ELISIO™-HX

A NOVEL SHARP CUT-OFF DIALYZER

NIPRO

A novel, sharp cut-off, next-generation HD dialyzer

ELISIO™-HX

Chronic kidney disease (CKD) affects more than 10% of the world's population. For end-stage renal disease patients, dialysis is one of the main life-sustaining treatments. However, **dialysis patients may have several comorbidities and variable medical needs.**

Inflammation is at the core of CKD, leading to protein energy wasting, **anemia, malnutrition and cardiovascular (CV) diseases.**[1]

Sarcopenia, characterized by the loss of muscle mass and **frailty** also **increases CV risk and overall mortality.**[2]

With the continuous advancement in dialysis technology, a wider range of uremic toxins can be cleared in patients. High-Volume HDF has become the gold standard in several countries with superior survival rates.[3]

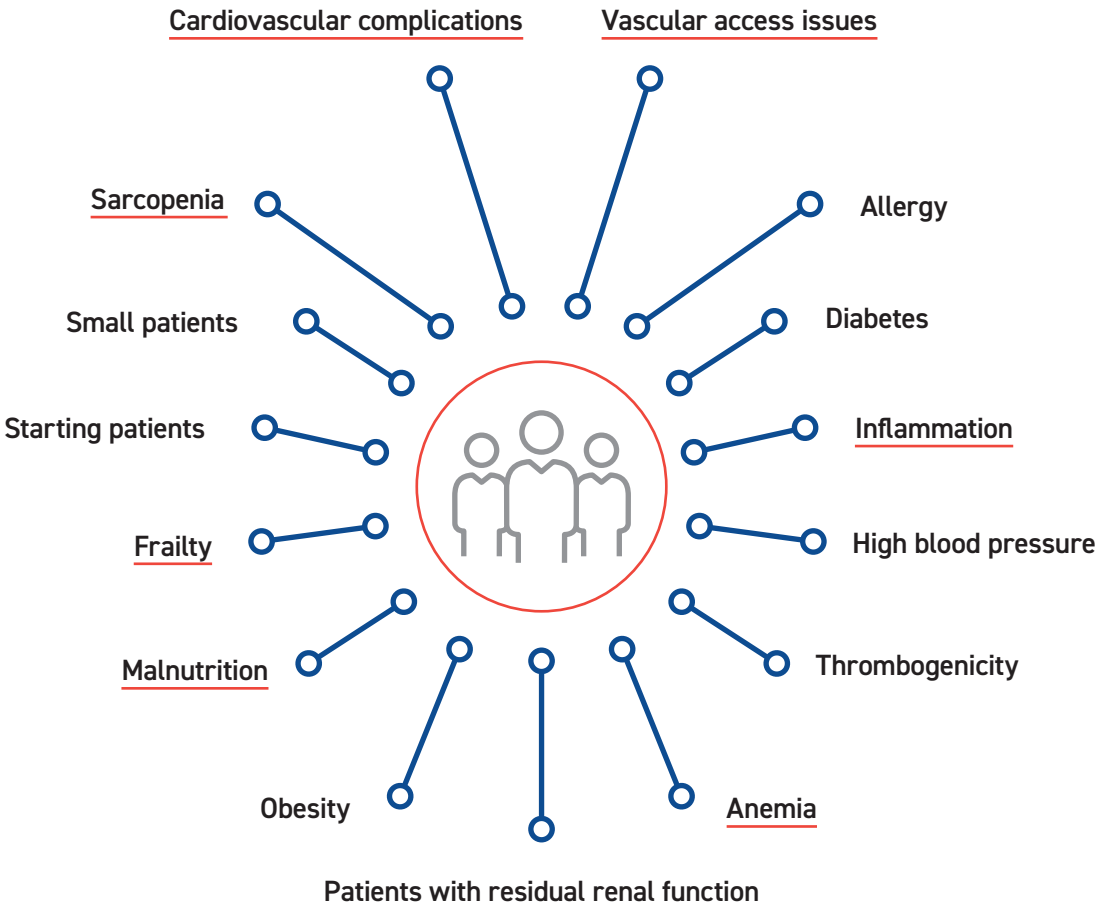
However, some patients are **not eligible for HDF treatment** due to:

- unsuitable vascular access

e.g. single needle, malfunctioning central venous catheter, new fistula, low access flow rate below 300 mL/min

- inability to reach efficient convective volumes (>25 L post dilution)[4]
- clotting problems
- high hematocrit levels

For this wide array of patients with variable medical needs, the best dialyzer should lose minimal albumin while maintaining high clearance of uremic toxins.[1]



NIPRO's novel super high flux sharp cut-off dialyzer, ELISIO-HX, with the combination of a bigger pore size and a specific geometry, is designed to remove a range of middle-molecule uremic toxins (12-60 kDa) which have a serious clinical impact on patients.[2]

Japanese classification of dialyzers

In the absence of HDF, conventional HD with high flux dialyzers falls short in removing **larger middle-molecule uremic toxins**. To overcome this limitation, **super high flux dialyzers, also known as medium cut-off,** with larger pore sizes have been introduced. In Japan, this class of dialyzers – also known as high-performance Class V membranes – are used for the treatment of more than 90% of patients on hemodialysis and are associated with **higher survival rates**.[5]

Uremic toxin	Molecular weight*
Urea	60 Da
Phosphate	96 Da
PTH	9500 Da
Beta-2 microglobulin	11.8 kDa
Myoglobin	17 kDa
Complement factor D	23.7 kDa
Interleukin-6	24.5 kDa
Kappa free light chain	25 kDa
Alpha-1 microglobulin	33 kDa
YKL-40	40 kDa
Pentraxin 3	41 kDa
Lambda free light chain	45 kDa
Albumin	67 kDa

Low flux class I

Mid-high flux class II and III

High flux class IV + HDF

Super high flux sharp cut-off class V

*approximate values

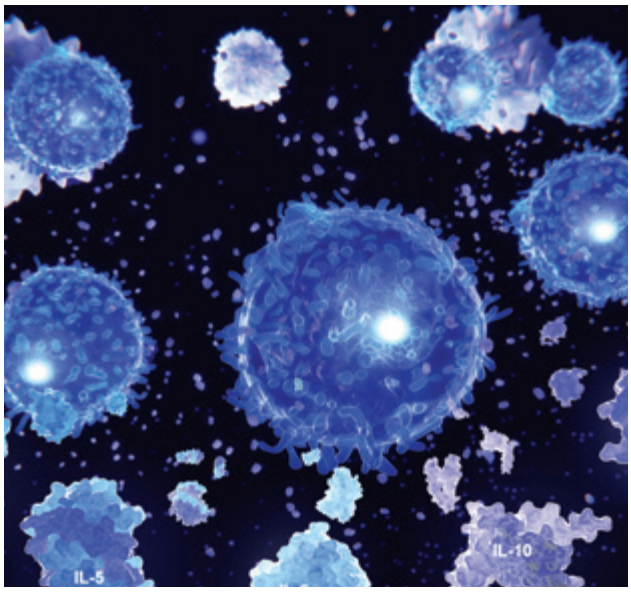
Efficacy of class V dialyzers in removing clinically impactful middle molecules

CLINICAL IMPACT OF MIDDLE MOLECULES

Inflammation

Inflammation is at the **core of the CKD pathology** leading to several complications. **A 21% increase in first-year mortality rates** has been shown **for high levels of C-reactive protein**.[6]

The RISCAVID study has demonstrated a higher **CV and all-cause mortality** risk with higher levels of **IL-6 and IL-8**.[7] **IL-18** is also linked with a higher risk of **cardiovascular mortality** in dialysis patients.[8]



Vascular calcification

An association between **serum beta-2 microglobulin (B2M) levels and vascular calcification** has been observed suggesting that B2M has a role in CV events.[9] A study with a follow-up of 6 years demonstrated this molecule as an independent predictor of **all-cause mortality.**[10]

Elevated B2M can deposit in the form of protein fibrils in various places in patients known as the **dialysis-related amyloidosis**. The effect of accumulated modified B2M is the stimulation of inflammatory molecules in the surrounding tissue leading to pain **(tendonitis, back pain, and neck pain)** in patients.[11]

Maladaptive immunity

Plasma levels of free light chains (FLCs) increase as a result of their diminished removal in CKD patients or their excess production in diseases such as multiple myeloma.[12] The increased serum levels of FLCs can interfere with the apoptosis of leukocytes leading to **increased inflammation**.[13] The **free kappa and lambda light chains** are associated with **vascular calcification**, and a higher level of these light chains may be a risk factor for **increased mortality** in CKD patients.[14-15]

Oxidative stress

In CKD, chronic inflammation, oxidative stress, and accumulation of uremic toxins lead to the accumulation of **advanced glycation end products (AGEs)** which can in turn aggravate the **oxidative stress and inflammation**. This vicious circle can lead to decreased muscle mass and the advancement of sarcopenia.[2]

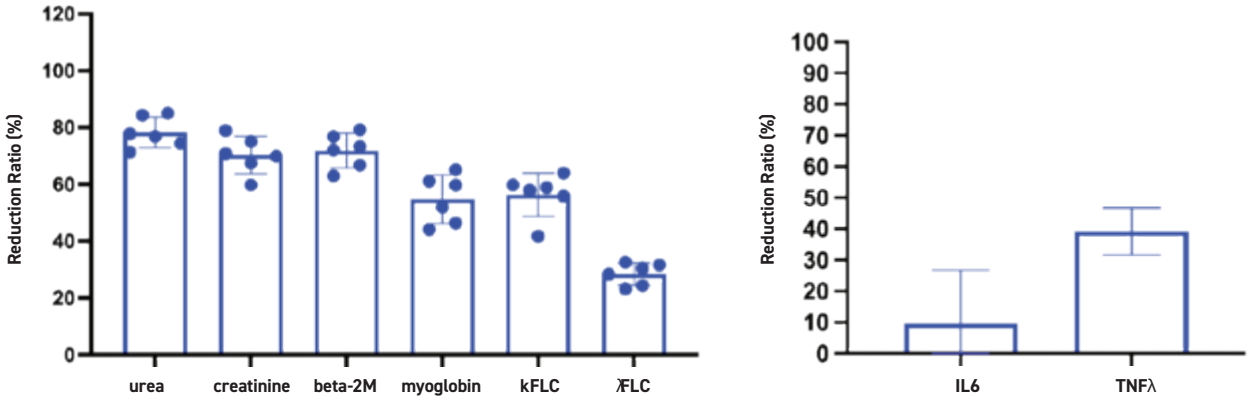
Dialysis quality dose

Glycoprotein YKL-40, an inflammatory mediator, is a significant predictor of all-cause and CV mortality in dialysis patients.[16]

The **lower serum YKL-40 concentration is associated with the higher dose (Kt/V) in dialysis**.[17] The use of the high convective volumes in this study to increase the efficiency of dialysis highlights that the **removal of middle molecules requires a higher dialysis efficacy**.

Optimal removal of middle molecule uremic toxins by ELISIO-HX

The objective of this prospective, single-center study was to determine the performance of the ELISIO-HX dialyzer in the removal of the following uremic toxins in 6 maintenance hemodialysis patients:[18]



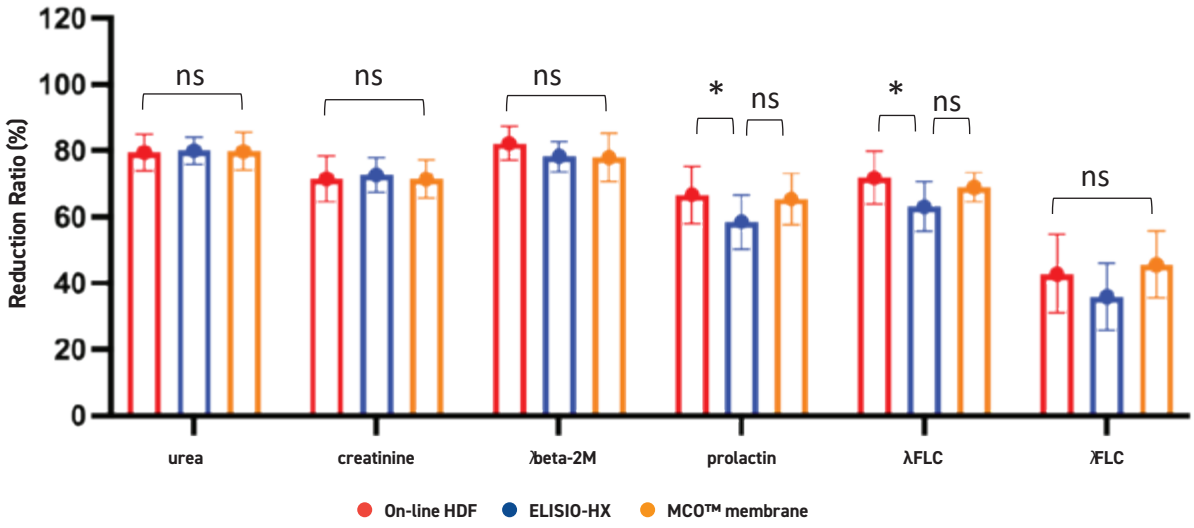
Blood flow rate: 300 mL/min; dialysate flow rate: 500 mL/min; treatment time: 240 min; N=6. Blood was collected pre- and post-dialysis to measure the reduction ratios.

ELISIO-HX is designed to remove a range of middle-molecule uremic toxins (12-60 kDa) which have a serious clinical impact on patients.[2]

Similar to hemodiafiltration and the medium cut-off membrane

This prospective, randomized, cross-over, single-center study was performed to determine the safety and efficacy of ELISIO-HX in comparison with a medium cut-off membrane and on-line HDF. 14 patients receiving HDF as baseline treatment were randomized to either ELISIO-HX or the medium cut-off membrane for 1 week. The results demonstrate that the removal of the middle molecules was mainly similar between ELISIO-HX and the medium cut-off as well as between ELISIO-HX and on-line HDF.[19]

This study indicates that the treatment with ELISIO-HX is a suitable alternative to on-line HDF and can be utilized for patients for whom HDF treatment is not possible.

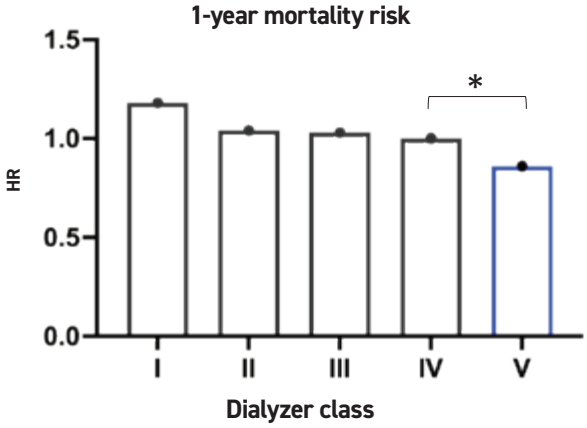


N=14; blood flow >370 mL/min; replacement volume >21 L; *p< 0.05; ns: not significant

Higher dialyzer performance, higher survival

Japan has been using a distinct 5-grade dialyzer classification based on B2M clearance at blood and dialysate flows of 200 and 500 mL/min respectively.

Based on this classification, **class IV and V**, also known as **super high flux** dialyzers, are identified by B2M clearance of <70, and ⩾ 70, and are used for the treatment of more than 90% of patients.[5]

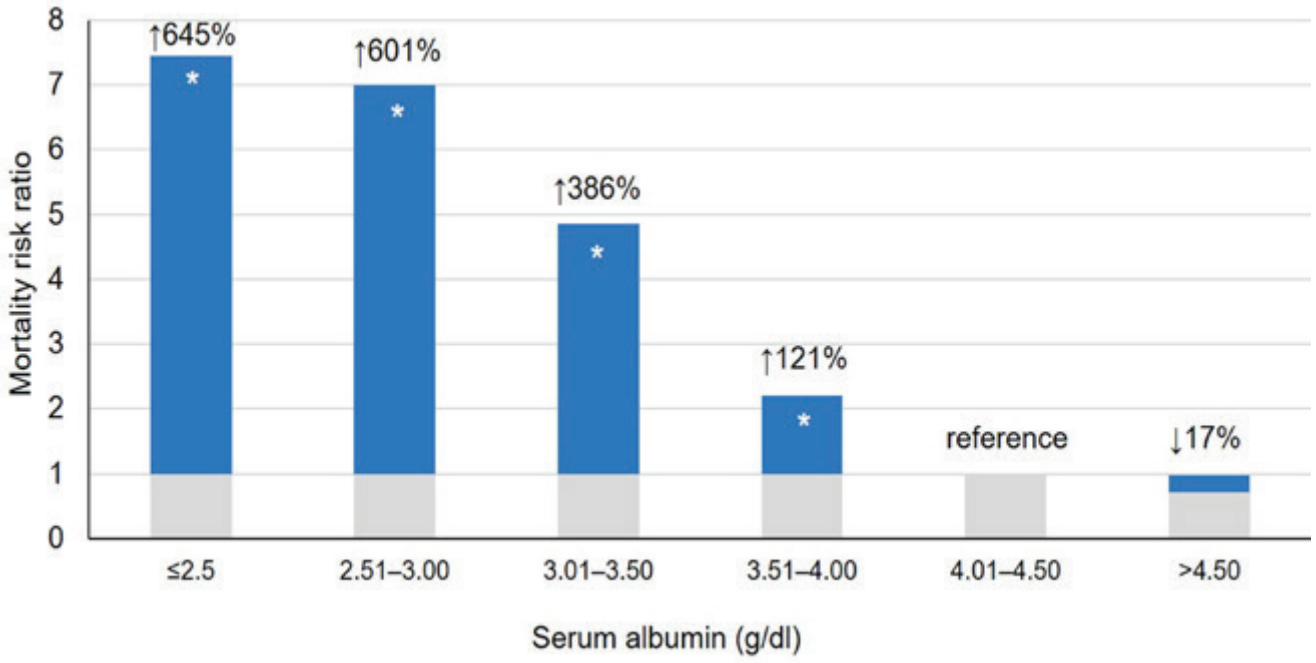


Using the nationwide data of the Japanese Society For Dialysis Therapy Renal Data Registry in a large cohort of more than 200,000 patients, **this study revealed a significantly lower risk of all-cause mortality for class V super high flux dialyzers including the sharp cut-off ELISIO-HX**.[5]

Graph from Abe et al.[5] 1-year all-cause mortality risk compared to class IV as reference. Cox proportional hazard regression. * p<0.05. Dialyzer classification based on B2M clearance (mL/min): I <10, II <30, III <50, IV <70, V ⩾70.

Minimal albumin loss in ELISIO-HX

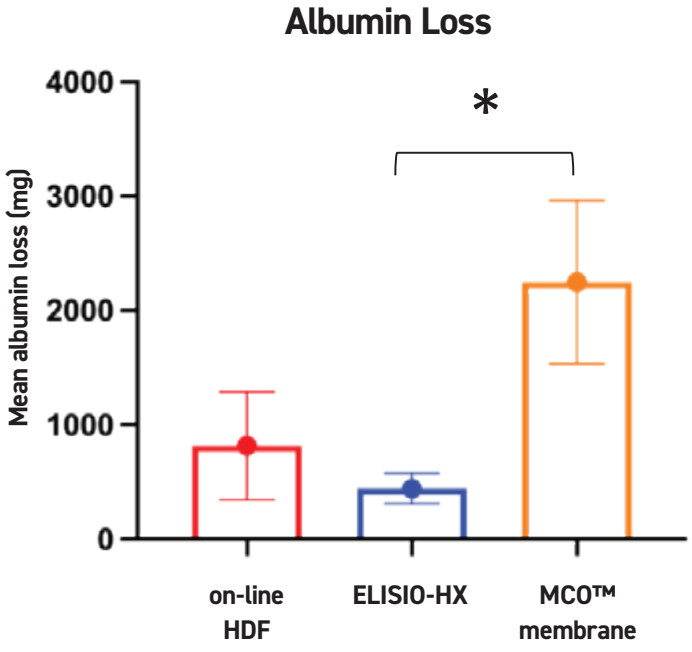
Hypoalbuminemia is common amongst CKD patients and is a **strong predictor of mortality.**[20,21] Dialysis can increase this condition by the extra loss of albumin through the dialyzer's pores.[1]



Graph adapted from.[20] Relative risk of death by albumin level among 19,746 patients receiving incenter hemodialysis.[20]

The type of therapy and the type of membrane can impact patients' albumin levels.[22, 23]

The minimal albumin loss in ELISIO-HX, distinguishes it as a sharp cut-off membrane in the larger class of medium cut-off membranes.[19]



N=14; blood flow > 370 mL/min; replacement volume > 21 L; *p< 0.05; ns: not significant

The sharp cut-off feature of ELISIO-HX distinguishes this membrane for patients vulnerable to albumin loss such as patients with malnutrition, frailty, sarcopenia or anemia.

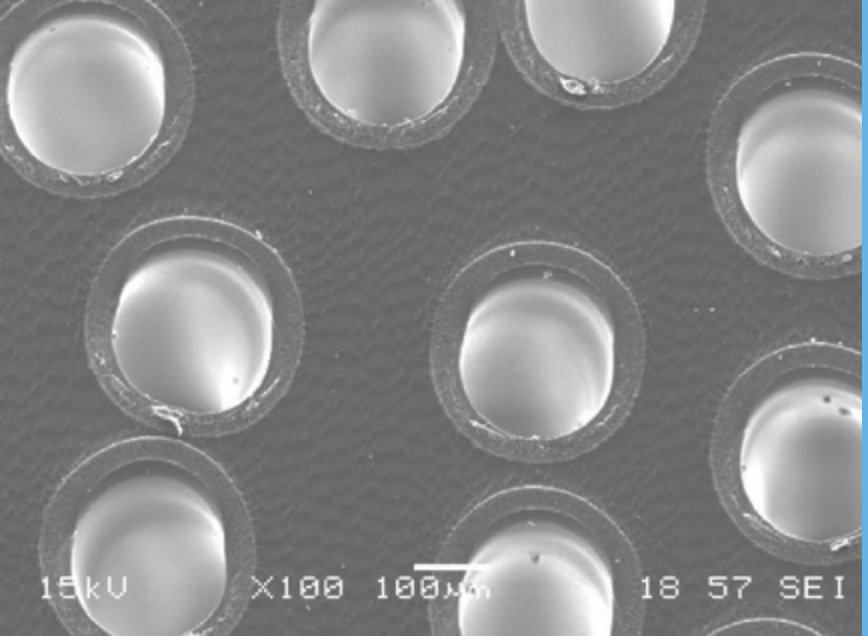


Image obtained at the R&D Center in Japan

ELISIO-HX

A Polynephron™ membrane made with polyethersulfone (PES) that is beneficial for patients and the environment:

- Clearance of middle molecular weight (MW) molecules[18,19]
- Retention of albumin[19]
- Not made with Bisphenol-A (BPA)
- Lower CO_2 emissions [27]

Conclusion

Following the paradigm shift from one-size-fits-all to a patient-centric approach, meeting the specific needs of dialysis patients is becoming increasingly important.

High-Volume HDF, as the gold standard of dialysis removes a wide array of uremic toxins associated with cardiovascular and all-cause mortality.[24] However for patients not medically eligible for High-Volume HDF, the best qualitative dialysis treatment is necessary.

For patients with no access to High-Volume HDF, a quality dialysis treatment should:

- remove the larger middle molecules (related to inflammation and CV diseases)[25]
- improve **amyloidosis, restless leg syndrome and pruritis**[26]
- improve quality of life

High performance dialyzers, known as class IV and V in the Japanese classification, have shown superior survival rates and unharmful albumin losses.[5] In patients with reduced capacity for albumin synthesis, or with poor nutrition, retaining sufficient **albumin is vital**.[1]

ELISIO-HX, with its combination of a larger pore size and specific geometry, is able to remove a range of middle-molecule uremic toxins whilst minimizing albumin loss. This provides a quality dialysis treatment for standard patients and those unable to access high-volume HDF.

Performance Data

Clearance at Qf 0 mL/min

Clearance (mL/min)*	Qb/Qd (mL/min)	09HX	11HX	13HX	15HX	17HX	19HX	21HX	25HX
Urea	200/500	188	191	195	197	198	199	200	200
	300/500	248	255	266	275	281	287	290	297
	400/500	280	296	313	327	338	348	355	369
Creatinine	200/500	174	179	185	190	194	197	198	200
	300/500	218	230	244	255	266	275	280	289
	400/500	250	260	280	297	310	321	331	349
Phosphate	200/500	166	173	180	186	190	194	196	198
	300/500	203	212	227	241	252	261	268	283
	400/500	223	235	253	272	286	299	310	337
Vitamin B_{12}	200/500	119	126	139	150	159	167	174	189
	300/500	136	146	163	179	192	203	214	239
	400/500	144	158	178	196	210	223	235	268
Myoglobin	200/500	61	69	80	92	102	112	121	136
	300/500	66	76	88	100	110	122	132	151
	400/500	70	81	96	108	119	130	142	165

KoA at Qf 0 mL/min

KoA (cm^3/min)**	09HX	11HX	13HX	15HX	17HX	19HX	21HX	25HX
Urea	801	888	1064	1265	1450	1714	1900	2778
Creatinine	543	629	757	888	1064	1265	1415	1832
Phosphate	456	506	606	726	849	977	1103	1527
Vitamin B_{12}	215	241	292	349	403	456	518	707
Myoglobin	80	95	115	137	156	182	205	255

Clearance at Qf 10 mL/min

Clearance (mL/min)*	Qb/Qd (mL/min)	09HX	11HX	13HX	15HX	17HX	19HX	21HX	25HX
Urea	200/500	190	193	197	199	199	200	200	200
	300/500	251	257	268	276	282	288	292	298
	400/500	284	298	316	329	341	351	358	372
Creatinine	200/500	178	181	188	193	196	198	199	200
	300/500	222	233	247	258	270	277	283	291
	400/500	254	263	284	300	314	325	334	351
Phosphate	200/500	170	175	182	187	191	194	197	199
	300/500	206	216	232	245	255	264	271	285
	400/500	227	239	256	274	290	302	314	339
Vitamin B_{12}	200/500	124	129	142	153	162	170	177	191
	300/500	141	150	168	183	195	206	217	242
	400/500	150	162	182	200	214	226	240	271
Myoglobin	200/500	66	74	88	97	108	118	128	141
	300/500	69	81	94	105	116	127	139	156
	400/500	75	86	100	113	124	137	148	170

KoA at Qf 10 mL/min

KoA (cm^3/min)**	09HX	11HX	13HX	15HX	17HX	19HX	21HX	25HX
Urea	836	916	1103	1292	1487	1771	2060	3078
Creatinine	570	654	789	930	1145	1321	1527	1976
Phosphate	472	530	645	767	888	1027	1167	1614
Vitamin B_{12}	228	252	309	364	417	472	537	736
Myoglobin	85	103	126	146	169	193	222	270

Ultrafiltration Coefficient†

KUF (mL/hr/mmHg)	42	47	53	60	67	75	82	97

Sieving Coefficient††

Vitamin B_{12}	1.00	beta2-microglobulin	1.00	Albumin	0.0024
Inulin	0.97	Myoglobin	0.86		

* *In vitro* test condition (EN1283, ISO 8637: 2010)
** KoA values at Qb 300 and Qd 500 mL/min.
† KUF (EN1283/ ISO 8637) : Bovine blood (Hct 32±2 %, Protein 60 g/L, 37 °C at Qb 300 mL/min)
†† SC (EN1283, ISO 8637: 2010): Qb 300 mL/min, Qf 60 mL/min.
Clearance data obtained in Japan. Clearance data can vary slightly depending on the test setup, lot number, and production site.

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NIPRO Renal Care is a global market leader with over six decades of experience 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.

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MM-4720 (2213) - Bro-Elisio HX (MDR) - EN - 02.Sept 2026

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