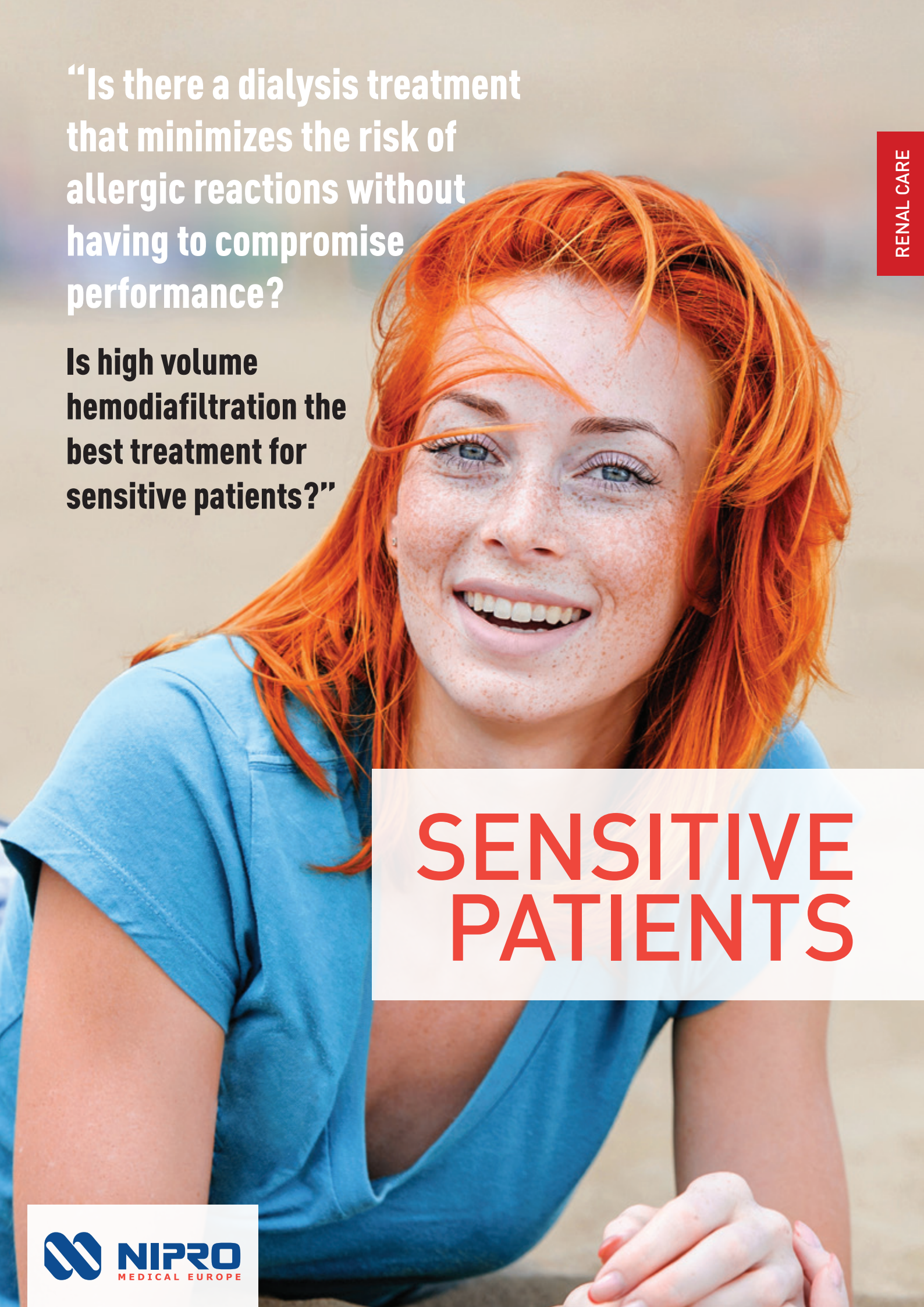

"Is there a dialysis treatment that minimizes the risk of allergic reactions without having to compromise performance?
Is high volume hemodiafiltration the best treatment for sensitive patients?"
RENAL CARE
SENSITIVE PATIENTS
NIPRO
MEDICAL EUROPE

Even though we are witnessing great technical advances and an increase in treatment choices for dialysis,

the prevalence of sensitive patients continues to increase and pose challenges for healthcare professionals.

Over the last decades, huge efforts have been made to protect dialysis patients from cardiovascular disease, a common complication for patients on hemodialysis that accounts for approximately 50% of deaths – much higher than the general population.[1]

The retention of uremic toxins in the middle and large molecular weight range is a major contributing factor to the high incidence of cardiovascular diseases in patients with compromised kidney function.[2] Thanks to the latest technical advances, hemodiafiltration (HDF) has improved the clearance of middle-to-large molecules by combining the techniques of diffusion and convection. Post-dilution online HDF is suggested to be the most efficient mode of HDF.[3]

Innovations in dialysis membranes, machines, and fluids have made post-dilution online HDF a safe and effective technique:

- **Dialyzers with high flux synthetic membranes**
- **New combination dialysis machines that conveniently carry out HD and HDF**
- **Online preparation of ultrapure dialysate**

What are the benefits of high volume post-dilution online HDF *versus* conventional hemodialysis?

Patients

- Reduced mortality rate[4]
- Lower risk of cardiovascular and infection-related mortality[4]
- Improved hemodynamic stability[5]
- Improved response to erythropoiesis-stimulating agents[5,6]
- Greater elimination of phosphates and β2-microglobulin[5]
- Decreased inflammatory markers/mediators[7]
- Lower incidence rate of dialysis complications from hypotension[5]
- Significantly greater patient satisfaction and quality of life[8]

Hospitals

- Lower incidence rate of all-cause hospitalizations[4]
- Reduced costs with replacement fluid made online[5]
- Reduced costs associated with reduced hospitalizations[9]

The European Dialysis Outcomes and Practices Pattern Study (DOPPS) associated **a decreased risk of mortality by 35% in patients treated with high volume online HDF compared to those treated with conventional hemodialysis**.[10]

And recently, the number of patients receiving this type of treatment in Europe has been on the rise. The prevalence of online HDF is close to 18% of the 80.000 chronic disease patients in Europe, Middle East, and Africa, with variations across countries from 0 to 100%.[11]

IF THE RESULTS ARE SO POSITIVE,
WHY DO WE NOT CONVERT 100% OF OUR PATIENTS
TO CONVECTIVE TECHNIQUES?

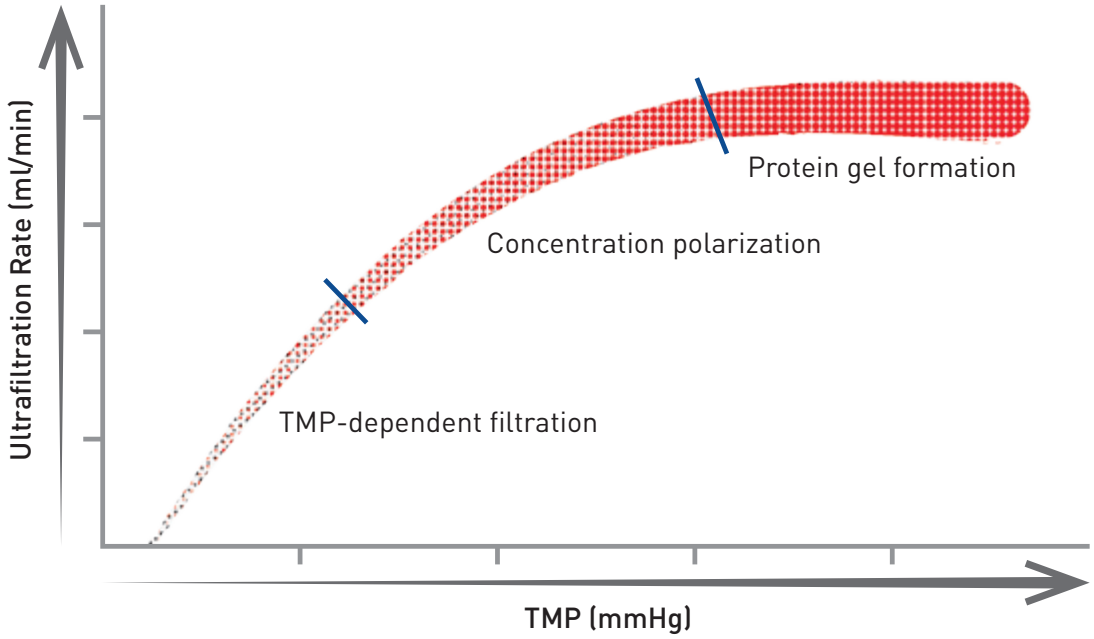
What are the limitations of high volume post-dilution online HDF?

HDF represents the most efficient technique in the replacement of renal function by dialysis.

High convective fluxes have been correlated with positive clinical outcomes.

However, there are technical barriers to performing effective convective therapies:[12]

- Increases in transmembrane pressures (TMP)
- Increases blood viscosity due to hemoconcentration
- Blood path resistance



What are the consequences associated?

In the attempt to achieve high ultrafiltration volumes, hemoconcentration results in high TMP, which triggers pressure alarms and may potentially cause cell damage. Ultimately, this may lead to:[13]

- Increased albumin loss
- Decreased number of treatments that achieve the prescribed convective volume, therefore reduced dialysis efficiency
- Increased workload due to increased interventions by nurses

Is there a solution to minimizing these unintended consequences?

Yes, there is. Increased efficiency in treatments with high volume post-dilution online HDF can be achieved thanks to the **choice of dialyzer**. In order to address the potential consequences associated with TMP, the dialysis membrane must have high permeability and be able to control albumin leakage.[14]

Polysulfone (PS) and polyethersulfone (PES) membranes have generally been used to meet these requirements.

However, patients with allergies to these synthetic membranes cannot access high volume post-dilution online HDF treatments because traditional semi-natural membranes, such as cellulose acetate-based membranes, cannot cope with high transmembrane pressures.[15]

What is the prevalence of allergic reactions?

- **4 out of 100.000** treatments were reported with anaphylactic reactions.[16]
- The relative risk of hypersensitivity reactions was **10 to 20 times higher** with synthetic membranes than with cellulose membranes. The prevalence of a severe reaction was 0,25% for the total population on dialysis, with 0,5% in patients treated with a synthetic membrane.[16]
- In another study, which analyzed the hypersensitivity reactions in **1536 patients** from 30 dialysis centers (122.694 sessions), the yearly incidence rate was 0,17 per 1000 sessions with semi-natural membranes versus 4,2 per 1000 sessions with synthetic membranes.[16]
- Non-specific reactions are more common, less severe than hypersensitive reactions, and probably under estimated because treatment can be completed.[16]

Which components have been associated with allergic responses?

- Synthetic polymer of the membrane[17]
- Bisphenol A (BPA)[18]
- Polyvinylpyrrolidone (PVP)[18]

What are the consequences of allergic responses and their associated costs?

- Mild to moderate effects: headache, chest or back pain, nausea, vomiting, fever[16]
- Severe effects: dyspnea, hypotension, cardiac arrest, death[16]
  - Requires immediate discontinuation of dialysis, without returning the blood
  - Requires medical intervention

Allergic reactions to dialyzers are serious complications that have a direct and severe impact on patients, healthcare professionals, and hospitals at large.[16-18]

Patients

- Increased hypotension
- Increased risk of blood loss
- Lower treatment efficiency
- Impact on patient inflammatory status
- Reduced life expectancy
- Patients become scared of the treatment

Healthcare professional

- Increased workload due to increased interventions by nurses
- Increased stress and pressure to perform

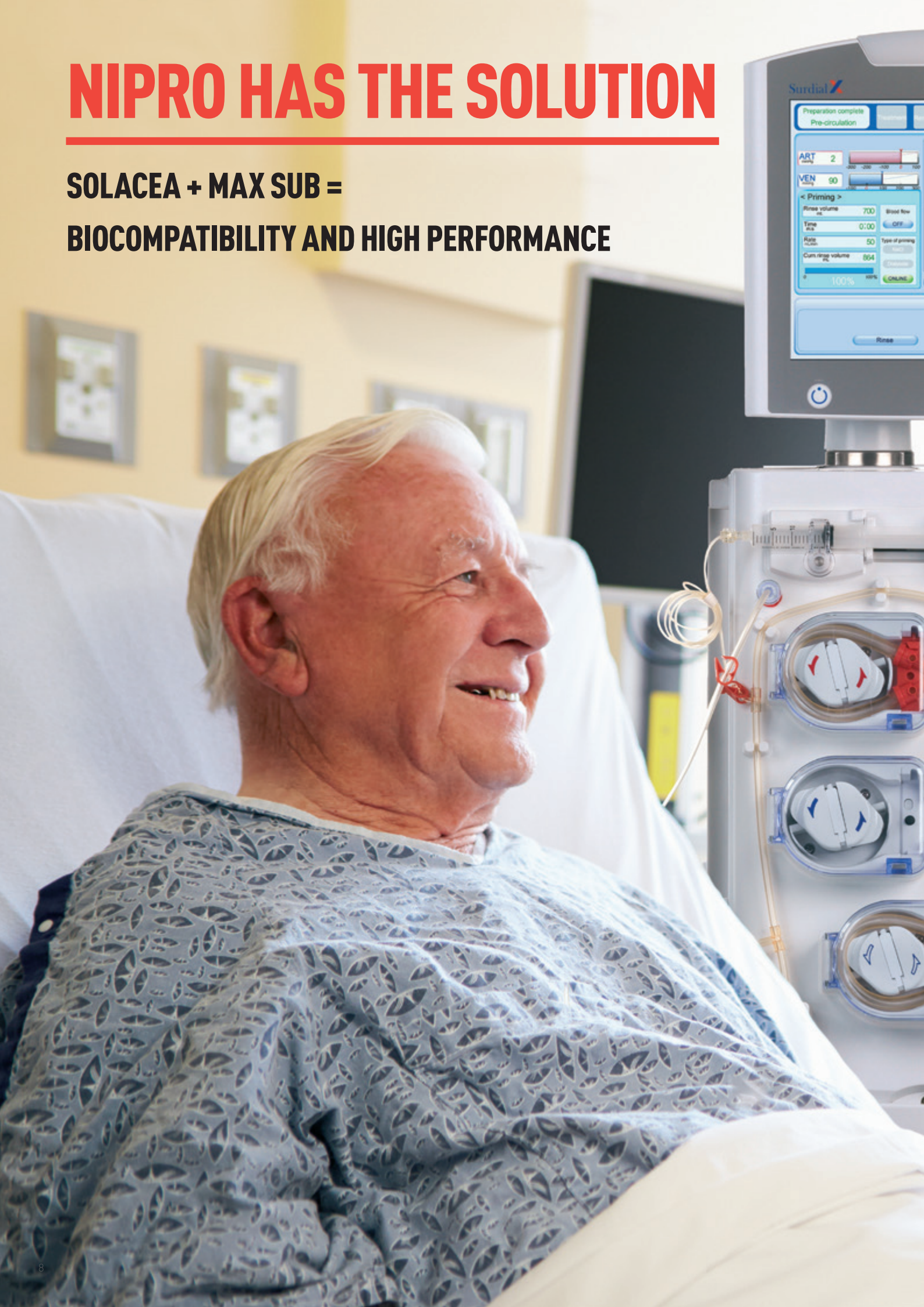
Hospitals

- Increased costs in medical products for interventional treatment
- Increased costs due to fluid compensation in case of hypotension

NIPRO HAS THE SOLUTION

SOLACEA + MAX SUB =

BIOCOMPATIBILITY AND HIGH PERFORMANCE



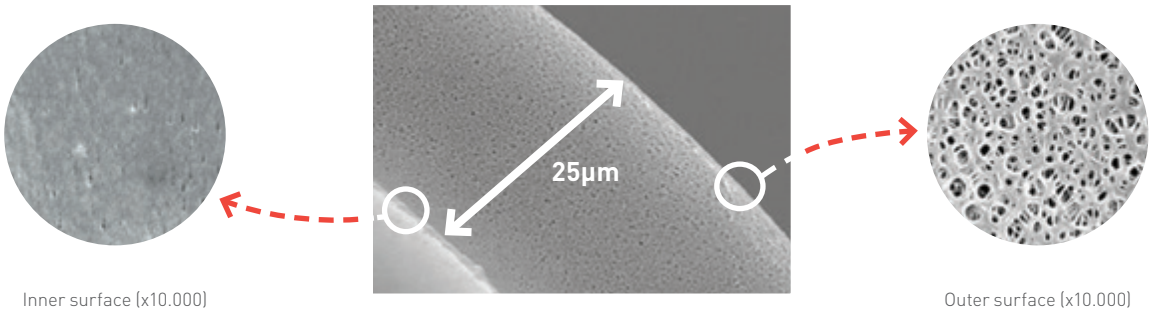
A high convective volume for sensitive patients is made possible by combining **SOLACEA**, a unique membrane developed specifically to perform HDF, with **automated "Max Sub" function**, a feature of Surdial X.

Nipro's Total Solution is straightforward and comprehensive:

- **SOLACEA dialyzer**
- **Surdial X machine with Max Sub**

SOLACEA™ | HIGH FLUX, ATA™ FIBER DIALYZER

SOLACEA features an asymmetric triacetate (ATA) membrane made by a state of the art spinning technique for dialyzer fibers. This results in **a membrane that can withstand high convective volume**. Its uniform pore distribution on the inner membrane safeguards high clearance of middle-to-large size molecules and minimizes albumin loss. This unique high flux dialyzer, with the new ATA structure, **combines the design of a synthetic membrane with the benefits of a semi-natural fiber**.

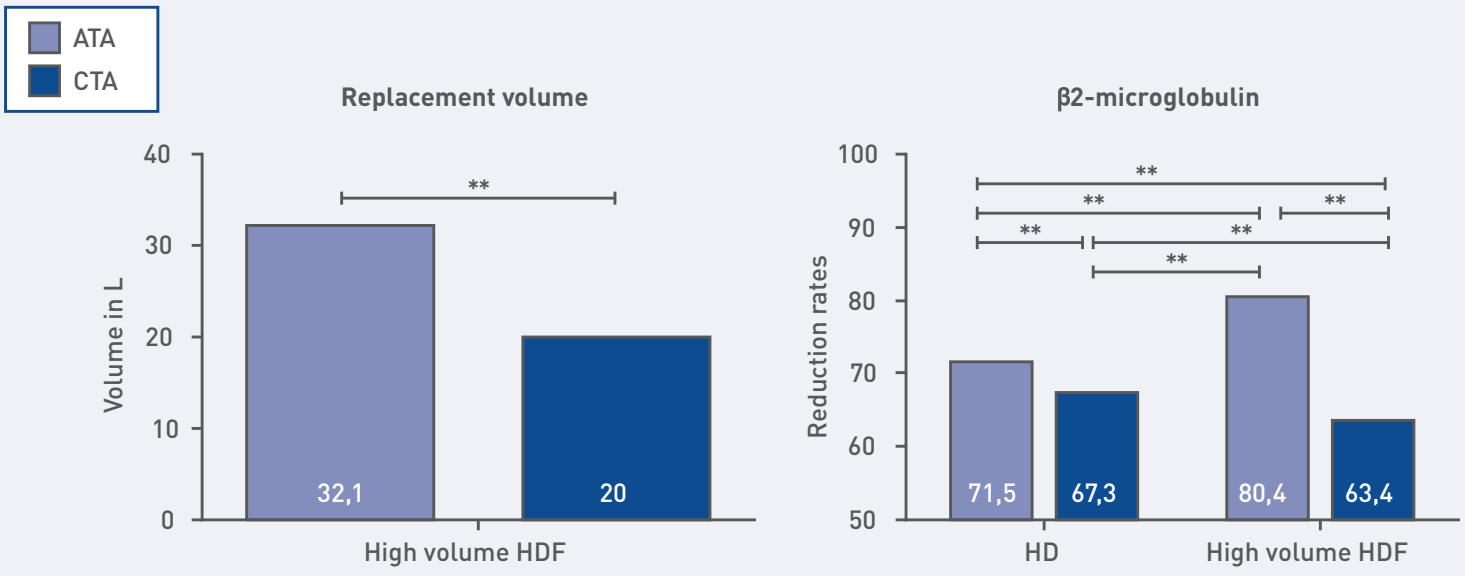


Inner surface (x10.000)
Smooth membrane surface with optimized pore distribution

Membrane cross section (x 5000)

Outer surface (x10.000)
Asymmetric supporting layer reduces pressure build-up

Housing and membrane are free of BPA, a proven endocrine disruptor and associated with an increased risk of residual kidney function loss. This makes SOLACEA the ideal membrane to be used in high volume HDF treatments for patients sensitive to synthetic dialyzers.

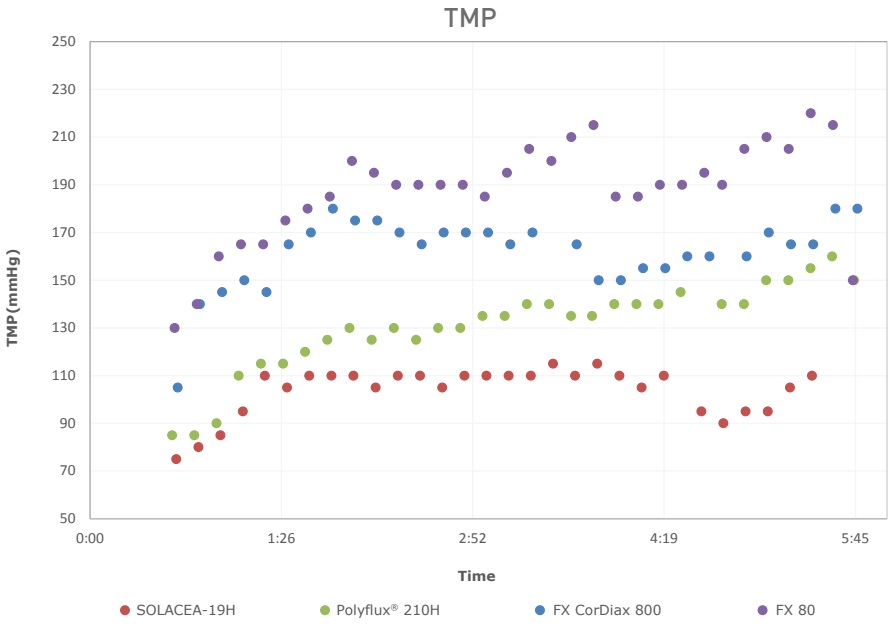


Performance comparison of the cellulose triacetate and asymmetric triacetate membrane. Comparison of the replacement volume in high-volume OL-HDF between the ATA and the CTA. A) reduction rates of ß2-microglobulin; B) and myoglobin; C) and the loss of albumin; D) between the ATA and CTA membrane in HD and high-volume OL-HDF. *p<0,05; **p<0,01.

ATA: asymmetric triacetate; CTA: cellulose triacetate; HD: haemodialysis; HDF: haemodiafiltration; OL-HDF: online haemodiafiltration. Figure has been adapted from Maduell F. et al. Nefrologia 2017 Nov 29.[15]

SOLACEA's ATA membrane:

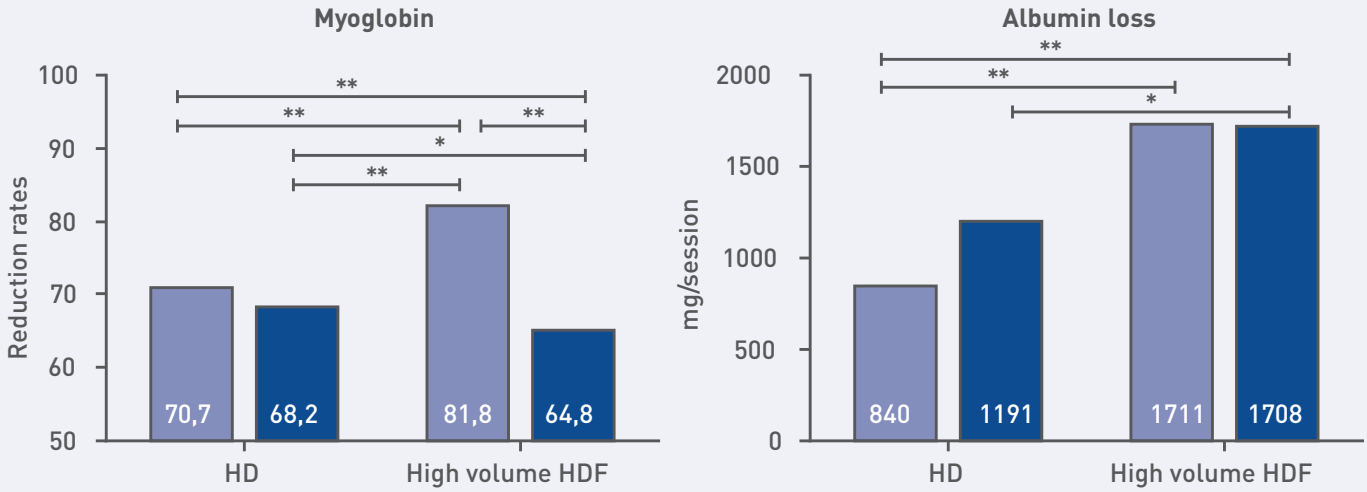
- addresses the needs of patients who experience hypersensitivity reactions
- copes well with high TMP, therefore is compatible with HDF.[19]



TMP values of different dialyzers in an *in vivo* experiment. Qb 350 ml/min, Qd 60 ml/min, Qs 85 ml/min. BioArtProducts, Rostock , Germany. 2015

Solacea is available in the following surfaces:

	15 H	17 H	19 H	21 H	25 H
Surface area	1,5 m²	1,7 m²	1,9 m²	2,1 m²	2,5 m²
Ultrafiltration coefficient	61	72	72	76	87

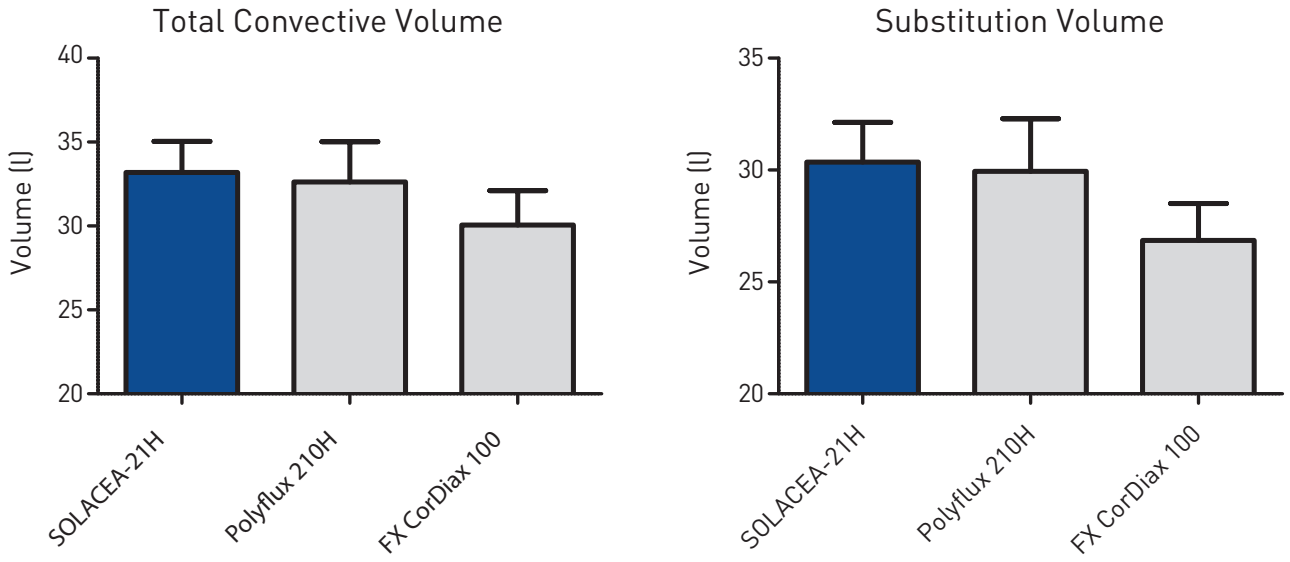


As illustrated by the graphs, SOLACEA has an excellent performance in high volume HDF, as proven by the removal rate of middle size molecules, as measured by ß2-microglubulin, with limited loss of albumin.

MAX SUB

Surdial X hemodialysis machine contains an automated feature called **Max Sub**. The automated Max Sub function calculates and measures the highest possible substitution rate **individualized for each patient** based on a pressure control system by following the TMP. Max Sub allows for higher substitute volumes in post-dilution HDF, thereby minimizing alarms and nurse interventions.

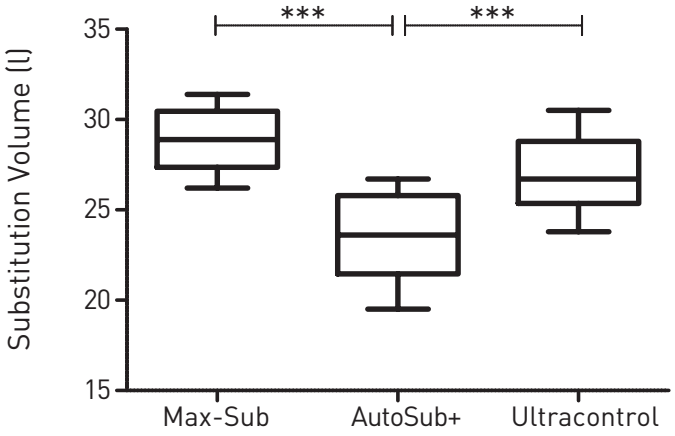
In an observational study, the functionality of Max Sub was assessed against different dialyzers.[20]



Based on the above results, Max Sub function demonstrates the ability to perform HDF high volume with convective volumes above the threshold required by the most recent studies.

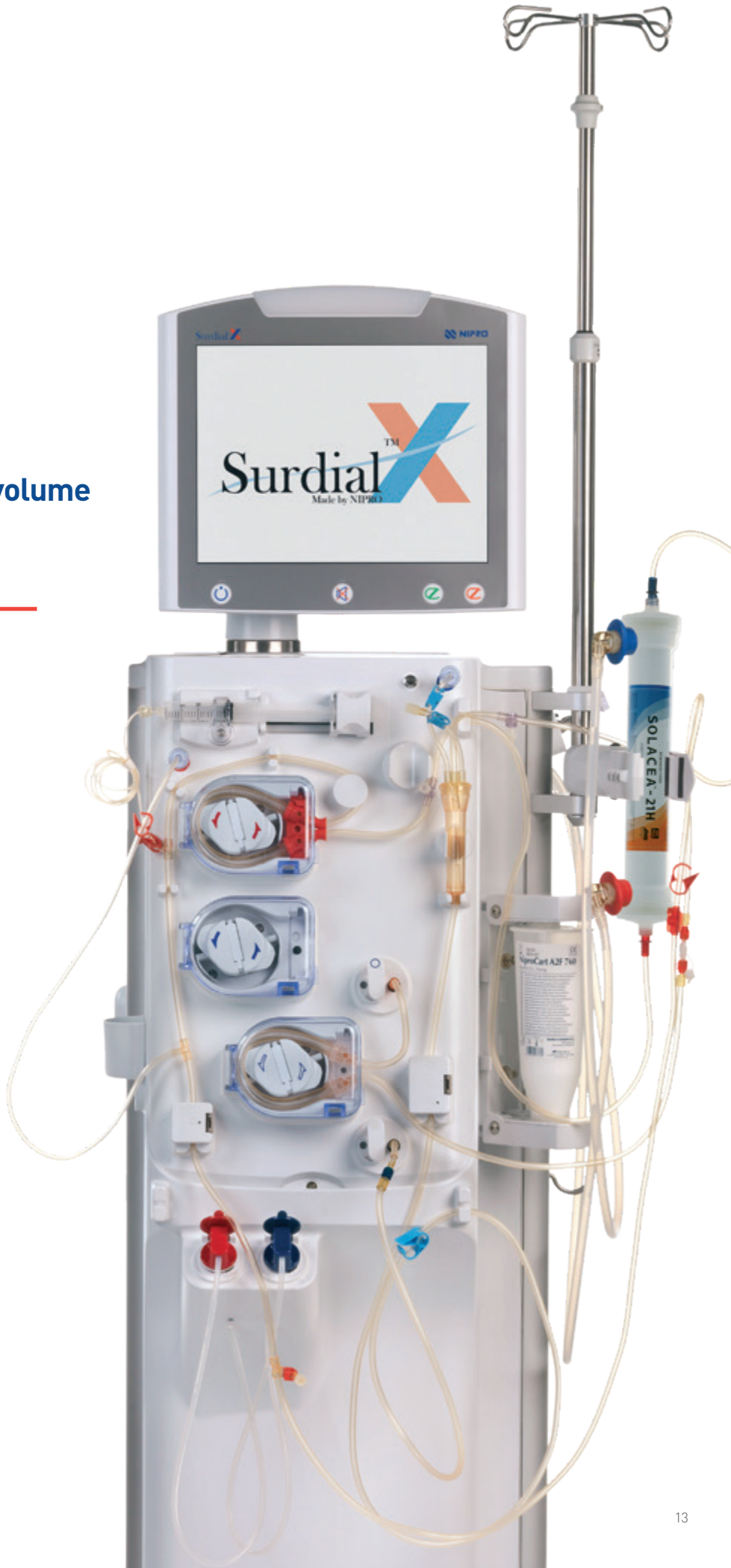
The highest substitution volume of 30,36 l and **a convective volume of 33,19 l** were achieved with **SOLACEA** membrane.

In a cross over study, where the same patient groups were treated with Max Sub and two other individualized HDF systems, those patients on Max Sub received the highest substitution volume.[21]



Substitution volume reached with different individualized HDF systems. *** p<0.001. Dr H. Dkhissi Convective Mekness study. H [21]

- **Automated**
- **Individualized**
- **Higher substitution volume**
- **Fewer alarms**



SOLACEA™ - H SERIES

HIGH FLUX

Clearance (mL/min)[1]	Qb/ Qd (mL/min)	15H	17H	19H	21H	25H
Urea	200/500	195	196	197	198	199
	300/500	262	269	274	280	285
	400/500	307	319	328	335	347
Creatinine	200/500	190	192	193	195	197
	300/500	247	256	262	269	274
	400/500	285	298	307	317	328
Phosphate	200/500	181	184	187	189	192
	300/500	230	241	249	255	266
	400/500	260	274	285	294	310
Vitamin B12	200/500	147	155	161	166	172
	300/500	172	184	195	205	215
	400/500	188	203	216	226	242

Ultrafiltration Coefficient

KUF [mL/hr/mmHg][2]	61	69	72	76	87

Sieving Coefficient[3]

Vitamin B12	1.00
Inulin	1.00
β2-M	0.85
Myoglobin	0.80
Albumin	0.013

Specifications

		15H	17H	19H	21H	25H
Effective surface area (m^2)		1,5	1,7	1,9	2,1	2,5
Priming volume (mL)		86	98	108	118	139
Effective length (mm)		227	233	245	254	280
Inner diameter (µm)		200	200	200	200	200
Membrane thickness (µm)		25	25	25	25	25
Maximum TMP (mmHg)		500	500	500	500	500
Pressure Drop	Qb/Qd [mL/min]	200/500	200/500	200/500	200/500	200/500
	Blood/Dialysate [mmHg]	51/16	47/16	47/16	45/15	43/8
Materials	Membrane	ATA™				
	Housing	Polypropylene				
	Potting	Polyurethane				
Sterilization		Gamma ray				
Packaging		24pcs/box				

In vitro testing conditions (ISO 8637)

[1] Clearance: Qf 0mL/min

[2] KUF: bovine blood (Hct 32+- 3%, Protein 60g/L, 37°C), Qb 200mL/min

[3] SC: Qb 300 mL/min, Qf 60mL/min

SURDIAL™ X

SYSTEM FOR HD-HDF-HF

Measurements

Unit size	Height: - 1625 mm (without IV pole) - 1745 to 1995 mm (with IV pole)	Width: 480 mm (monitor: 390 mm) Depth: 895 mm 4 castors and 2 brakes
Unit mass	Approx. 120 kg (dry mass)	

Protection

Protection class and grade	Class I Type B applied part (cuff for BPM: type BF applied part)
Protection against water penetration	Drip proof machine IPX1 (all panels closed)

Dialysate flow

Dialysate flow	Min: 100 ml/min Max: 800 ml/min	100 ml/min step linked with blood flow

UF control

UF control method	Sealed volume control method using piston pump	
Setting range	0,00; 0,10-4,00 l/h	0,01 l/h step

Blood pump, s/n double pump, on-line HDF pump

Blood pump method	2 rollers (auto space adjustment method)
Rotation direction	Counterclockwise rotation
Flow range	Normal tube: 10 to 600 ml/min - Normal tube: exclusive circuit Ø 8,00 x Ø 12,00 ± 0,15 mm - Obtaining maximum flow may be impossible due to fatigue of the rolling tube

Heparin pump

1-tube method	10, 20, 30 ml syringe
Injection direction	Leftward, only facing the equipment front side
Flow setting	0,0 to 10,0 ml/h
Overload detection	Discharge pressure 1200 ± 50 mmHg

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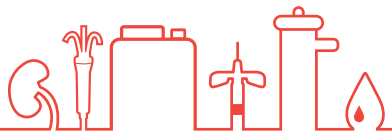
Nipro Renal Care is a global market leader with over 5 decades providing renal solutions for dialysis and dialysis-related treatment. We specialize in developing dialysis machines, water treatment systems, and a comprehensive portfolio of disposable medical equipment.

In order to address the needs of patients, healthcare professionals, and procurement managers alike, Nipro Renal Care is driven by innovation and patient safety to offer the highest quality products that optimize time, effort, and costs.

BECAUSE EVERY LIFE DESERVES AFFORDABLE CARE



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