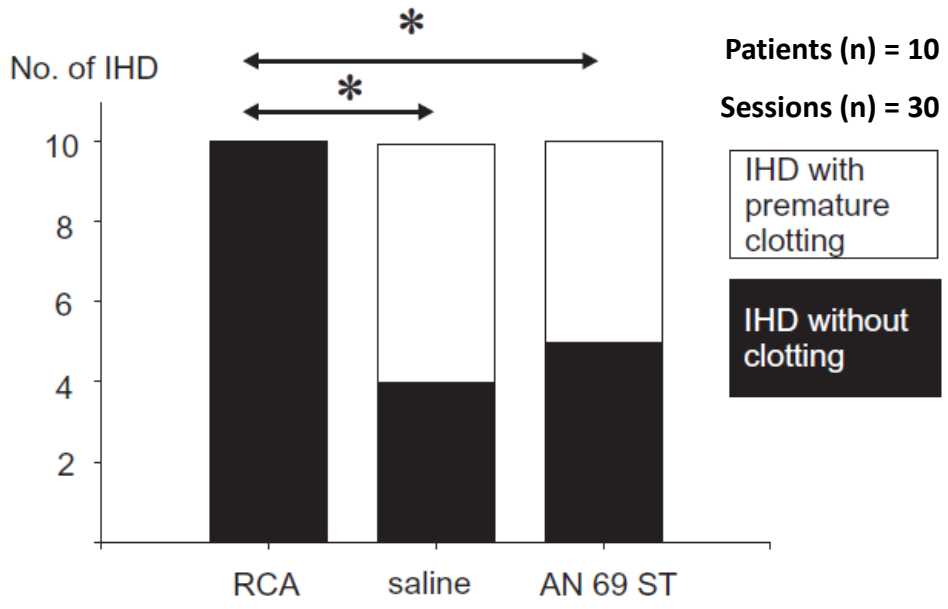


FIG. 1. Successful completion of hemodialysis procedures. *$P < 0.05$.

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.

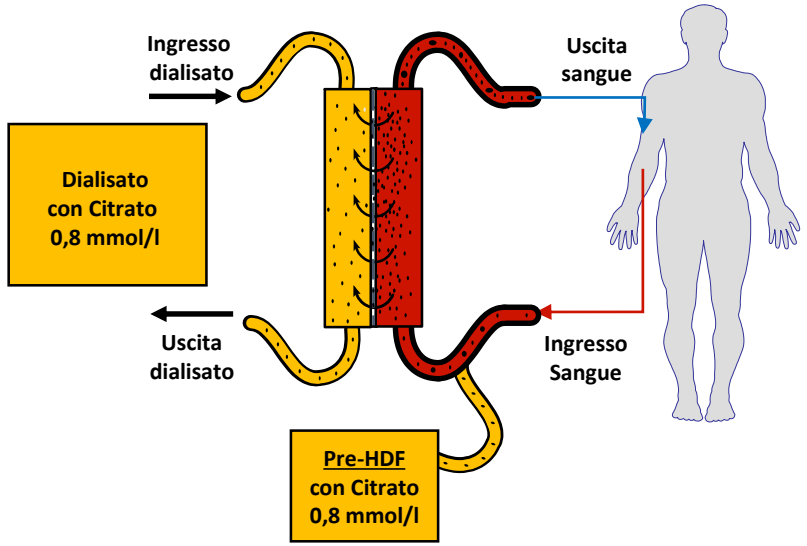
Pre-HDF con Citrato e Anticoagulazione

Artificial Organs

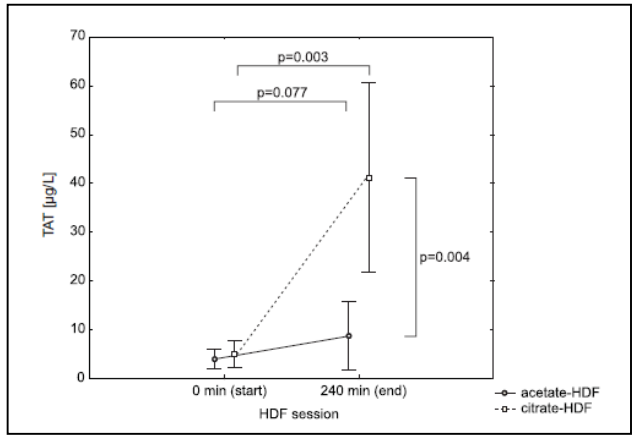
TABLE 1. *Compositions of acetate- (SW127/286) and citrate-based (Citrasate) dialysis solutions*

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]

[a]Fresenius Medical Care North America, Celebration, Fla., [b]Renal Research Institute, and
[c]Beth Israel Medical Center, New York, N.Y., [d]University of Michigan Health System, Ann Arbor, Mich., and
[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

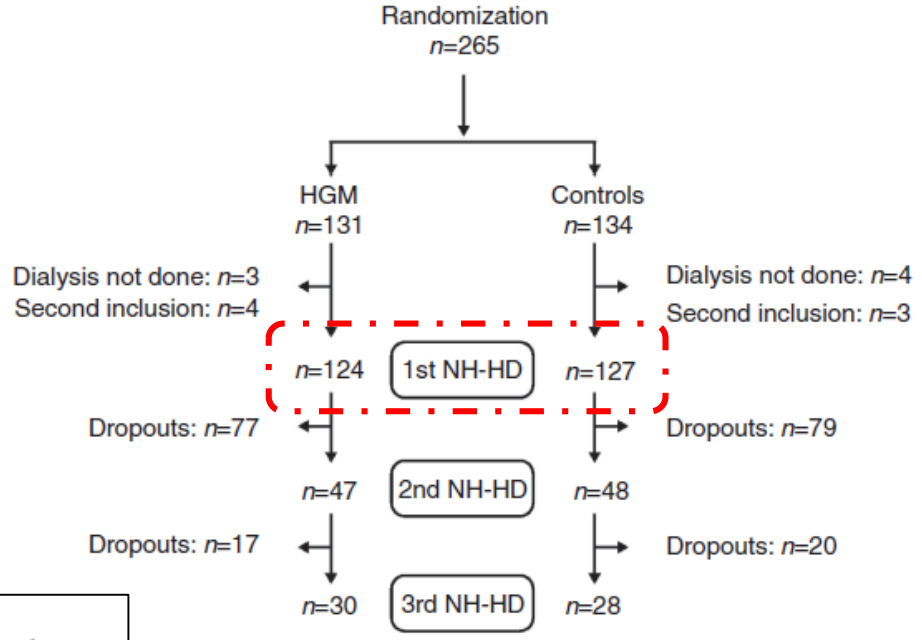
Artificial Organs 2017, 41(8):759–766

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]



1st No-Heparin Hemodialysis

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

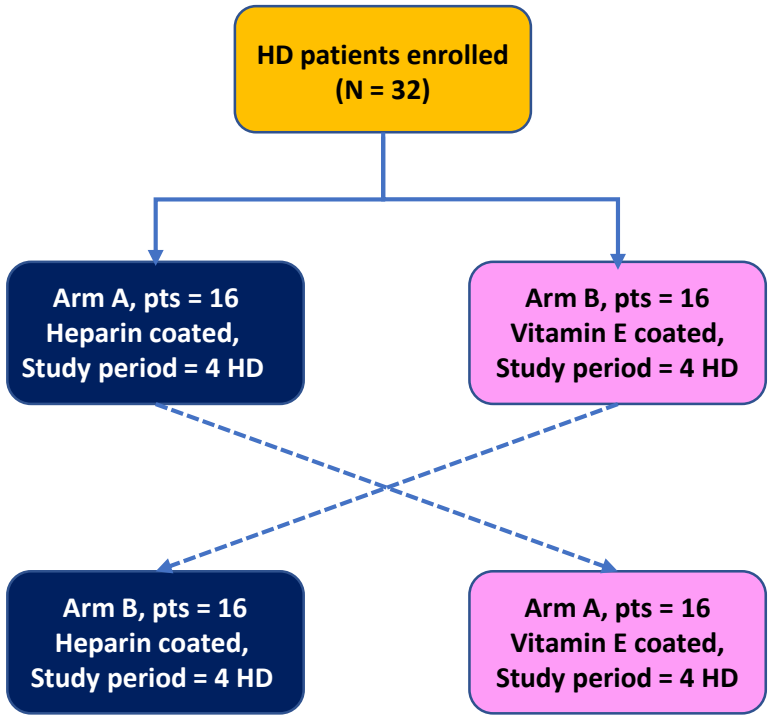
Usual practice	Treatment	Success	Success rate (95% CI)	*P*-value
Predilution	Evodial	36/63	57.1 (44.1–67.9)	
	Controls	26/65	40.0 (28.3–51.4)	0.078
	Difference E-C[a]		17.1 (2.6–30.7)	
Saline flushes	Evodial	49/61	80.3 (67.8–87.7)	
	Controls	38/62	61.3 (48.0–71.7)	0.034
	Difference E-C[a]		19.0 (5.4–32.0)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

AJKD
Original Investigation

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

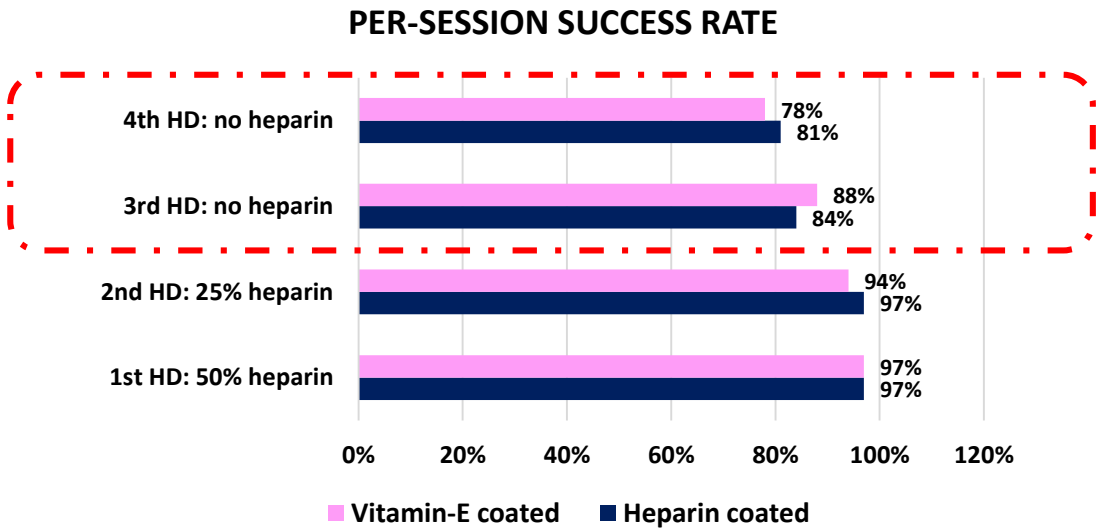
Mohamed Shariful Islam, MBBS,[1] Zarih Alcheikh Hassan, MD,[2] Florence Chalmin, MD,[1] Sandor Vido, MD,[1] Mohamed Berrada, MD,[1] David Verhelst, MD,[2] Patrick Donnadieu, MD,[2] Olivier Moranne, MD, PhD,[1] and Vincent L.M. Esnault, MD, PhD[1,3]



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
Nº of successful study period	25/32 (78%)	26/32 (81%)
Nº of sessions without clotting	114/128 (89%)	115/128 (90%)
Nº 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

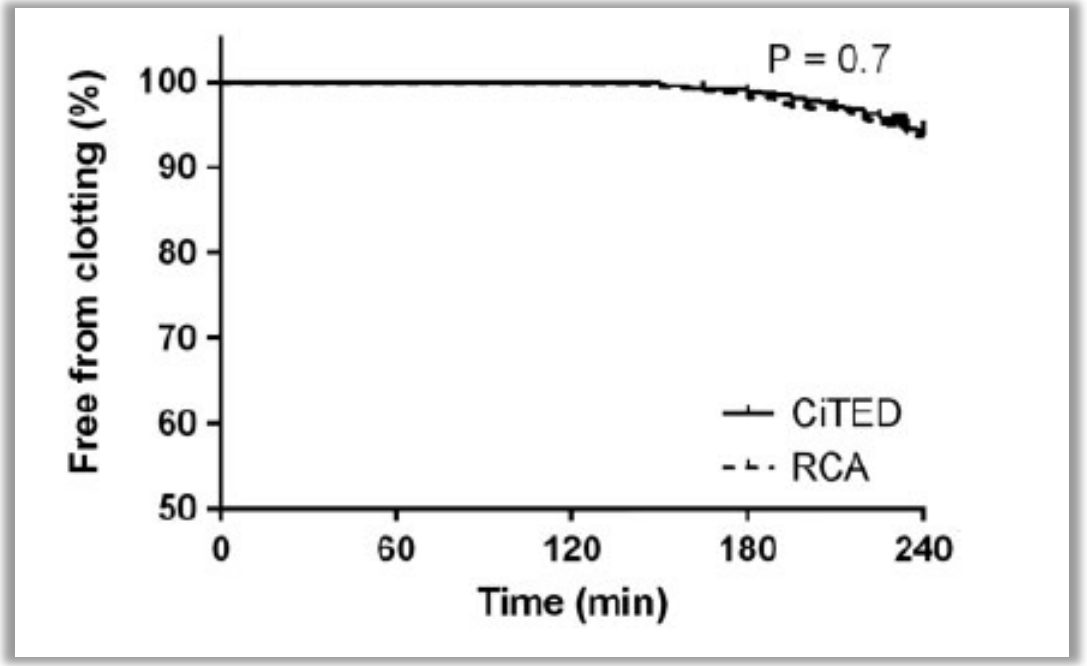
The combination of heparin grafted membrane and citrate containing dialysate

versus

Regional citrate anticoagulation

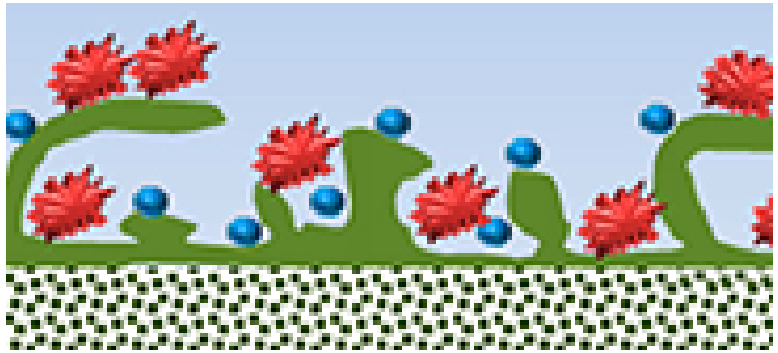
Citrate-containing dialysate was produced using Selectbag® Citrate 1/200 A concentrate (Gambro Dasco, Sondalo, Italy). We used the **E**vo**d**ial 1.6 (Gambro Industries) with an effective membrane surface area of 1.65 m². This device is a precoated heparin-grafted membrane.

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

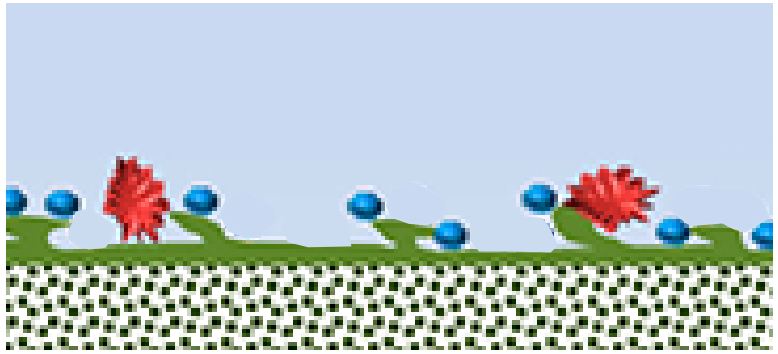


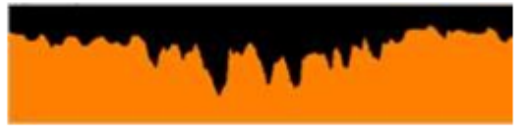
Fouling e Rugosità delle Membrane per Emodialisi

Superficie rugosa



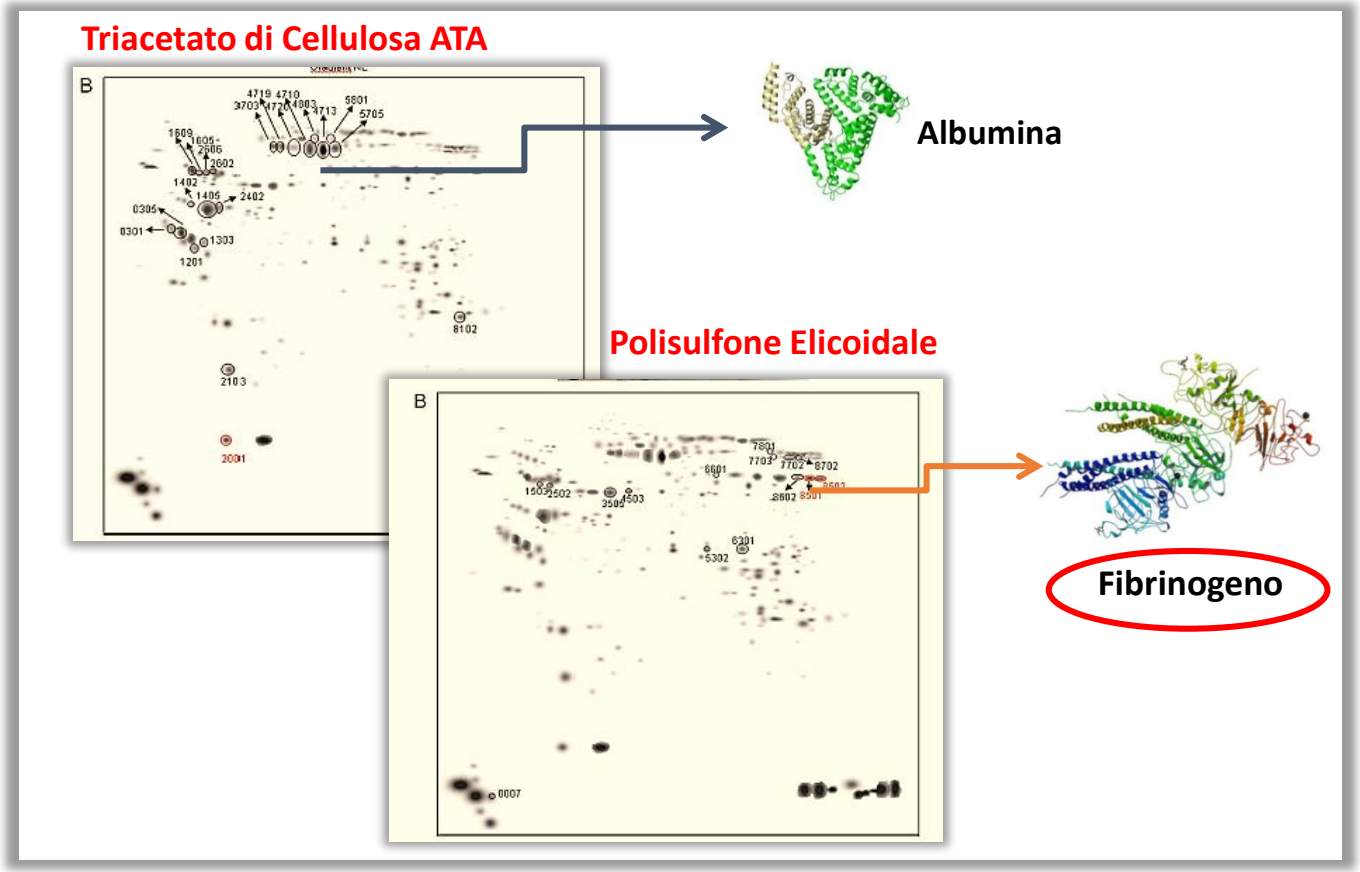
Superficie liscia



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

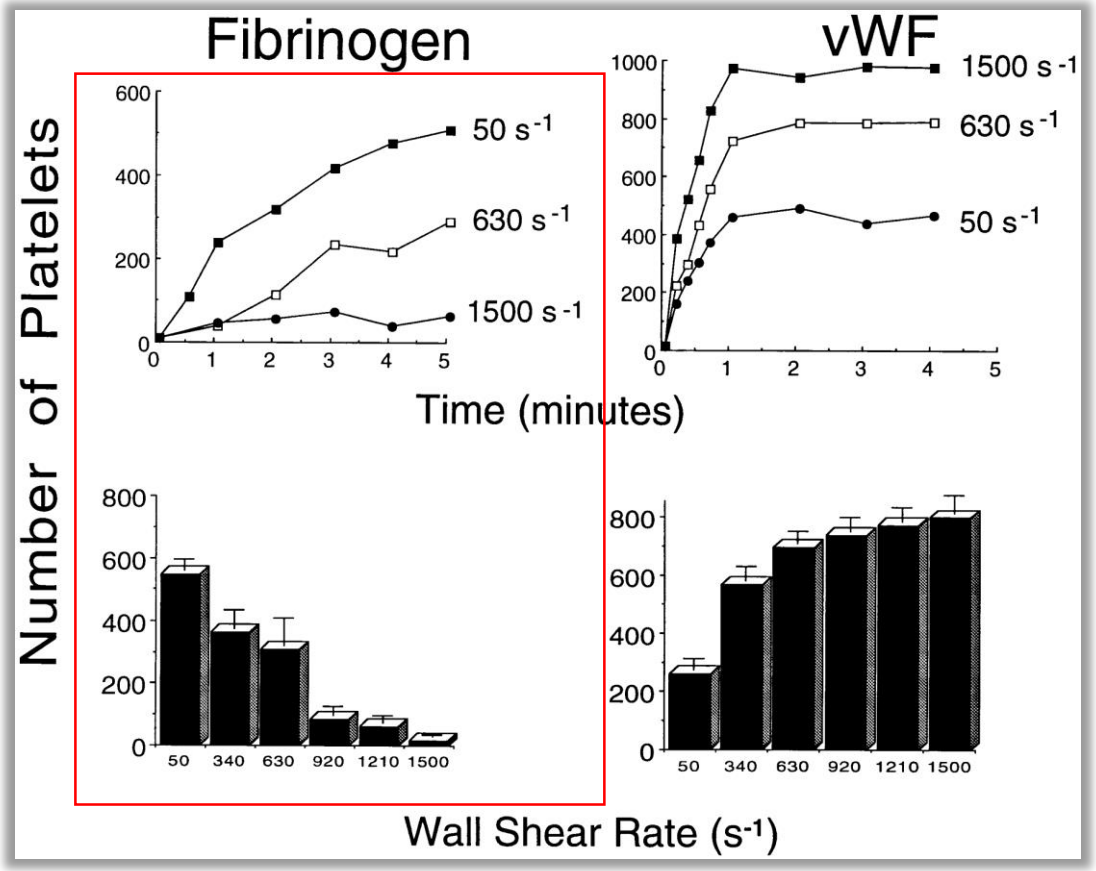
Sunohara T & Masuda T. Contrib Nephrol. 2017; 189: 215–221

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

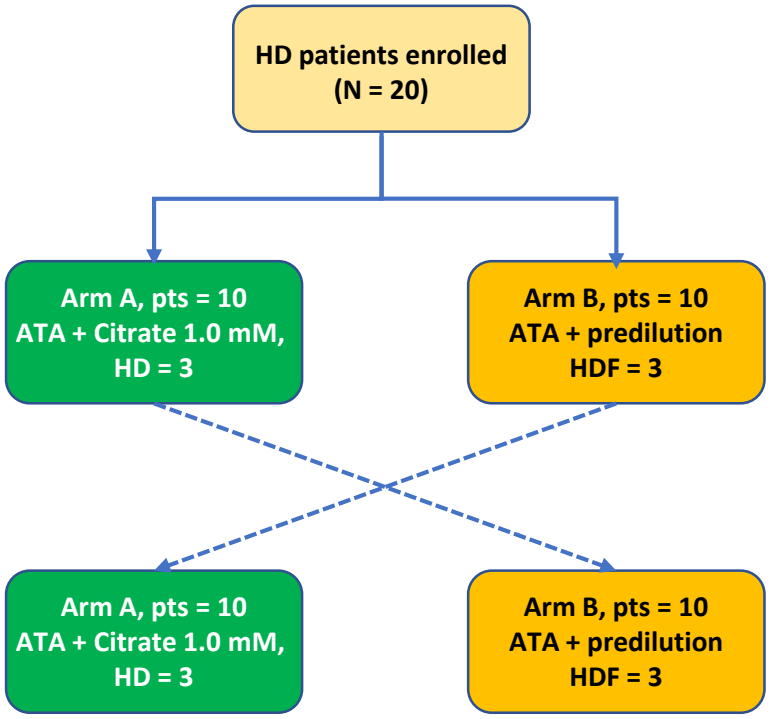
Clinical Kidney Journal, 2021, vol. 14, no. 8, 1901–1907

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]



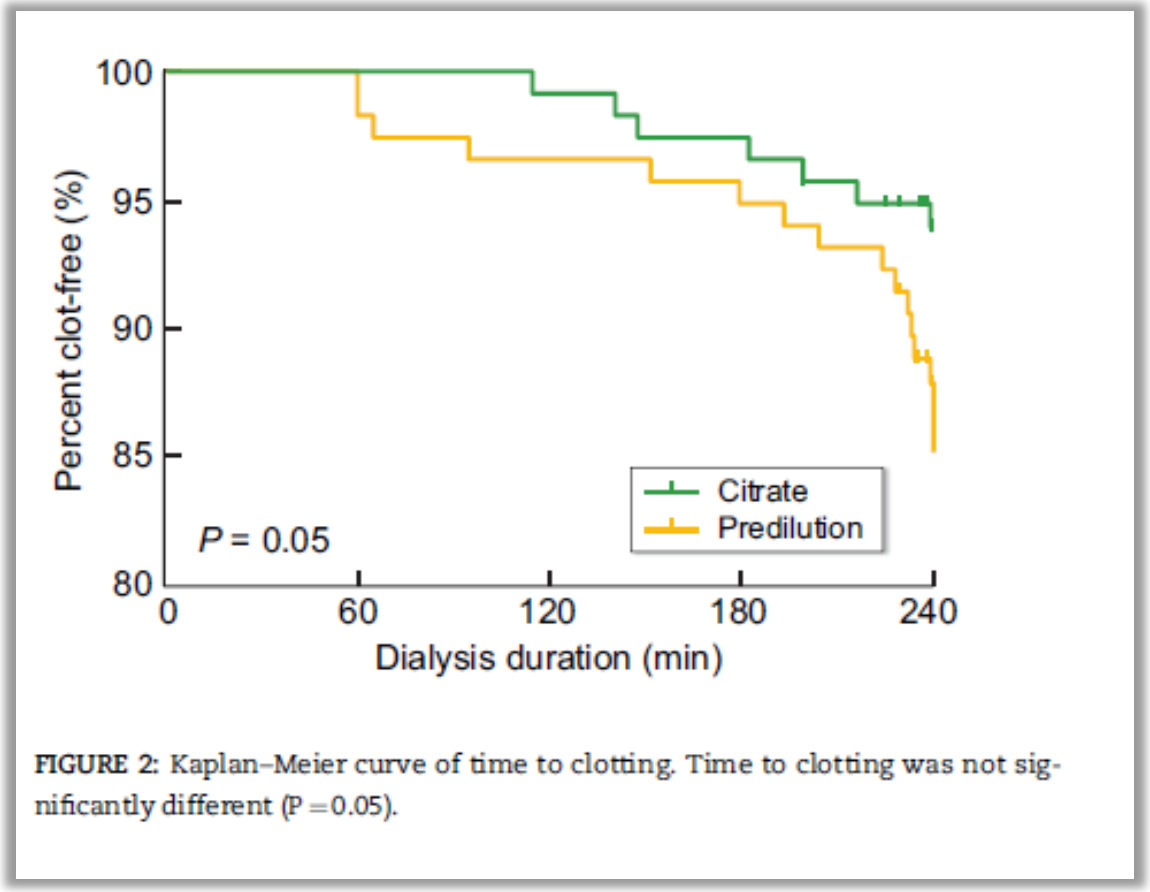


FIGURE 2: Kaplan–Meier curve of time to clotting. Time to clotting was not significantly different (P = 0.05).

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

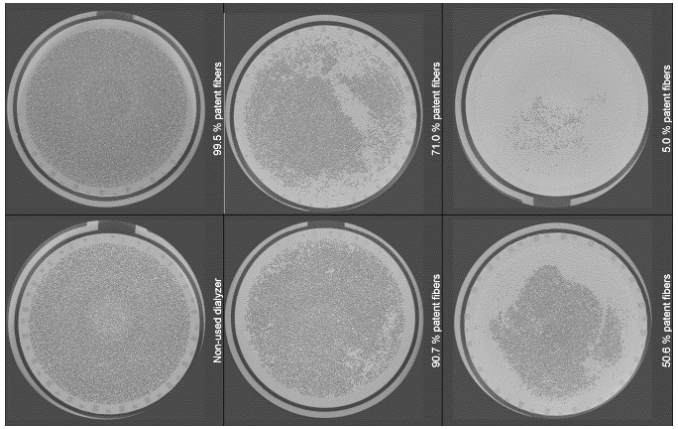
- HD patients (n)= 10
- Study: Randomized cross over
- Dialyzers: ATA vs. Helixone
- Dialysis at mid week
- Anticoagulation: ¼ dose LMWH

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. **UFH e LMWH sono sovrapponibili come efficacia nell'anticoagulazione del circuito extracorporeo**

2. **Il rischio di attivazione piastrinica e di HIT è maggiore con l'eparina non frazionata**

3. **La dialisi senza eparina è un'opzione indispensabile in qualsiasi contesto clinico «acuto»**

4. **La dialisi senza eparina più efficiente sembra la combinazione di membrane speciali con un dialisato a basso contenuto di citrato**

Diapositive di Back up

Pz con fistola artero-venosa (FAV)

- Eparina non frazionata (UFH):
  diluizione → 2 ml (10.000 U) di eparina in 28 ml di soluzione fisiologica → concentrazione finale: 333 U/ml

  - Bolo: 10-15 U/Kg
  - Infusione: 15-20 U/Kg/h per tutta la durata della seduta dialitica

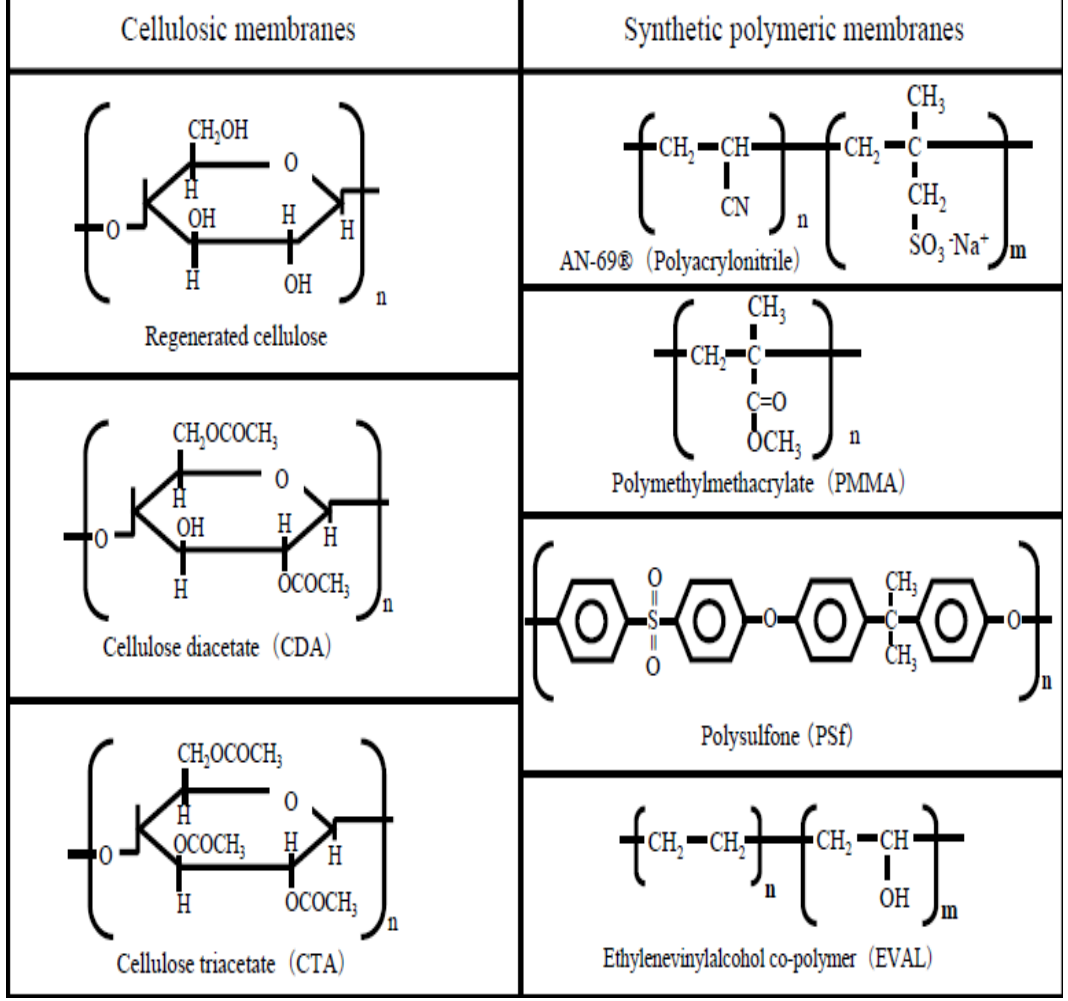
+

ACT periodico alla 2° ora di HD (range 160-180)

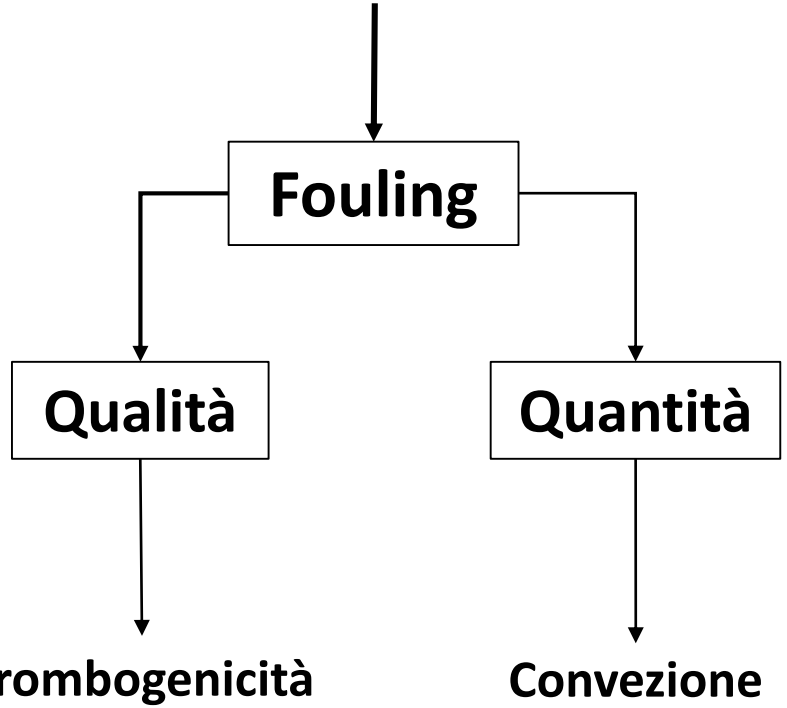
Pz con catetere venoso centrale (CVC)

- Eparina a basso peso molecolare (LMWH):

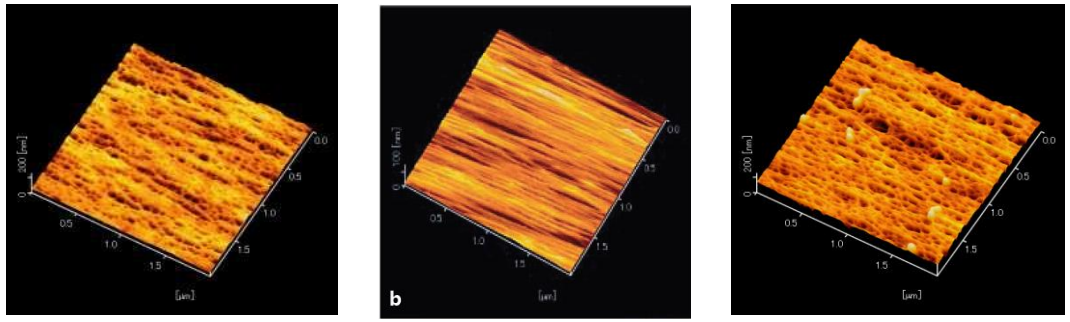
Peso (kg)	Enoxaparina (UI)
<50 kg	2000
50-80 Kg	4000
>80 Kg	6000



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

Categorie di Rischio per Emorragia

Rischio Medio

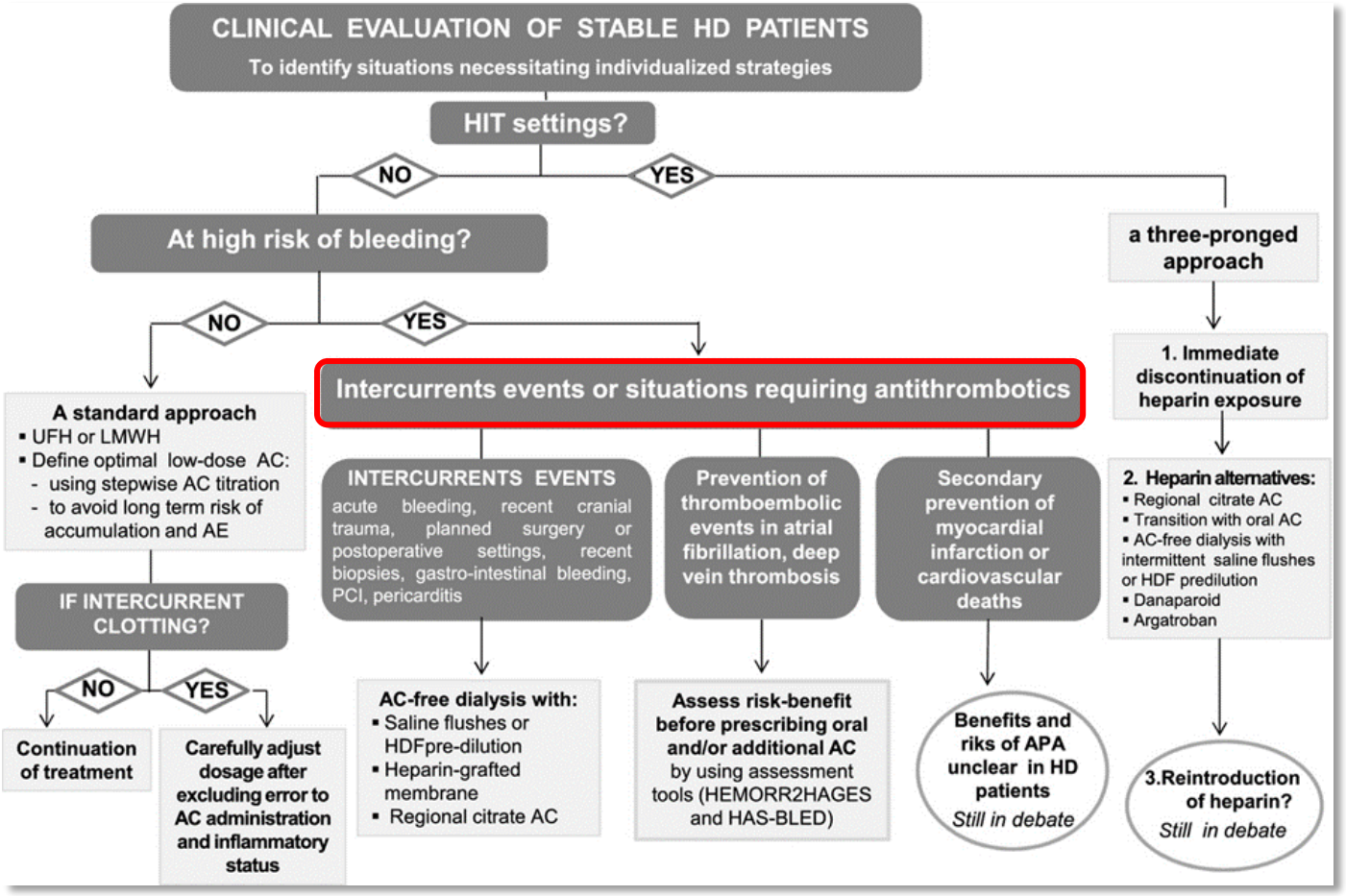
- **Pericardite**
- **Emorragia < 48 h**
- **Posizionamento CVC tunnellizzato < 24 h**
- **Chirurgia minore < 72 h**
- **Chirurgia maggiore o oculistica 3-7 gg**

Rischio Alto

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

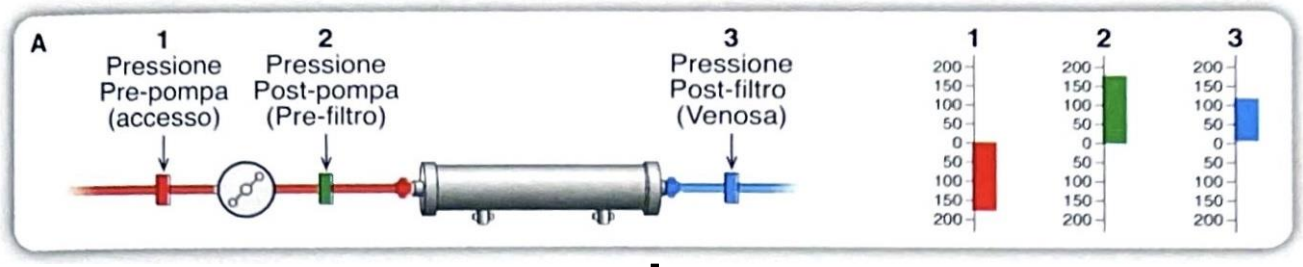
Nissenson AR & Fine RN, *Handbook of Dialysis Therapy, 4th edition, 2008*

Anticoagulation in Chronic Hemodialysis: Progress Toward an Optimal Approach



Kessler et al. Seminars in Dialysis, Volume: 28, Issue: 5, Pages: 474-489, First published: 25 April 2015, DOI: (10.1111/sdi.12380)

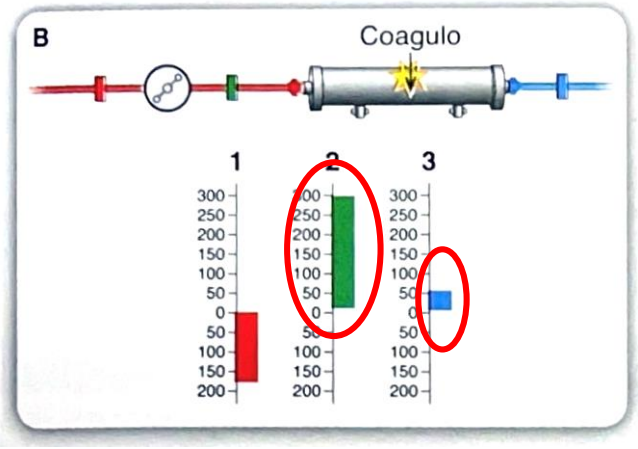
Differenza fra Pressione Pre-filtro (post-pompa) e Post-filtro (venosa)



⬆ **Pressione Differenziale**

↓

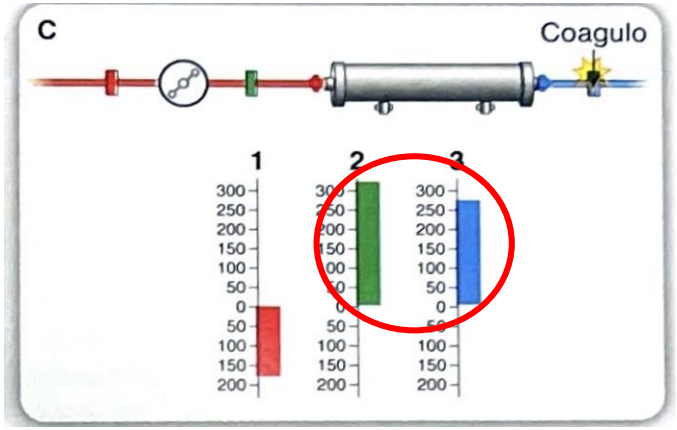
Coagulo nel Filtro



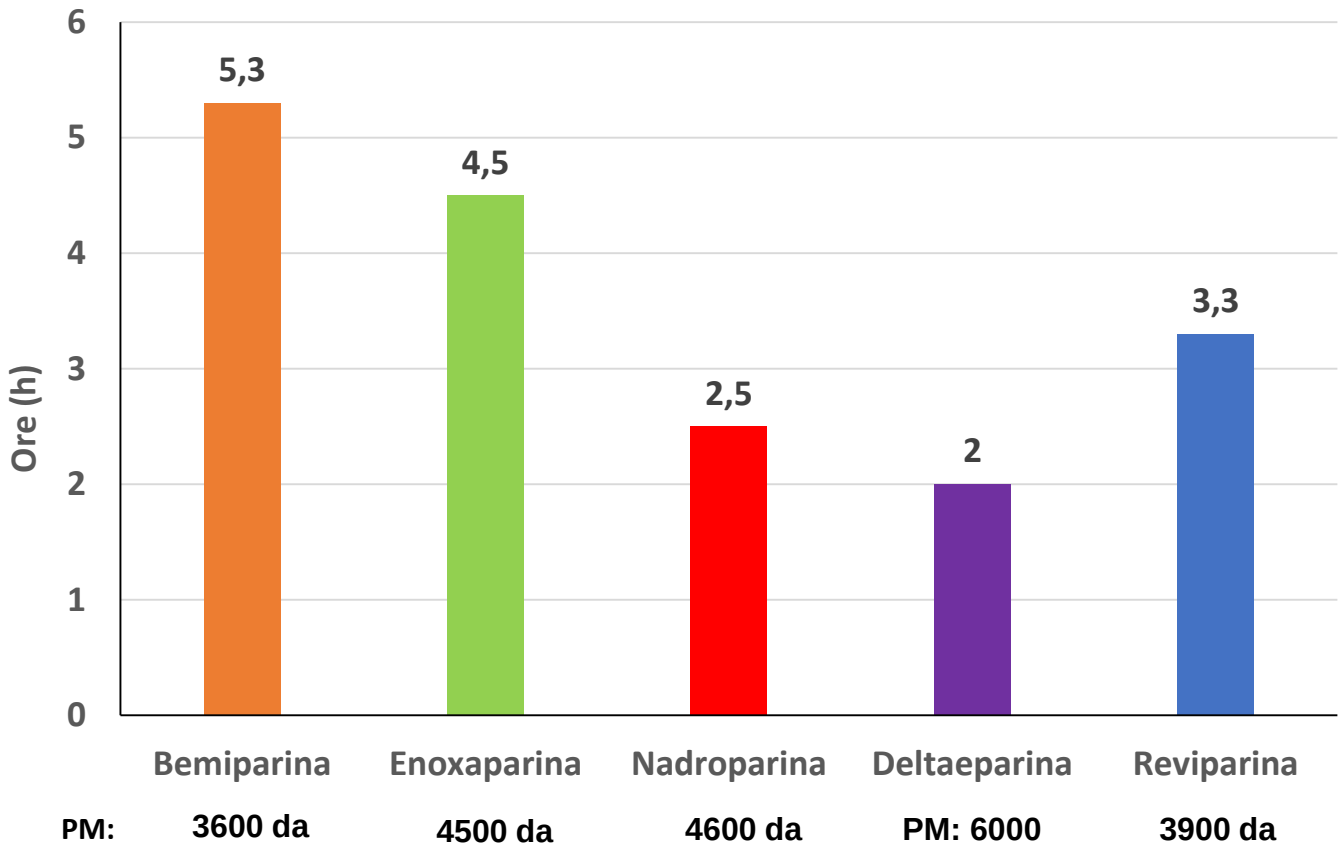
⬆ **Pressioni Consensuale**

↓

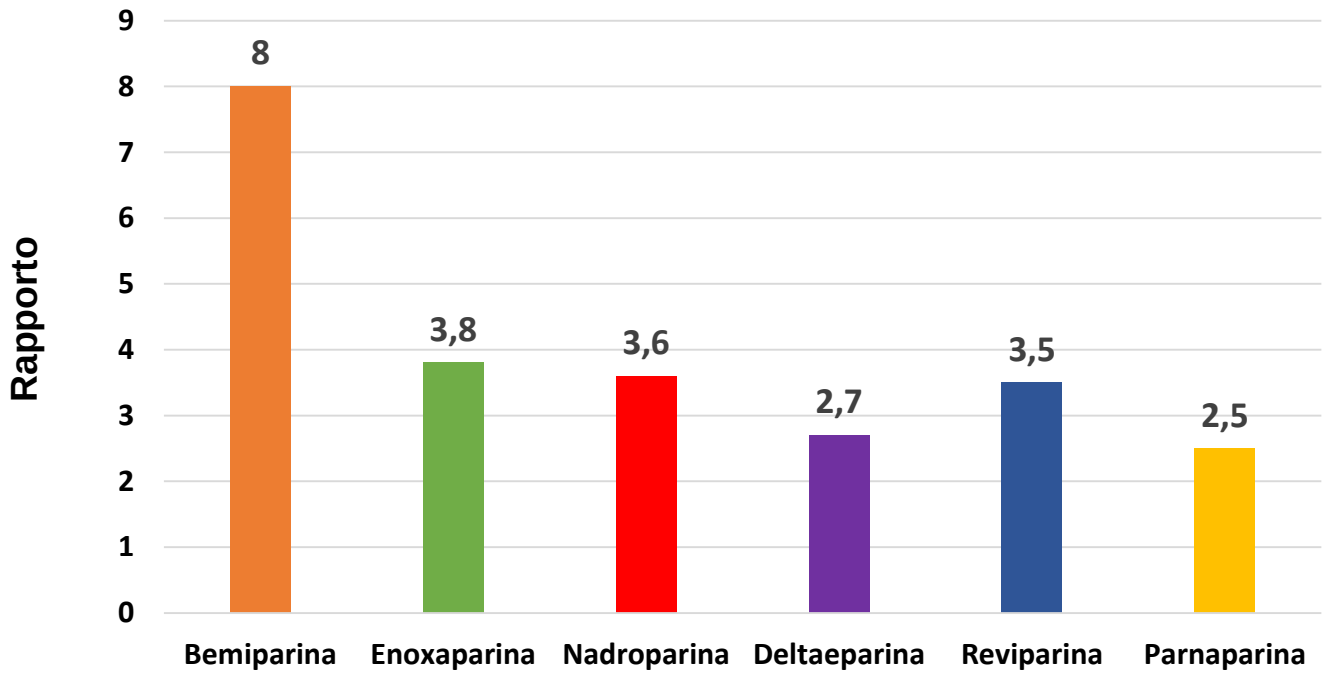
Coagulo nel Pozzetto venoso e/o linea



Distribuzione delle LMWHs in base all'Emivita



LMWH: Rapporto anti-FXa/anti-FIIa

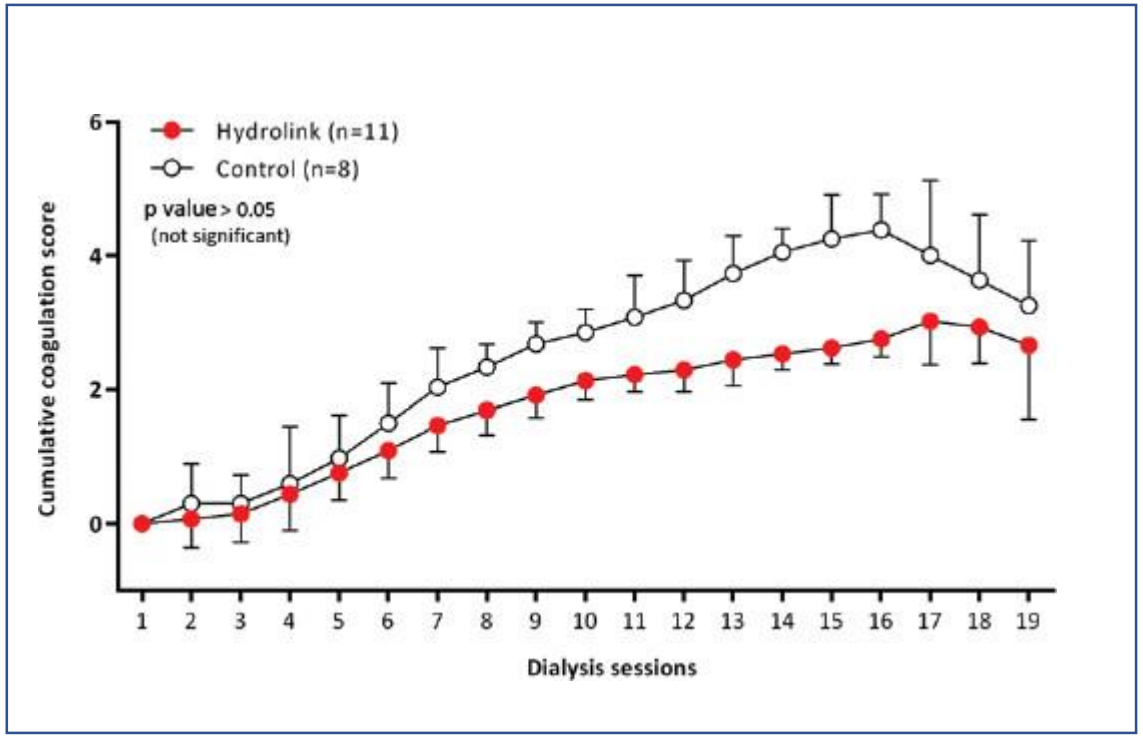


Speight - Fernández Pavón A. Emergencias 2002

Le varie eparine a basso peso molecolare sono preparate in base a differenti metodi di depolimerizzazione, per cui differiscono nelle rispettive proprietà farmacocinetiche e anticoagulanti. Per questo motivo non sono interscambiabili clinicamente.

Hirsh J, Chest. 2008;133(6 Suppl):141S-159S

Prospective, randomized, multicenter, controlled trial (TRIATHRON 1) on a new antithrombogenic dialysis membrane



CLOTTING SCORES:
1 = clean filter;
2 =a few blood stripes (less than 5% of the fibers at the surface of dialyzer);
3 = many blood stripes (more than 5% of the fibers at the surface of dialyzer);
4 = coagulated filter.

CLOTTING SCORE ADJUSTED FOR HEPARIN DOSAGE:
∑((*clotting score-clotting score at baseline*)heparin percentage*).**

Heparin dosage	Hydrolink	Control
100 %	Weeks 1-3	Weeks 1-3
80 %	Week 4	Week 4
60 %	Week 5	Week 5
40 %	Week 6	Week 6
20 %	Week 7	Week 7
0%	Week 8	Week 8

Ronco C, et al. Int J Artif Organs. 2017;40(5):234-239

Comparison of the injection of low-molecular weight heparin in the arterial vs. venous blood line for preventing extracorporeal circuit clotting during hemodialysis

When LMWH were first introduced, anti-Xa activity targets were higher than 0.4–0.6 IU/mL,[12] although in current clinical practice lower targets are advisable, 0.2–0.4 IU/mL,[13] particularly in patients with increased risk for haemorrhage.

Davenport A et al. Nephrology 2009

LMWH 40 mg (4000 IU)		OL-HDF (n=12)	MCO-HD (n=13)	HF-HD (=18)	p
Arterial line	Post dialysis AntiXa activity (IU/mL)	0.14 (0.1-0.35)	0.33 (0.1-0.6)	0.32 (0.15-0.49)	0.02
Venous line	Post dialysis AntiXa activity (IU/mL)	0.31 (0.20-0.55)	0.39 (0.21-1.3)	0.4 (0.32-0.67)	NS

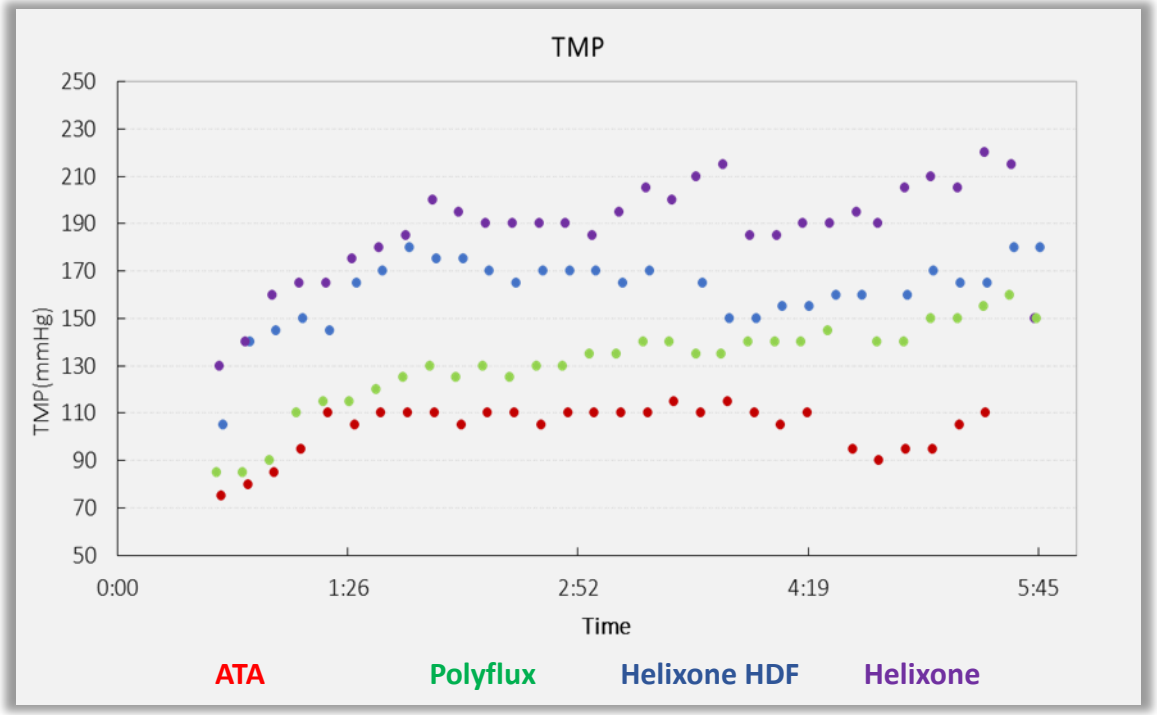
LMWH 20 mg (2000 IU)		OL-HDF (n=12)	MCO-HD (n=13)	HF-HD (=18)	p
Arterial line	Post dialysis AntiXa activity (IU/mL)	0.1 (0.1-0.15)	0.1 (0.1-0.17)	0.1 (0.1-0.33)	NS
Venous line	Post dialysis AntiXa activity (IU/mL)	0.1 (0.1-0.14)	0.16 (0.14-0.24)	0.17 (0.1-0.47)	NS

LMWH 20 and 40 mg	Arterial line bolus	Venous line Bolus after 1 week	Venous line Bolus after 1 month	p
Ultrafiltration (L) (n=31)	2.7 (1.4-4)	2.6 (1.5-4)	2.5 (0.6-4)	NS
Substitution volume (L) (n= 12)	19.3 ± 4.5	22 ± 2.9	21 ± 3.5	NS
Manual compression time (min) (n = 12)	7 ± 4	9 ± 3	8 ± 2.9	NS

Coagulation tests 1 week before and after change of administration site		Arterial line bolus	Venous line bolus	p
LMWH 40 mg (4000 IU)	Pre dialysis AntiXa activity (IU/mL)	0.1 (0.1-0.1)	0.1 (0.1-0.1)	NS
	Post dialysis AntiXa activity (IU/mL)	0.29 (0.1-0.6)	0.38 (0.2-1.3)	0.005
LMWH 20 mg (2000 IU)	Pre dialysis AntiXa activity (IU/mL)	0.1(0.1-0.1)	0.1(0.1-0.1)	NS
	Post dialysis AntiXa activity (IU/mL)	0.11(0.1-0.33)	0.16(0.1-0.47)	0.03

Belmouaz M, et al. Hemodial Int. 2022;26(3):314-322.

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**

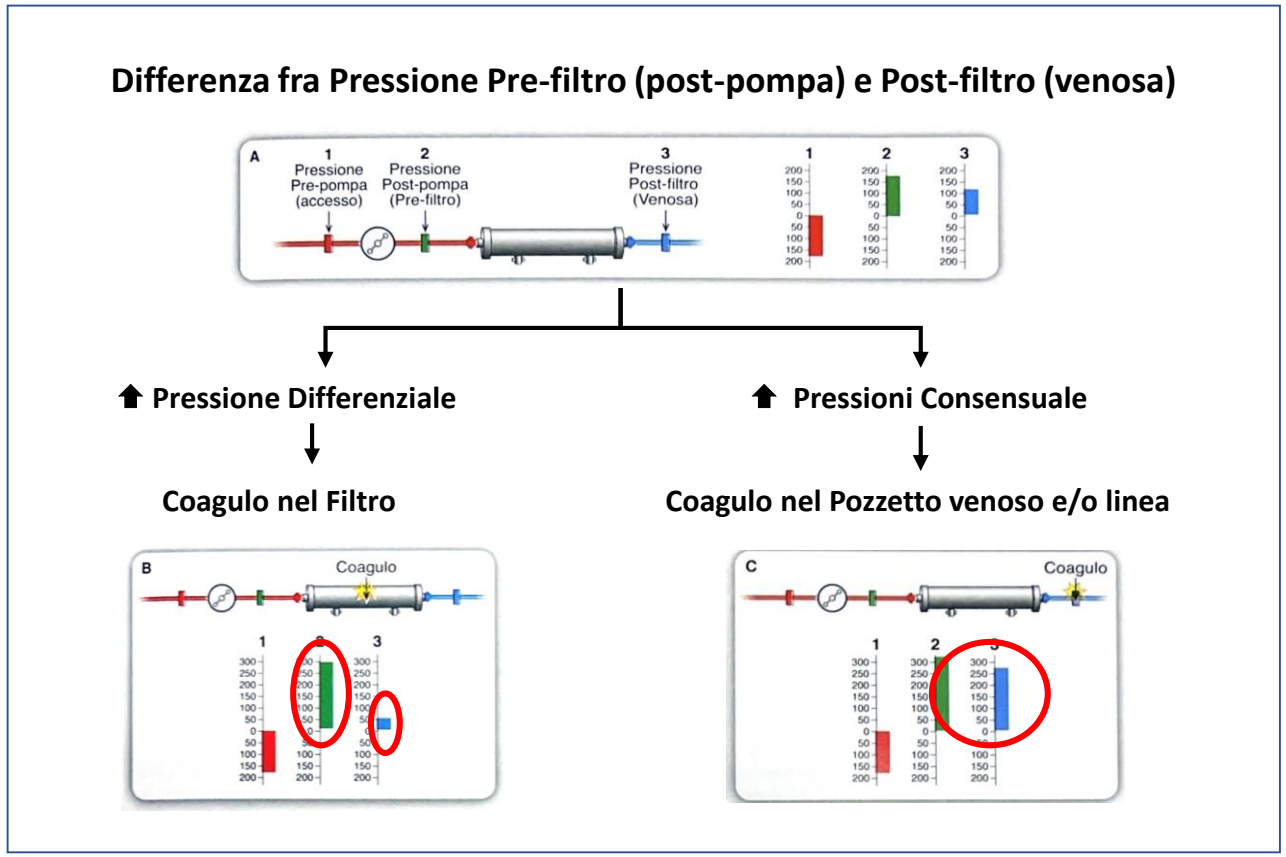
BioArtProducts, Rostock, Germany, 2015

L’Anticoagulante Ideale per la Circolazione extracorporea

- **A Basso costo**
- **Efficiente**
- **Rapidità d’azione ed emivita ridotta**
- **Facilmente somministrabile e monitorabile**
- **Disponibilità di un antagonista**
- **Minimi effetti collaterali**

Monitoraggio dell'efficacia del trattamento: l'Ispezione visiva

- Presenza di coaguli nelle testate del dializzatore
- Fibre o fasci di fibre coagulati
- Coaguli nel pozzetto e nella linea venosa
- Riempimento rapido di sangue dei tubi di trasduzione
- Sangue refluo nella linea di infusione di eparina



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

Tecniche di Anticoagulazione in Dialisi

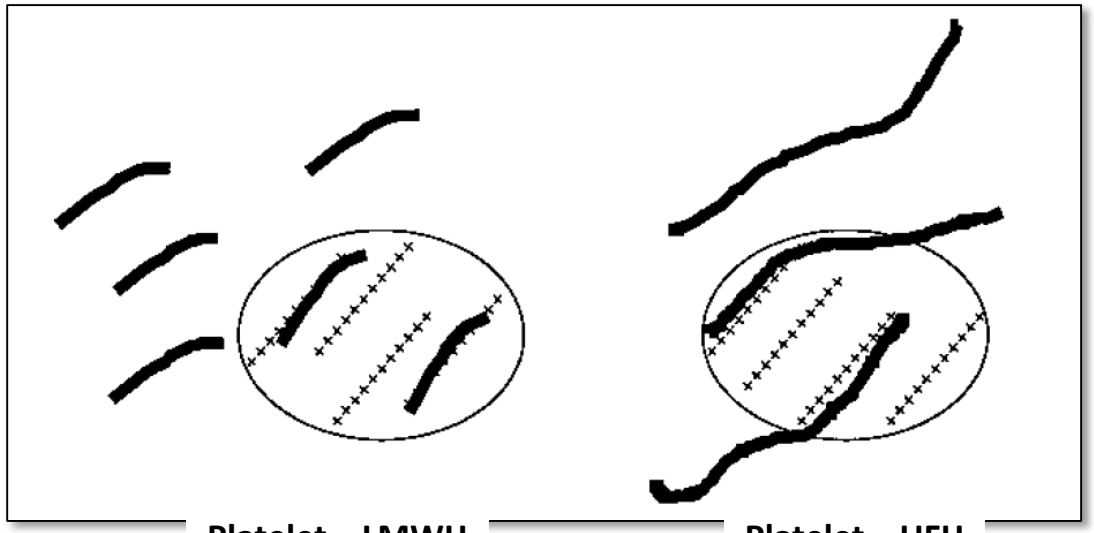
UFH	LMWH
• Boli ripetuti • Infusione continua • Combinazione • Laboratorio: aPTT / ACT • Antidoto: Protamina	• Bolo singolo • No monitoraggio • Emivita maggiore • Laboratorio: anti Xa • Antidoto: Protamina

Hirsh J, Chest 2008
Lim W. JASN 2004

Hetzel GR, Sucker C. NDT 2005
Singer M. Intensive Care Med 1994

Nonimmune Heparin–Platelet Interactions: Implications for the Pathogenesis of Heparin-Induced Thrombocytopenia

McDonald K. Horne III
Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland, U.S.A.



Platelet – LMWH interaction

Platelet – UFH interaction

Platelet binding parameters for Different Heparin fractions

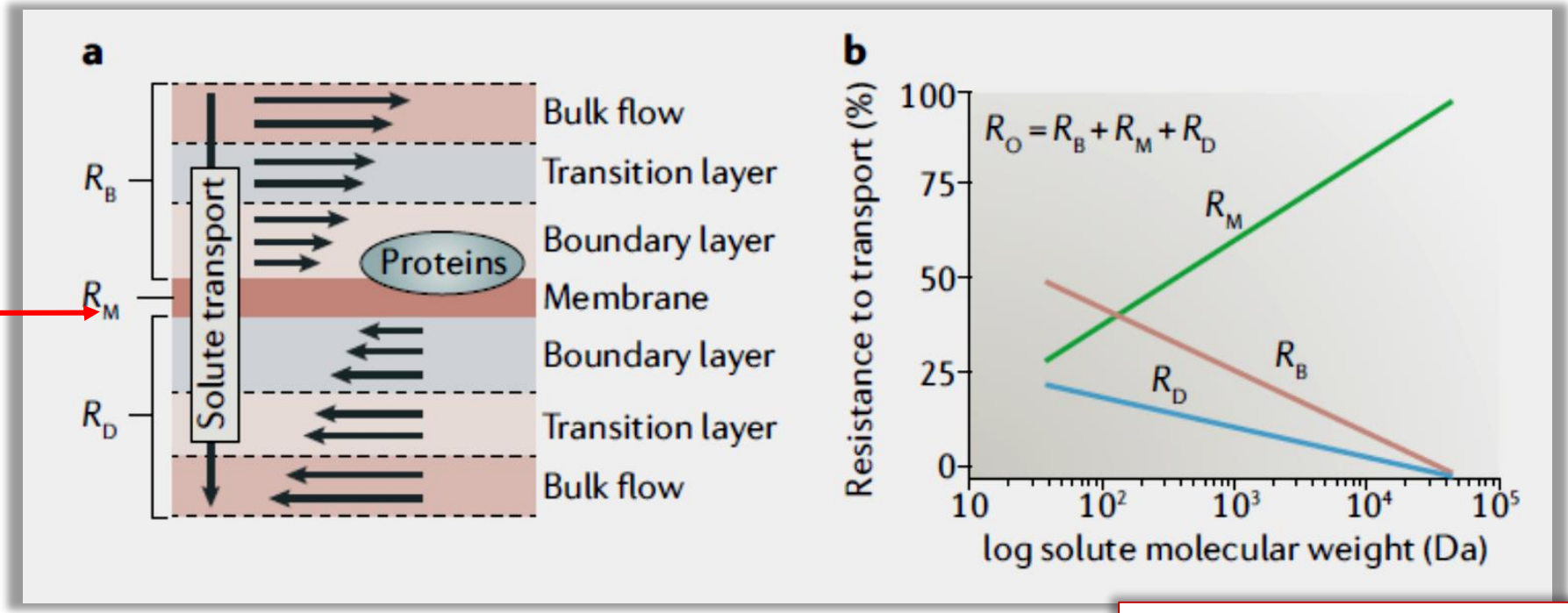
Heparin M_r range (Da)	Sulfate/ carboxylate (mol/mol)	Dissociation constant (mg/L)	Dissociation constant (nM)	Binding capacity (mg/10^{15} cells)	Binding capacity (molecules/cell)
14,000–16,000	2.0 ± 0.29[a]	4.6 ± 1.1	310 ± 73	66 ± 2.5	2600 ± 100
9,500–10,500	1.8 ± 0.26	3.9 ± 2.1	390 ± 210	56 ± 8.4	3400 ± 500
4,500–5,500	1.9 ± 0.15	3.2 ± 1.0	640 ± 200	23 ± 5.7	2800 ± 680
2,700–3,300	1.7 ± 0.25	4.0 ± 2.0	1300 ± 650	10 ± 5.4	2000 ± 1100

[a] Values are means ±1 standard deviation.
Source: Horne and Chao, 1990.

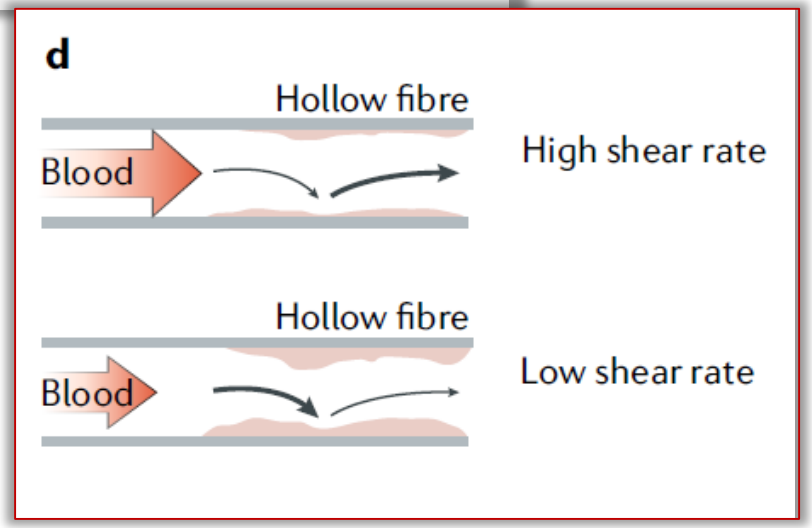
	LMWH	UFH
Molecular weight (da)	5,000	15,000
Platelet-binding domains per heparin	1	2
Platelet binding capacity (heparin molecules)	4	4
Platelet binding capacity (molecular weight)	20,000	60,000

Horne MK. In: Warkentin TE and Greinacher A eds. Heparin-induced thrombocytopenia (4°) edition. New York; Informa Heath Care: 2007, 117-130.

Resistenza al Trasporto

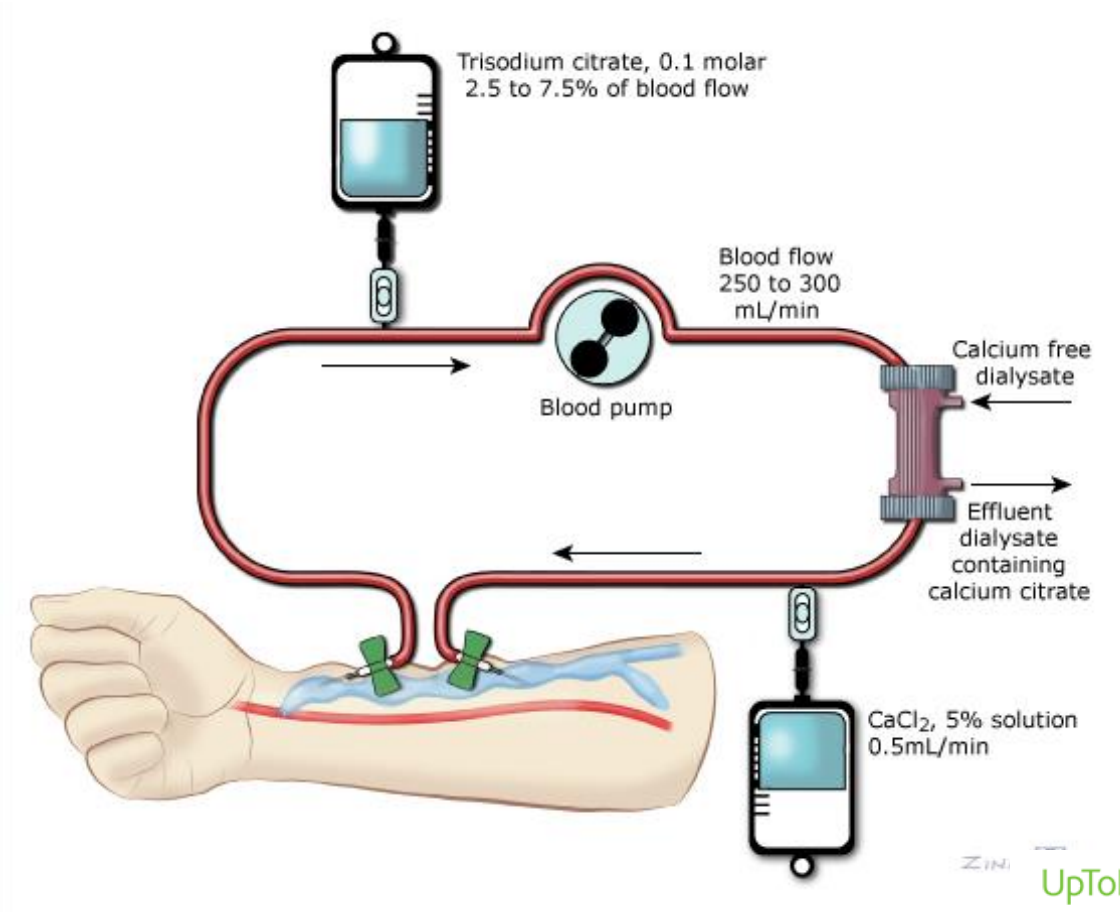


R_M è la Resistenza opposta dalle Caratteristiche della Membrana al Trasporto dei soluti



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

Anticoagulazione regionale con Citrato-Calcio



Anticoagulation for the hemodialysis procedure