Dissertation

High-sensitivity cardiac troponin T profiles in patients treated with medium cut-off membranes compared to high-flux, low-flux membranes and hemodiafiltration.

submitted by

Dr. med. univ. Michael Kolland

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Ass.-Prof. Priv.-Doz. Dr. Alexander Kirsch, PhD

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Statutory Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the guidelines of "Standards of Good Scientific Practice and Ombuds Committee at the Medical University of Graz

Graz, 27.03.2024 Dr.med.univ.Michael Kollandeh

Disclosures

Parts of this thesis has been published in the following article:

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List of abbreviations

HD	Hemodialysis
ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
APD	Automated peritoneal dialysis
AVF	Arteriovenous fistula
AVG	Arteriovenous grafts
CAD	Coronary artery disease
CAPD	Continuous ambulatory peritoneal dialysis
CKD	Chronic kidney disease
cTn	Cardiac Troponin
cTnI	Cardiac Troponin I
cTnT	Cardiac Troponin T
CV	Cardiovascular
CVC	Central venous catheter
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ESKD	End stage kidney disease
FLC	Free light chains
GFR	Glomerular filtration rate
HCO	High cut-off
HDF	Hemodiafiltration
hs-cTnI	High-sensitivity cardiac Troponin I
hs-cTnT	High-sensitivity cardiac Troponin T
IDH	Intradialytic hypotension
K/DOQI	Kidney Disease Outcomes Quality Initiative
kDa	KiloDalton
LSM	Least square mean
Mab	Monoclonal antibodies
MCO	Medium cut-off membrane
MPO	Membrane permeability outcome study
MWCO	Molecular weight cut-off
MWRO	Molecular weight retention onset
NSTE-ACS	Non-ST-elevation acute coronary syndrome

ÖDTR	Österreichisches Dialyse und Transplant Register
RAAS	Renin angiotensin aldosterone system
SE	Standard error
SGLT-2	Sodium-glucose linked transporter type 2
SONG-HD	The Standardized Outcomes in Nephrology Group—Hemodialysis
URL	Upper reference limit

List of variables

A	Surface area
C_b	Solute concentration in plasma
D	Diffusion coefficient
d_c	concentration difference across the semipermeable membrane
d_x	Travelled distance by the crossing molecule
H	hematocrit
J_c	convective flux
J_d	Solute diffusive flux
K_0A	Mass-transfer coefficient
K_{UF}	Ultrafiltration coefficient
L	length
P	pressure
Q_D	Dialysate Flow rate
Q_f	Ultrafiltration rate
r	radius
S	Sieving coefficient
t	Time
V	Volume
Δ1h	Delta 1 hour
η	viscosity

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Zusammenfassung

Hintergrund:

PatientInnen, welche mit Hämodialyse (HD) behandelt werden, zeigen im Rahmen eines akuten Myokardinfarktes (AMI) seltener typische Symptome oder EKG-Veränderungen, weshalb die Diagnostik stärker auf kardialen Biomarkern (cTn) beruht. Die intradialytischen Auswirkungen von verschiedenen Hämodialyseverfahren auf cTn sind nicht ausreichend bekannt, weshalb diese Studie die intradialytischen Veränderungen untersuchen sollte.

Methoden: In dieser randomisierten, kontrollierten Crossover-Studie wurden asymptomatische, klinisch stabile HD-PatientInnen inkludiert, zu einer zufälligen Abfolge von Low-Flux-HD, High-Flux-HD, Hämodiafiltration (HDF) und Medium-Cut-off (MCO)-HD randomisiert und intradialytisch die Konzentrationen von Troponin T (cTnT) und I (cTnI) bestimmt.

Der primäre Ergebnisparameter war die relative Veränderung von cTn vom Ausgangswert nach einer Stunde HD (Δ1h) für die verschiedenen HD-Verfahren. Sekundäre Endpunkte umfassten die absoluten Veränderungen von cTn nach Δ1h und Δpost HD. Die Endpunkte wurden mit gemischten linearen Modellen analysiert.

Ergebnisse: Neunzehn PatientInnen (47.4% weiblich) mit einem durchschnittlichen Alter von 65.5± 13.4 Jahren und einer medianen Dialysedauer von 19 Monaten (min. 3, max. 165) wurden in der finalen Analyse inkludiert. Die relativen Veränderungen von cTnT nach 1h MCO-HD (Methode der kleinsten Quadrate (MKQ) -21,9 ± 2,7%) waren höher im Vergleich zu Low-Flux (LSM +2,2± 2,7%, p<0,001), High-Flux (LSM -6,8 ± 2,7%, p<0,001) und HDF-Behandlung (-21,2± 2,7%, p=0,81). Die LSM für die absoluten Veränderungen (Δ1h) mit MCO betrugen -21,2 (± 3,2 pg/ml), -6,4 (± 3,2 pg/ml) bei High-Flux, -20,2 (± 3,2 pg/ml) bei HDF-Behandlung und +2,3 (± 3,2 pg/ml) bei Low-Flux-HD mit ähnlichen Ergebnissen für Δpost HD. Für cTnI wurden keine signifikanten Änderungen beobachtet.

Schlussfolgerungen: Die Veränderungen des cTnT Werts, ohne Anzeichen einer Myokardischämie, lagen deutlich über den in den Leitlinien empfohlenen diagnostischen Grenzwerten. Darüber hinaus fanden wir eine signifikante Variabilität ohne jegliche Tendenz in der Kinetik des cTnI, was dessen Nützlichkeit für die Diagnose von AMI in dieser Situation stark in Frage stellt und somit auch die Anwendung von Standardalgorithmen zur AMI-Diagnose während der HD kritisch hinterfragt werden sollte.

Abstract

Background

During hemodialysis (HD), patients frequently show hemodynamic instability and symptoms such as nausea and chest pain. This may raise the suspicion of acute myocardial infarction (AMI). At the same time, diagnosis of AMI in this setting is challenging since HD patients less often present with typical symptoms and are more likely to present with non-ST-segment elevation myocardial infarction. Thus, the diagnosis more heavily relies on cardiac troponins (cTn). However, there is no study systematically examining the effect of different HD modalities on cTn kinetics during HD, thus we aimed to explore intradialytic changes of cTn.

Methods

In this randomized, controlled cross-over study we included prevalent, asymptomatic, and clinically stable patients treated with maintenance HD and measured cardiac troponin T (cTnT) and I (cTnI) concentrations with last-generation assays, before, one hour after start and after HD sessions. Patients were treated with a random sequence of low-flux HD, high-flux HD, hemodiafiltration [HDF], and medium cut-off (MCO)-HD, all of which are used in routine clinical practice. The primary aim was to compare the relative changes of cTn from baseline to after one hour of HD (Δ1h) for the different HD modalities. Secondary outcomes included absolute changes of cTn during and after treatment. Endpoints were analyzed using linear mixed models with subjects as random and sequence, period and treatment as fixed effects.

Results

Significantly different relative changes after 1h were observed for MCO (least square mean (LSM) -21.9 ± 2.7%) compared to low-flux (LSM +2.2± 2.7%, $p<0.001$) and MCO to high-flux (LSM -6.8 ± 2.7%, $p<0.001$). No difference was observed for MCO versus HDF treatment with high-flux membrane (LSM -21.2± 2.7%, $p=0.81$). Similar results were observed post HD, with the most pronounced change during the first hour.

For absolute changes, LSM for MCO were -21.2 (± 3.2 pg/mL), -6.4 (± 3.2 pg/mL) for high-flux, -20.2 (± 3.2 pg/mL) for HDF treatment and +2.3 (± 3.2 pg/mL) for low-flux hemodialysis after one hour. There were no significant effects for relative changes of cTnI.

Conclusion

Without clinical evidence of myocardial ischemia, guideline-recommended diagnostic thresholds for changes in cTnT were significantly higher while cTnI is likely not applicable which should be considered when applying standard diagnostic AMI-algorithms during HD.

1 Introduction

1.1 CKD

1.1.1 Definition

Chronic kidney disease is a condition which is characterized by structural and functional changes of the kidneys, which lead to a progressive decline in kidney function, assessed by reduced estimated glomerular filtration rate (eGFR), lower than 60ml/min/1.73m^2 or other markers of damage present for at least 3 months, i.e., albuminuria, urine sediment abnormalities, electrolyte or other abnormalities due to tubular disorder, abnormalities on histology or structural abnormalities detected by imaging or the history of a kidney transplantation (2).

1.1.2 Epidemiology

The burden of CKD is not only substantial but also increasing, as this condition affects over 10% of the worlds' population (3). Most common risk factors for CKD include diabetes and hypertension, but also monogenic kidney diseases or congenital abnormalities are causative mechanisms (4).

Globally, the prevalence of CKD and the respective underlying kidney diseases varies substantially, depending on ethnicity, socioeconomic status, and health care access.

Table 1 lists the main causes of end stage kidney disease (ESKD) in 2020 in Austria according to the ÖDTR report of 2020/2021 (5).

Underlying Kidney Disease	Percentage
Diabetes mellitus (Type 1)	3,5%
Diabetes mellitus (Type 2)	21,2%
Glomerulonephritis	8,6%
Hereditary Kidney Disease	7,2%
Interstitial Nephritis/Pyelonephritis	4,3%
Vascular Disease	24,0%
Other	12,8%

Table 1: Underlying kidney disease of patients on renal replacement therapy in Austria in 2021

The most common treatment modality of ESKD in Austria in 2020 was hemodialysis (HD) with 50.3%, followed by kidney transplantation (46.0%) and peritoneal dialysis (PD) (3.7%) of a total of 9940 patients. The mean age for prevalent HD patients was 68.0 years.
There is also some evidence for a sex and gender paradox in kidney disease.(6) While women experience a higher prevalence of CKD, men are more likely to suffer kidney failure and have higher mortality rates in predialysis CKD (7, 8).

1.1.3 Management of CKD

Preservative management in CKD care has gained increasing recognition and relies on multiple pillars including diet and lifestyle (plant-dominant, low-protein diet, low salt intake, physical activity, weight loss and smoking cessation), pharmacotherapy for disease progression (renin-angiotensin-aldosterone (RAAS) blockade, Sodium-glucose-type-2 inhibitor (SGLT-2), mineralocorticoid receptor antagonists), pharmacotherapy for cardiovascular (CV) risk management (blood pressure management, glucose control, lipid-lowering medication) and management of comorbidities such as acidosis, anemia or mineral bone health (9).

1.1.4 End stage kidney disease

When patients with chronic kidney disease develop ESKD, survival without a kidney replacement therapy, namely hemodialysis (HD), peritoneal dialysis or kidney transplantation will become impossible. Patients with ESKD who are older, frail and have multiple comorbidities frequently have palliative care needs, and do not start or even withdraw from dialysis and are in need of supportive care to alleviate a high symptom burden.

1.2 Hemodialysis

HD is a procedure, which uses a dialysis machine and a special filter (dialyzer) to purify blood. There are various HD regimens, including conventional in-center hemodialysis, nocturnal hemodialysis, or home hemodialysis. The following chapters and our study focus on conventional in-center HD, which is the by far most common regimen in Austria.
HD uses a special HD apparatus which is divided in a blood circuit and a dialysis solution circuit which interact at the dialyzer. Blood enters the circuit at the patients' vascular access

point, which is routinely either a central venous catheter (CVC) or an arteriovenous shunt, called fistula (AVF). It is pumped along the arterial inflow blood line by a blood flow pump to the dialyzer. After the dialyzer, blood is returned to the patient via the venous blood line. Dialysate, a sterile, buffered, electrolyte containing solution is either provided in bags or, in the case of in-center intermittent HD, produced on-line.

1.2.1 Conventional Hemodialysis

1.2.1.1 Physical principles

Dialysis is a process, whereby a solute is separated from a second solution by a semipermeable membrane, with solute transport occurring across the membrane, mainly via diffusion following concentration gradient. Hemodialysis describes the medical application of this principle, where one solution is the patient's blood, the other the dialysate.

1.2.1.1.1 *Diffusion*

The movement of solutes is caused by random molecular motion, which decreases with increasing molecular size of the solute. The underlying physical principle, Brownian motion, is particularly important for small particles, such as urea, ions such as potassium, or creatinine, with multiple other influencing factors, such as the electrical charge and concentration gradient. Diffusion is dependent on several variables, expressed in Fick's law as diffusive solute flux (10):

Equation 1: Diffusive flux

$$J_d = D \times A \times \frac{dc}{dx}$$

With J_d as the solute diffusive flux [mmol/m^2/h], D = diffusion coefficient [cm^{2}s^{-1}], A= surface area [m^2], dc= concentration difference across the semipermeable membrane, dx= travelled distance by the crossing molecule [m], i.e., membrane thickness.
The diffusive solute transport capacity for a given solute and a given dialyzer is typically expressed in hemodialysis as the mass-transfer area coefficient K_0A for that solute (11).

With visualization using electron microscopy, it has been concluded that the complexity of the membrane is not only determined by the pore sizes and distribution, as previously

thought, but also by the topology of the pores, which added the term hydraulic tortuosity to the literature (12).

Hemodialysis is most effective during the first hour as the concentration gradient diminishes and, thus, the main driving force for diffusion attenuates and consequently the absolute clearance continuously decreases over time. Consequently, the decline of concentration of small solutes such as urea is logarithmic and not in a linear fashion, while with larger molecules, the gradient is maintained longer (13).

1.2.1.1.1.1 Convective clearance and osmosis

Osmosis is defined as the passage of the solvent (e.g., water) through a semipermeable membrane (i.e., dialyzer membrane) from a lesser to a higher concentrated solution, until concentration equilibrium is reached. The so-called oncotic pressure is created via dissolved particles, which are unable to cross the semi-permeable membrane, mediating this solvent shift respectively convection. This solvent shift also initiates a solvent drag (13) or convective flux (J_c) [L/m^2/h]which depends on ultrafiltration rate (Q_f) [mL/min], membrane surface area (A) [m^2], solute concentration in plasma water (C_b) and a solute's sieving coefficient (S) [dimensionless] (10, 14):

Equation 2: Convective flux

$$J_c = \frac{Q_f}{A} \times C_b \times S$$

In HD, the sieving coefficient, S, is the relationship of the concentration of a solute in the ultrafiltrate, divided by its concentration in plasma water, ranging from 0 to 1.0 and depending on transmembrane solvent flow rate and degree of concentration polarization, and degree of solvent turbulence. In contrast to the solute mass transfer mediated via diffusion, the sieving coefficient declines more slowly with increasing molecular weight, thus, convection is less sensitive to molecular size compared to diffusion (13).

Both clearance mechanisms, diffusion and convection, occur at the same time simultaneously and influence each other which can be described according to (15, 16) as:

Equation 3: Total clearance

$$K_T = K_D + Q_F \times T_r$$

K_T…the total (diffusive + convective) clearance [L/h)]

K_D…diffusive clearance under conditions of no net ultrafiltration [L/h]

Q_F… ultrafiltration rate [L/h]

T_r …transmittance coefficient [Dimensionless]

The transmittance coefficient is a experimentally derived factor, depending on the diffusive removal. At very low values of K_D/Q_B, diffusion has little impact on blood compartment concentrations and the convective component of clearance equals almost the S*QF, but with increasing efficiency of diffusive solute removal, blood compartment concentrations are significantly influence, which results in a decrease of T_r, thus, in the convective contribution K_T.

Even without net ultrafiltration, there is still convective mass transport in a hollow fiber dialyzer, due to a phenomenon called starling flow (12), or internal filtration, which is mediated via axial hydrostatic and oncotic pressure gradient along the hollow fiber within the dialyzer in counter-current flow configuration. In the proximal part, closer to the header or arterial inlet of the dialyzer, the hydrostatic pressure in the hollow fiber is higher than the oncotic pressure, while along the length of the fiber, the hydrostatic pressure constantly decreases and eventually leads to back-filtration (17). Filtration and back-filtration is illustrated in figure 1.

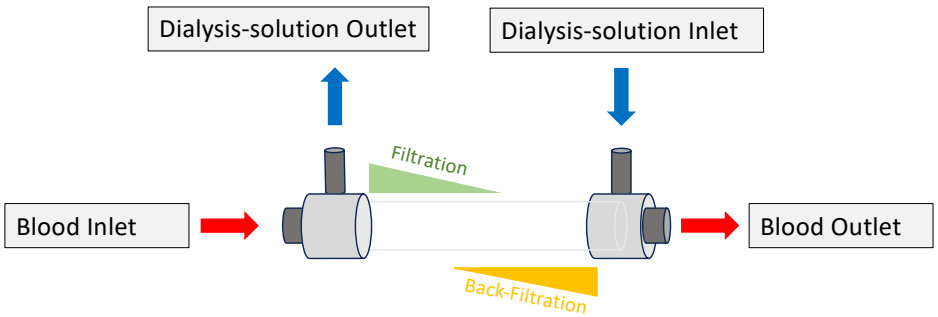

Figure 1: Filtration and Back-Filtration Process as internal filtration.

The transmembrane convective transport is largely dependent on transmembrane pressure (18), as a reduction of the inner diameter of a hollow-fiber results in an increase of resistance, and, consequently increased pressure which leads to internal filtration and back-filtration, which affects especially larger molecules (19).

1.2.1.1.1.2 Adsorption

Some solute clearance also derives from adsorption to the dialyzer's membrane, which is dependent on multiple physical properties, such as hydrophilicity, surface area, charge and chemical composition (20), thus, adsorptive removal is very much dependent on the membrane on the one hand and the solute studied on the other hand (21, 22).
On the other hand, sieving coefficient values are strongly influenced by nonspecific binding of plasma proteins, the formation of a secondary membrane or protein cake, which reduce membrane permeability (23-26), which is distinct from the aforementioned adsorption, see chapter "1.2.1.1.5.3 Concentration polarization and membrane fouling" below.

1.2.1.1.2 *Impact of blood flow rate (Q_B)*

Generally, in intermittent hemodialysis, the higher the blood flow rate, the higher the diffusive clearance, which reaches a plateau after a certain rate of Q_B (10). Blood flow rate in countries vary substantially (27). As derived by the urea clearance Kt/V (K referring to dialyzer clearance which is mainly dependent on the dialyzer itself, the blood flow and the dialysate flow), increases in dialyzer clearance can be achieved by either augmenting Q_B or Q_D (28). Compared to in vitro, the in vivo clearances are substantially lower, presumably due to blood's viscosity(29). The limiting factor of Q_B is often the vascular access, with typical flow rates of 300mL/min in central venous catheters, whereas blood flow rates of 400 can typically only be reached by arteriovenous access types (30), mainly caused by lower access resistance achieved via needles used for arteriovenous access types (31).
Multiple studies have shown that higher blood flow rates lead to better clearance of uremic toxins and are associated with a mortality benefit (32, 33), but this observation may be at least partly biased by a healthier patient collective, as sicker patients often have lower blood flow rates or central venous catheters as vascular access. A contributing factor to better clearance may be that higher a Q_B leads to greater shear effects along the membrane, which detach proteins from the membrane, and there is less formation of a secondary membrane at higher blood flow rates (34).

1.2.1.1.3 *Impact of dialysis solution flow rate (Q_D)*

Dialysis solution flow rate, in intermittent hemodialysis, is also an important factor for solute clearance, but only to a certain extent, with likely no benefit of rates >600mL/min (35), thus the dialysis solution flow rate is typically set at 1.5 times of Q_B. The increase of Q_D leads to an enhanced concentration gradient and subsequently diffusive clearance. A higher Q_D also

features more back-filtration in the distal parts of high-flux or medium cut-off (MCO) dialyzer, which can lead to a "back-flush" and protein detachment of the dialyzers' surface (36). Furthermore, impacting the dialysate-sided mass transfer, is the dialyzer's packing density, as spatially too closely packed hollow fibers may reduce the perfusion area, but this issue can be resolved by using inter-fiber spacer yarns (37). Also, the dialysate sided mass-transfer is dependent on the packing density of the hollow-fiber dialyzer, i.e., the number of hollow-fibers per cross-section, which – in turn – is inversely related to the fiber diameter.

1.2.1.1.4 *The dialyzer*

Contemporary dialyzers are typically hollow-fiber dialyzers. The blood enters through the header and is distributed into small capillaries (hollow fibers) which are surrounded by dialysate and exits on the opposing side.

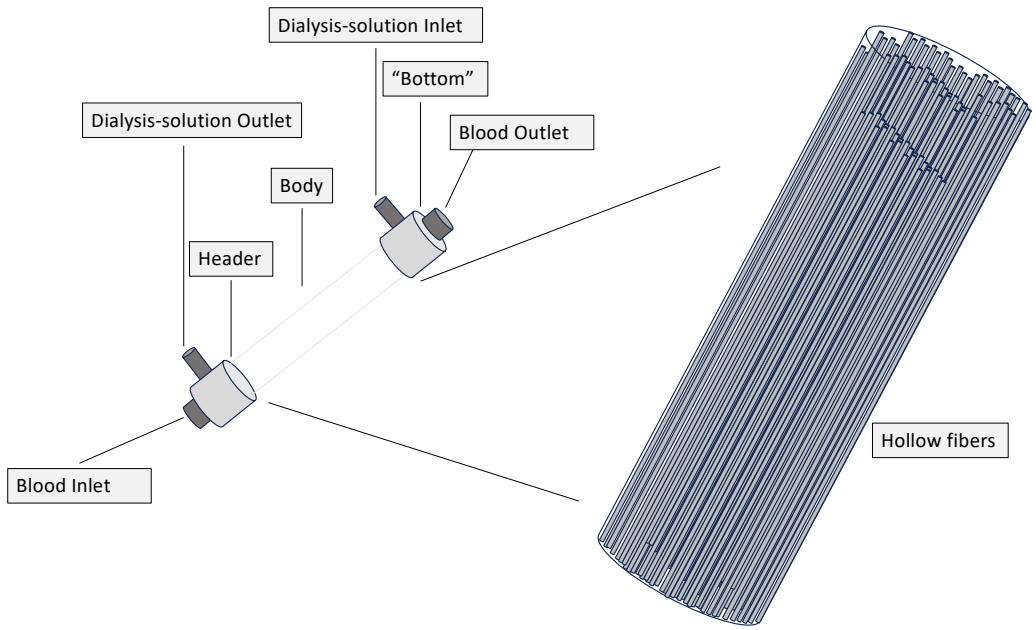

Figure 2: Dialyzer structure

Typically, dialysis membranes are produced using a diffusion-induced phase separation technique, which utilizes the characteristic of precipitation of polymers from solutions after extrusion of the solution trough a spinneret (18). Substantial efforts have been made to reduce the random pore size distribution to make the pores more uniform and less variant. Poor size distribution is the main determinant of molecular weight retention onset (MWRO) and molecular weight cut-off (MWCO). The MWRO is defined at the molecular weight at which the sieving coefficient (see above) for a given solute is 0.9 and the MWCO at which

the sieving coefficient is 0.1. These in vitro specifications are often derived in laboratory conditions, using human whole blood or human plasma at 37°C with a specified hematocrit to enable reproducibility of results.

The surface area, i.e. the maximum area which has contact with blood and a frequently reported characteristic of dialyzers, depends on the number of fibers, typically estimating 9.000-16.000 per dialyzer, fiber length and radius (15).
Thus, assuming a radius (r) of 100µm (i.e., a diameter of 200µm), a length (L) [m] of 0.24m an individual fiber's surface area (A_{fiber}) [m^2], can be calculated as:

Equation 4: Fiber's surface area

$$A_{fiber} = 2 \times \pi \times r \times L$$

With a given number of 16.000 fibers, totalling a maximum surface area of 2.4 m^2.
Diffusive clearance also appears to be higher in the middle fibers of a dialyzer, as the blood flow in the outer fibers tends to be slower, with increased risk of clotting and secondary membrane formation at the edges (20).

1.2.1.1.4.1 Influence of the inner diameter of the hollow fiber

Significant efforts have been made to make diffusive clearance more efficient, and as a result, the fiber's inner diameter and thickness were reduced to shorten the diffusion path (18). The inner diameter, which is part of the blood compartment, typically measures about 180-220µm with an average fiber length of 20-24cm (15).
Considering the Hagen–Poiseuille-law, which describes the longitudinal flow of a fluid through a cylinder:

Equation 5: Resistance

$$R = \frac{8 \times \eta \times \mathrm{L}}{\pi \times r^4}$$

where R is resistance [$kg*m^2*s^{-3}*m^{-2}$], η is the blood viscosity (assuming blood is a Newtonian fluid) [Pa*s], L is the length of the cylinder (hollow-fiber) [m] and r is the radius of the hollow-fiber [µm], one can assume, that with every increase in flow resistance, a pressure drop along the cylinder occurs, which is required to accomplish a certain Q_B:

Equation 6: Blood Flow

$$Q_B = \Delta P / R$$

Using and substituting R with the result of the equation 5, results in Equation 7, in which Q_B is the blood flow rate and ΔP is the axial pressure drop (38).

Equation 7: Blood flow along a hollow fiber

$$Q_B = \frac{\Delta \mathrm{P}}{\frac{8 \times \eta \times \mathrm{L}}{\pi \times r^4}}$$

Thus, since flow resistance is indirectly proportional to the fourth power of the diameter, the inner hollow fiber diameter can only be reduced to a certain extent without losing adequate flow because of overwhelming resistance. Finally, another limiting factor for the reduction of inner diameter in membrane design is the occurrence of hemolysis which increases with increasing blood flow resistance (18).

1.2.1.1.4.2 Influence of membrane pores of the hollow fiber

The flow of the ultrafiltrate through the membrane itself can be also described by the Hagen Poiseuille law. It is directly proportional to the pore radius (r^4) and the transmembrane pressure gradient and consequently depending on the pore size, pore size distribution and pore density on the membrane (38). As mentioned above, also the membrane pore tortuosity is a complicating influencing factor, which can be expressed in the following equation:

Equation 8: Membrane's hydraulic permeability

$$K_f = \frac{n \times \pi \times r^4}{\tau \times \eta \times \Delta \mathrm{x}}$$

K_f is the membrane's hydraulic permeability, n the total number of pores per unit area (i.e., pore density), r the pore radius [µm], τ a factor accounting for pore tortuosity, η the ultrafiltrate viscosity [Pa*s], and Δx the membrane wall thickness [µm] (15). Also, the diffusive capacity is heavily impacted by pore density and increases of molecular weight.

1.2.1.1.4.3 Concentration polarization and membrane fouling

Concentration polarization refers to a reversible mass transfer related effect (i.e., molecule build-up) that may subsequently cause irreversible fouling (solute adhesion through physical, and chemical bonds), as molecules are deposited by diffusive or convective transport to a membrane's surface. This fouling – or secondary membrane-layer formation – reduces pore size, increases the resistance to mass transfer, and consequently decreases clearance (39). This protein layer is thought to be mainly formed during the first hour of dialysis (40).

Secondary membrane formation is due to molecules such as immunoglobulins or fibrinogen. These relatively large plasma constituents are in limited contact to the dialyzer, namely only the blood-contacting surface of the hollow-fiber, without having contact to the surface area of the internal pore structure, while low-molecular-weight proteins may be cleared by adsorption (38), bonded by Van Der Waals, hydrophobic or ionic forces (26, 41, 42).

As a consequence of the in-vivo formation of this layer, which occurs after exposure to blood, in-vitro studies that do not account for this phenomenon may be inadequate to describe in-vivo clearance (24). In one study, examining cellulose membranes, especially larger molecules >10kDa were affected by this phenomenon of concentration polarization and subsequent fouling (25).

Heparin, as a commonly used antithrombotic medication for dialysis circuits, has been described to improve water permeability in coated cuprophan membranes (43). Modification of the membrane itself to make it more hydrophilic, may also affect the formation of a secondary membrane (44).

1.2.1.1.4.4 Dialyzer flux

A dialyzer's flux, derived from the Latin word "fluxus" which means flowing, is also often termed permeation rate, and refers to the amount of transported volume of permeate from one compartment of the membrane to the other. Flux can be directional, thus from the blood compartment into the dialysate compartment and vice versa (45, 46).

The flux (permeation rate; j), is defined as (47):

Equation 9: Dialyzer's flux

$$j = \frac{V}{\frac{A}{t}}$$

V…amount of fluid [litres]

A … membrane surface area [m^2]

t…time [h]

If a concurrent pressure is applied to the membrane, flux is then defined as the ultrafiltration coefficient K_{UF}, derived from in vitro measurements using bovine or human blood (48) and described as Flux (j) (49):

Equation 10: Flux expressed as ultrafiltration coefficient

$$j = \frac{\frac{V}{t}}{\frac{P}{A}}$$

V…amount of fluid [millilitres]

t…time period [hours]

P… pressure applied as transmembrane pressure (TMP) [mmHg]

A… membrane surface area [m^2]

TMP refers to the gradient between the blood and dialysate compartments. Flux, is also often used to describe the ability to remove larger molecules and, unfortunately, interchangeably with other distinct processes in HD such as clearances or sieving coefficients of membranes, which makes the interpretation of data from clinical trials more difficult (50). There is no uniform definition and currently no agreement of international guidelines, thus, "flux" is often described using ultrafiltration coefficients (K_{UF}), clearances (51, 52) and occasionally also sieving coefficients, with β_2-microglobulin sieving coefficients >0.6 for high-flux dialyzers (18, 20).

Furthermore, flux is determined using theoretical estimations in laboratory conditions, often not reflecting realistic in-vivo situations (50).

1.2.1.1.4.5 Membranes used in hemodialyzers

In the modern era of hemodialysis, most dialyzers use a synthetic polymer blend including polysulfone or polyethersulfone, which are more biocompatible and allow more "flux". Currently used membranes are low-flux, high-flux and high cut-off membranes and, more

recently, medium cut-off membranes, which can be seen as a further development of high-flux membranes, see table 2.

Additionally, manufacturers are using variable terms such as super-, ultra-flux without clear definition.

Type of membrane	Ultrafiltration coefficient[§] (mL/h/mmHg/m²)	β2-microglobulin		Albumin	
		Clearance[#] (mL/min)	Sieving coefficient[§]	Loss into dialysate[*] (g)	Sieving coefficient
Low-flux	<12	<10	-	0	0
High-flux	14-40	20-80	<0.7-0.8	<0.5	<0.01
Medium cut-off	40-60	>80	0.99	2-4	<0.01
Protein-leaking	>40	>80	0.9-1.0	2-6	0.01-0.03
High cut-off	40-60	n.a.	1.0	9-23	<0.2

Table 2: Classification of hemodialysis membranes.

Adapted from Storr and Ward (18). [§] in vitro. [#] for HD with a blood flow rate of 300-400mL/min. [*] for a 4-hour treatment.

Low-flux membranes

Low-flux membranes describe a filter with low K_{UF} and β2-microglobulin clearance, below 12 mL/h/mmHg/m² and <10 mL/min, respectively and feature a low MWRO and MWCO. Albumin loss into the dialysate is negligible with these membranes and over decades, low-flux membranes were standard in hemodialyzers, but have now mostly been replaced by high-flux membranes (see below), which are considered state of the art. Solute clearance in low flux dialyzers is almost exclusively achieved via diffusion with hardly any internal convection.

High-flux membranes

High-flux membranes are characterized by a higher MWCO and MWRO and combine the physical principles of solute transport of internal convection and diffusion. Two large randomized controlled studies, now considered landmark studies in the field of hemodialysis, compared low-flux versus high-flux hemodialysis.

In the HEMO Study, the authors found no benefit of high-flux dialysis compared to low-flux dialysis (52). The membrane permeability outcome study (MPO) study found a small, but

significant survival benefit in diabetics and those with a serum albumin of less than 4 g/dL (53). A more recent systematic review found a small reduction in cardiovascular mortality with high-flux dialysis (54). High-flux dialyzers are the mainstay of dialyzers used currently.

Medium Cut-off (MCO) membranes

MCO membranes were designed to deliver enhanced toxin removal, especially of larger middle molecules and feature a narrower pore size distribution, reflected by a steep sieving curve, which leads to a high MWRO, closer to the MWCO. Subsequently, larger molecules are enabled to pass through the semipermeable membrane, while retaining most of the albumin (55). After contact with blood and formation of a secondary membrane, MCO membranes have been shown to maintain performance in terms of sieving curves (56).

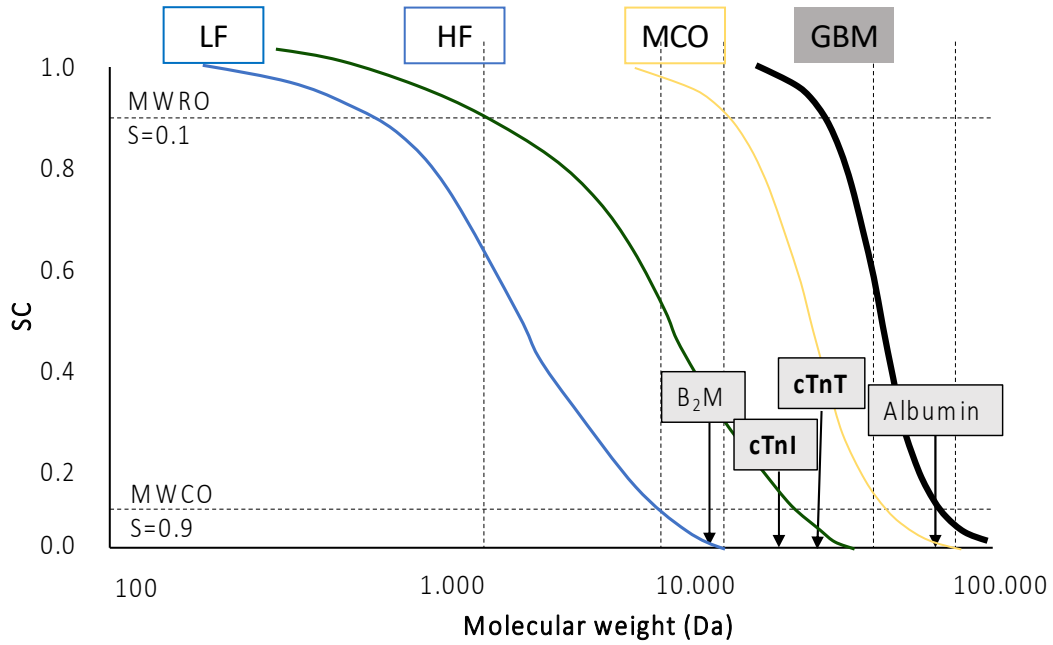

Figure 3: MWRO and MWCO according to types of membranes.

Adapted from Ronco and Clark, Nature Reviews 2018 (38). LF low-flux, HF high-flux, MCO medium cut-off, GBM glomerular basement membrane; B2M Beta-2-Microglobulin, cTnT cardiac Troponin T, cTnI cardiac Troponin I.

Furthermore, due to the reduced inner diameter of the hollow fibers, the MCO membranes offer substantial internal filtration, which enhances clearance of larger molecules, despite no net ultrafiltration rate, which has been shown in a nuclear emission study (45).

At low blood flow rates and low convection volumes, MCO shows higher reduction ratios of middle molecules compared to high-flux HD and HDF (57, 58). Use of MCO membranes increases the clearance of larger middle molecules and possibly reduces mRNA expression of TNF-α and IL-6 (55) which may improve patient related outcomes but this has so far not been studied in a large clinical outcome study powered for mortality or a similarly hard endpoint (59).

High Cut-off membranes

High cut-off (HCO) dialyzers clear molecules up to 45 kDa (60) and remove large middle molecules more effectively. They also result in high losses of albumin, which limits the routine clinical applicability of these membranes (60-62). This class of membranes have mostly been studied in special conditions such as acute kidney injury secondary to cast nephropathy in patients with multiple myeloma (63). In a recent trial, examining clinical outcomes in patients with de novo multiple myeloma and myeloma cast nephropathy who required HD for AKI and who received a bortezomib-based chemotherapy regimen, there was no difference in dialysis dependence with HCO dialysis compared to high-flux dialysis, but with more infections in patients treated with HCO HD (64).

1.2.1.1.5 *Dialysis efficiency*

The solute mass transfer mediated via diffusion is often described as the mass-transfer area coefficient K_0A (K_0= permeability coefficient of the dialyzer membrane for a given solute; A= total effective surface area of the dialyzer), expressed in mL/min, which is the theoretical maximum of clearance for a dialyzer at infinite blood and dialysate flow (11).

Increases of K_0 can be achieved by decreases in the membrane thickness, adjusting the pore density and pore size distribution and optimizing the fluid path, respectively resistance of the dialysate (30). Dialyzer with a K_0A of > 1200 ml/min are often termed "high-efficiency" dialyzer (65)

1.2.1.1.6 *Dialysis adequacy*

To determine the optimal dose of dialysis, that should be prescribed and to quantify the amount of dialysis that is delivered to an individual patient, a measure of adequate dialysis had to be introduced. Although not without controversy, a dialysis adequacy is typically derived from Kt/V urea, a dimensionless ratio which represents the volume of a patients'

plasma cleared of urea (K) in a certain time, or session length (t in hours), divided by the urea distribution volume (V in litres) (66). Other measures include the urea reduction ratio, assessed by the blood urea nitrogen level before and after dialysis or solute removal indices. The Kt/V is mathematically derived from the urea reduction ratio, but also takes into account the urea generated by the patients during dialysis and urea removed by ultrafiltration of excess fluid.

1.2.1.1.6.1 Impact of treatment time (t)

Treatment time varies across countries (27). According to the dialysis adequacy measurement of urea clearance Kt/V, an increase is possible by adapting either K (dialyzer clearance) or t (treatment time). Extending the total time on dialysis is often restricted by either economic or patient-related factors, even though increased treatment time has been shown to lower mortality among HD patients (67).

1.2.1.1.7 *Uremic toxins and molecules.*

Until recently uremic toxins were classified as such, when fulfilling the proposed criteria of the European Toxin Work Group of 2003 (68), but this classification of uremic toxins did not take into account whether there was a benefit from increased clearance of a class of uremic toxins. Thus, recently a new classification of uremic toxins was proposed, trying to account for new hemodialysis strategies, membranes, and removal patterns.

This new definition includes small molecules (molecular weight < 0.5 kDa, such as urea or uric acid), small-middle molecules (ranging 0.5-15 kDa, e.g. β_2-Microglobulin,), medium middle-molecules (ranging >15-25 kDa, such as κ-free light chains (FLC), Myoglobin), large-middle molecules (ranging >25-58 kDa, e.g. λ-FLC, YKL-40) and large molecules (>58 kDa, such as albumin). While only small molecules are assumed to be properly cleared by low-flux HD, small-middle molecules are believed to be efficiently removed by high-flux HD and larger molecules only by MCO membranes or with high-flux HDF (69).

1.2.1.2 Hemodiafiltration

Hemodiafiltration (HDF) is an extracorporeal treatment mode, which combines the physical principles of hemodialysis (i.e., diffusion) and hemofiltration (i.e. convection). Because of the large volumes of plasma water that are filtered and removed, this modality requires

relatively large amounts of a substitution fluid, in addition to a dialyzer, and a dedicated HDF machine.

HDF utilizes both diffusion, which is, as described above, particularly important for low molecular weight toxins, and convection, which results in effective removal of larger molecules to achieve adequate removal of uremic toxins (70). Importantly, effective convective clearance and clinical benefit is dependent on a sufficient convection volume of more than 23 litres per session (71).

During HDF, a large quantity of plasma water is removed via ultrafiltration, which has to be replaced isovolumetrically with a non-pyrogenic, sterile substitution fluid (70, 72).

HDF is further defined by where the substitution fluid is infused into the circuit – either before the dialyzer in pre-dilution HDF or after the dialyzer in post-dilution HDF. The most commonly used mode of HDF is post-dilution HDF which achieves higher convective clearance rates but with the caveat of membrane fouling, especially when hematocrit is high (73). It is recommended that filtration fraction stays below 20-30% as with higher filtration fractions, there is an increased risk of clotting (74).

Pre-dilution HDF has reduced risk of secondary membranes but requires more substitution volumes compared to post-dilution HDF to achieve equivalent clearance. Other modality options include mixed-dilution or mid-dilution HDF. Typically, high-flux dialyzers are used for HDF.

In the beginnings of HDF, the substitution fluid had to be provided in plastic bags, which limited the total exchange volume, but currently, the fluid is produced "online" as a refinement of similarly produced dialysate. Problematically, limiting the use of HDF, it requires the use of ultrapure dialysate which is costly. As stated above, the amount of convective clearance is mainly a function of the total convective volume. It is thus recommended to maximize convection volumes and target a minimum of 23l per session, as there seems to be a dose-related association between survival rate and convection volume (75) (defined as total ultrafiltration volume, i.e., the sum of the substitution volume plus the intradialytic weight loss (76)).

Membrane fouling, as described above, is of higher significance in HDF, as due to the high filtration fraction, more plasma proteins are transported at a faster speed to the membrane surface, which can lead to higher transmembrane pressures (77), reduced achievable exchange volume and reduced sieving coefficients for larger middle molecules (72).

Recently, the CONVINCE Trial reported that high-dose HDF, may result in a survival benefit (78), which confirmed previous observations (79).

1.3 Peritoneal dialysis

Peritoneal dialysis remains one of the options for kidney replacement therapy in ESKD. Here, the peritoneum is used as a semipermeable membrane, which utilizes the same physical principles used in HD, i.e., ultrafiltration, osmosis, and convection, to allow solute and water clearance. A solution is thereby instilled into the peritoneal cavity and exchanged several times per day, acting as a dialysis solution. Multiple different types of peritoneal dialysis have been developed, with continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) being to most common types.(30)

Complications differ compared to HD, and include abdominal hernias, abdominal wall or pericatheter leaks, (genital) edema, respiratory complications such as hydrothorax and altered mechanics of breathing, dislocation of the catheter, exit-site-infections, tunnel-infections and most importantly peritonitis (30).

1.4 Kidney transplantation

Deceased and living kidney donor transplantation is the third option for kidney replacement therapy. Kidney transplantation is associated with lower mortality and higher quality of live compared with dialysis. A systematic review of over 1.9 millions of participants found lower mortality with increasing magnitude of the benefit over time, partly driven by lower cardiovascular events (80).

For further description of kidney transplantation, the reader may be referred to the specific literature, since kidney transplantation remains out of the scope of this dissertation.

1.5 Comparison of morbidity and mortality for different kidney replacement therapies

According to the ÖDTR (5) registry, main causes for mortality in 2020 on hemodialysis were cardiac (29.6%) followed by infectious complications (23.7%), undetermined (18.7%), other reasons (16.6%) and malignancy (6.9%) of a total of 813 deaths. In patients treated with peritoneal dialysis, cardiac and undetermined reasons were most common (each 28.9%) followed by infectious complications (23.6%) other reasons (10.5%) and vascular reasons of 38 deaths. In patients treated with kidney transplantation, main reasons for death were

undetermined (39.1%), infectious complications (21.2%), malignancy (14.6%), cardiac (11.9%), other reasons (11.2%) and vascular reasons (1.9%) of 151 total deaths.

In a systematic review, kidney transplantation was found to be associated with lower mortality, lower risk of cardiovascular events, significantly higher quality of life (80).

In a large retrospective analysis, annual death rates per 100 patient-years at risk were reported to be 16.5 for dialysis, 2.4 for patients on the waiting list and 1.2 for transplant recipients (81). During the first three months, mortality risk is higher, which continuously decreases with the time.

Causes of death early after kidney transplantation include cardiovascular disease (82), surgical complications and side effects of immunosuppressive medication.

1.6 Complications of ESKD

Multiple complications including infectious complications, which derive mostly from blood stream infections due to the vascular access and cardiovascular complications may arise during the course of hemodialysis treatments.

1.6.1 Cardiovascular complications

Cardiovascular mortality is more than 50% higher in patients with GFR less than 60ml/min/1.73m^2 and over 60% higher in patients with micro-albuminuria compared to people without any CKD, (83, 84) with increasing risk of myocardial infarction as GFR declines and albuminuria increases. Since CKD patients are commonly excluded and underrepresented in large clinical trials (85), results of studies and application of assessment tools cannot be generalized. Interestingly, as CKD progresses and cardiovascular disease complications become more common, non-atherosclerotic events, such as left ventricular hypertrophy, arrythmias, sudden cardiac death or hemorrhagic stroke contribute more to cardiovascular events than atherosclerotic cardiovascular disease (86). Also, the use of implantable cardioverter defibrillators, which is the mainstay of prevention of sudden cardiac death in patients with heart failure with reduced ejection fraction and a left ventricular ejection fraction <35%, has been questioned in ESKD as their use was associated with increased antitachycardia pacing/shocks and mortality compared to patients without ESKD (87).

Current guidelines recommend antiplatelet therapy algorithms, based on the general population, but despite being effective in terms of reducing myocardial re-infarction, it

seems to bear increased risk of adverse events, including more major bleeding compared to non-CKD patients (88). Statins seem to reduce all-cause mortality and cardiovascular events in patients with CKD, not on dialysis (89).

For patients on dialysis, initiation of statin therapy is not routinely recommended since the major trials regarding this topic did not show clinical benefits with statins (90-92). If patients already on statin therapy are started on dialysis continuation is currently recommended.

1.6.2 Complications during hemodialysis

Common complications include intradialytic hypotension, intradialytic hypertension, myocardial stunning, arrhythmias, seizures, muscle cramps, dialyzer reactions, hemolysis, hemorrhage, air embolism, or unspecific complications such as nausea and vomiting, headache, chest and back pain (93), see also table 3,

Emergency	Pathogenesis	Clinical presentation	Management/Prevention
Intradialytic hypotension	High ultrafiltration rate, false dray-weight	Paleness, light-headedness, fainting, vomiting, cramps	Accurate dry weight assessment, prevention of high interdialytic weight gain, no intradialytic food consumption
Intradialytic hypertension	Chronic volume overload, high vascular resistance, high dialysate sodium	Headache	Dry weight reduction, use of less dialyzable antihypertensive drugs
Arrhythmias	Electrolyte shifts, left ventricular hypertrophy	Dyspnea, fainting, death	Manage cardiomyopathy, minimize arrhythmic triggers, evaluate for risk/benefit ratio of implantable devices
Dialyzer reaction	Hypersensitivity reaction	Type A: pruritus, urticaria, dyspnea, vomiting usually within first half an hour of HD treatment. Type B chest pain, back pain or vomiting but less severe and later during HD session	Type A: stop dialysis without blood return to patient, intravenous fluids, epinephrine, corticosteroids. Type B: Change dialyzer
Hemolysis	High blood flow, high negative arterial pressures, malposition of needle, kinked tubing	Vomiting, back pain, chills, hypertension, arrhythmias, dyspnea Cherry red blood in the HD circuit.	Stop HD without blood return; Dialyze for hyperkalemia.
Hemorrhage	Rupture of Fistula of graft at aneurysm, disconnection, venous needle dislodgement	Blood loss, paleness, light-headedness, hypotension, cardiac arrest	Stop bleeding, intravenous fluids, blood transfusion
Air embolism	Air enters the bloodstream through dialysis access points which leads to pulmonary edema, hypoxia and eventually in cardiac arrest or stroke	Altered mental status, neurologic deficits, stroke, death	Stop HD without blood return; Trendelenburg positioning

Table 3: Complications during hemodialysis.
Adapted according to Greenberg et Choi (94). HD Hemodialysis

1.6.2.1 Intradialytic hypotension

Intradialytic hypotension (IDH) is reported to be the most common complication during dialysis, occurring in about 11% of dialysis sessions in a recent meta-analysis (95). There are different definitions used for IDH. Most recommendations include an intradialytic blood pressure decline in absolute or relative values and some definitions include the presence of symptoms such as muscle cramps, abdominal pain or nausea, dizziness, yawning, anxiety or fainting and/or the need for an intervention, such as Trendelenburg positioning, fluid bolus administration, reduction of ultrafiltration or blood flow rate or treatment stop (96).

KDOQI (Kidney Disease Outcomes Quality Initiative) clinical practice guidelines (97) and a Japanese society of Dialysis Therapy Guidelines (98) define IDH as a decrease in systolic blood pressure ≥20 mmHg or ≥ 30mmHg, respectively, or a decrease in mean arterial pressure by 10 mm Hg associated with symptoms that include abdominal discomfort, yawning, sighing, nausea, vomiting, muscle cramps, restlessness, dizziness or fainting and anxiety.

1.6.2.2 Myocardial stunning

Myocardial stunning describes a phenomenon of transient myocardial ischemia with left ventricular dysfunction, which has been described in the dialysis and non-dialysis population. This dysfunction persists prolonged even after return to regular perfusion of the coronary arteries and is thought to be a cause of heart failure (99, 100).

1.6.2.3 Dialysis-induced ischemia

Early studies in the field of HD found silent ST segment depression on ECG in patients during HD (101) and more recently, using Technetium (^{99m}Tc) sestamibi single-photon emission computed tomography (102), significant perfusion defects, which do not necessarily correlate with ST segment deviations were observed. Similarly, a positron emission tomography measuring myocardial blood flow during dialysis showed, that HD precipitates reductions in flow consistent with the development of myocardial ischemia, even in absence of significant coronary artery disease (103), which is probably related to ultrafiltration (104) and hemodynamic instability.

1.6.3 Acute myocardial infarction

Acute myocardial infarction (AMI) is classified in five different types, according to the fourth universal definition of AMI (105). The most common types are type 1 and 2 which are caused by ischemia due to a primary coronary event or due to an increased oxygen demand, respectively.

Type 1 is defined as the detection of a rise and/or fall of cTn values with at least 1 value above the sex-specific 99th percentile upper reference limit (URL), and at least one of the following: symptoms of acute myocardial ischemia, new ischemic ECG changes, the development of pathologic Q waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology, or the identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy. The definition of a type 2 myocardial infarction includes the detection of a rise and/or fall of cardiac cTn values with at least 1 value above the sex-specific 99th percentile URL and evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute coronary atherothrombosis in addition to the symptoms, ECG findings, and imaging criteria as mentioned above for type 1 myocardial infarction (105). The outcome of AMI is poor among the hemodialysis population with mortality rates up to 73% in two years after AMI (106).

1.6.3.1 Diagnosis of AMI in the dialysis population.

The diagnosis of acute coronary syndromes is based on symptoms, electrocardiogram and cardiac biomarkers (97). Regrettably, dialysis patients have often been excluded in studies which established optimal cut-off for cardiac troponin levels for diagnosis of AMI (107). The current ESC guidelines (108) do not contain a statement regarding diagnostic information of cardiac troponin in ESKD patients, which might be due to large inter-individual differences which limit the utility of fixed cut-off levels. This leaves the clinician with the challenging task of interpreting cardiac troponin levels in the acute setting without established reference levels. Furthermore, there is also no statement of the 2005 KDOQI Clinical Practice Guidelines for Cardiovascular disease in dialysis patients about use of cardiac troponins in the acute setting of suspicion for myocardial infarction in ongoing hemodialysis treatment at time of presentation (97).

The Standardized Outcomes in Nephrology Group— Hemodialysis (SONG-HD) Working group recommended that in HD patients with an initial cTn value above the 99th percentile

URL, a rise and/or fall of more than 20% is suggestive of an AMI in addition to clinical criteria (109).

1.6.3.1.1 *Comparison to general population*

Diagnostic evaluation regarding acute cardiac events is challenging in HD patients as, compared to non-CKD patients, patients on chronic dialysis presenting with acute myocardial infarction (AMI) are less likely to present with typical chest pain (<20% of patients)(110) and ST elevation (<20%) (111) or depression but rather with non-specific ST deviations (112). Furthermore, adding to the complexity, a third of patients have ECG abnormalities at baseline (111).

Thus, diagnosis of acute myocardial infarction more heavily relies on measurement of biomarkers such as cTn. Problematically, in stable HD patients without evidence of AMI, cTnT are in 50%–90% and cTnI in 5%–25% above the 99th percentile URL (113-115).

Finally, in an analysis of the Global Registry of Acute Coronary Events (GRACE) patients on dialysis were more likely to present with non-ST-segment elevation myocardial infarction and had significantly higher in-hospital and 6-month mortality (116).

1.6.4 Cardiac troponins

1.6.4.1 Physiology and basics of cardiac troponins

As components of the contractile apparatus of myocardial cells, cardiac troponins are expressed almost exclusively in the heart. The basic structure necessary for muscle contraction is the sarcomere, which consists of a thick part (myosin) and a thin part (actin), where one myosin is surrounded by six actin filaments. Sarcomeres are then assembled to myofibers. The actin filament is embedded in a long, coiled protein, tropomyosin, which prevents myosin adherence to actin. Within tropomyosin proteins are complexes of a heterotrimeric troponin which is comprised of the subunits Troponin T, I and C. While Troponin T acts as an anchor of the troponin complex to the tropomyosin structure, troponin C is responsible for binding calcium ions, and, when calcium flux occurs, this leads to a conformational change of Troponin I which exposes the actin filament to myosin. There are multiple isoforms including slow- and fast skeletal and cardiac troponins (117, 118).

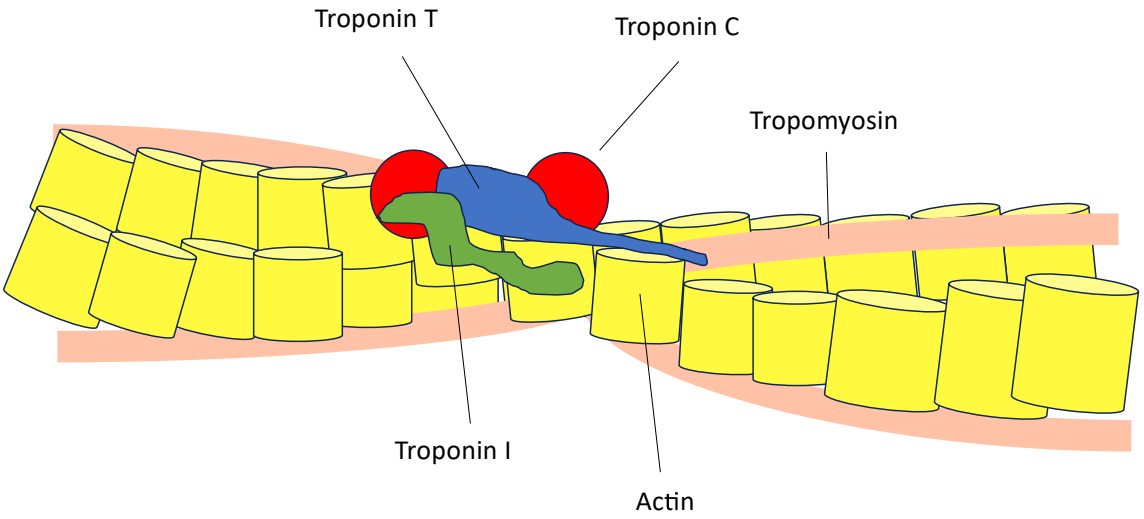

Figure 4: Structure of cardiac troponins

The biochemical properties of cTn vary, as not only the molecular weights of cTn differ with cTnT and an estimated weight of 36kDa and cTnI of 24-26kDa, but also the configuration as cTnI is arranged as four α helices, which are intercalated by flexible regions while cTnT is divided into three structural domains (119). The remaining biochemical properties are poorly described, and different isoelectric points for cTnI were described (120).

1.6.4.2 Release of cardiac troponins

An elevation of cTn levels is indicative of myocardial injury but does not allow to conclude which pathomechanism leads to cTn release. Myocardial injury might be due to increased turnover of myocardial cells, apoptosis, cellular release of cTn degradation products, increased cellular wall permeability, the formation and release of membranous blebs, or due to myocyte necrosis (121). Furthermore, there is also a fraction of cTnI (5%) and cTnT which is not compartmented in myofibrils but lies unbound in the cytosol, acting as a storage pool to be released first in ischemia, before myocyte necrosis occurs (122).

Besides myocardial injury related to acute myocardial ischemia or oxygen supply/demand imbalance, there are multiple other causes including sepsis, pulmonary embolism, stroke, amyloidosis, chemotherapeutic agents and, importantly, CKD (105).

Also, distinct to a rise after cardiac injury, there might also be a release of cTnT from skeletal muscle cells, as recently shown in a study with hereditary and acquired skeletal myopathies (123) with elevated cTnT in 69% patients but only in 4% of cTnI, and release of cTnT and to a lesser extent of cTnI after intensive exercise (124).

1.6.4.3 Comparison of cTnI and cTnT in diagnosis of acute myocardial infarction.

Although the APACE study showed good correlation (r=0.89) between hs-cTnT (high-sensitivity cardiac Troponin T; Roche Diagnostics) and hs-cTnI (high-sensitivity cardiac Troponin I, Abbott) with AUROC for diagnostic accuracy of 0.93 for both assays, other studies (125, 126) showed lower correlation between the assays which points out that these assays might not be used interchangeably and reference values depend on age, sex, body mass index or comorbidities. When using both assays, this only marginally improves discrimination of diagnosis of an AMI (127).

Whether either one of these markers – cTnT or cTnI – outperforms the other is up to debate since hardly any studies have studied both biomarkers in the acute setting (128). Both troponins seem to circulate in complexes and free forms (129), but there are also antibodies which might interfere with assays.

1.6.4.4 Measurement of cardiac troponins

1.6.4.4.1 *Assays*

A variety of assays are commercially available. Currently, high-sensitivity cTn (hs-cTn) assays are used, which are required to have a coefficient of variation ≤10% at the 99th percentile URL and concentrations below the 99th percentile URL must be detectable in more than 50% of a healthy population of interest (130).

The fifth-generation cTnT assay (Roche Diagnostics) assay hs-cTnT (high sensitivity cTnT assay) is using fragment antigen binding (FAB) portions of 2 cTnT-specific mouse monoclonal antibodies (mAb) against epitopes of the central region of human cTnT with a 99th percentile URL of 30ng/L (131).

CTnI assays are using mAb specific to different epitopes of cTnI. Since different forms of the cTnI antigen have been used as standards or calibrators, different results and reference levels exist, according to the manufacturers and there is no standardization yet. CTnI is influenced by proteolytic degradation, phosphorylation or complexing with other molecules

(130). Most cTnI in blood occurs as cTnI-cTnC complex, thus introduction of anti-cTnC antibodies might be useful in diagnosis (131).

The 99th percentile upper reference limit is the decision level for myocardial injury and is different for each assay, but there is no consensus for how the 99th percentile URL is defined with substantial variations with increasing age or sex (105).

1.6.4.4.2 *Dynamics of cardiac troponins*

After an initial ischemia with ST elevation, followed by percutaneous reperfusion, there is a heterogeneity of cardiac biomarkers regarding their dynamic. In a previous study (132), a first peak of cTnT (Roche) was observed after 11.8h (10.4-13.3) and after 11.8h (10.7-11.8) for cTnI from Abbott, followed by a nearly log linear decrease for cTnI in contrast to cTnT, which appeared with a biphasic shape curve marked by a second peak at 76.9h (69.5-82.8) and a significantly slower decrease than other markers. Furthermore, cTnI seems to increase more rapidly than cTnT in a population with non-ST-elevation myocardial infarction (133). Another study found higher levels of cTnI than cTnT and a fast monophasic reduction of cTnI and a relatively slow, progressively decreasing reduction of cTnT. There seems to be a difference in absolute, relative, and rate of change in troponin concentrations with highest values in patients with type 1 myocardial infarction but troponin concentrations alone are insufficient to distinguish type 1 myocardial infarction from other causes of myocardial injury or infarction (134).

Furthermore, animal studies (135) have shown that cTnI is degraded and released faster than cTnT from necrotic cardiac tissue, which may be the reason why cTnI reaches higher peak concentrations and returns to normal concentrations faster in patients with AMI.

There is also a intraindividual variability due to fluctuation of about 7.9% (136) for weekly measurements in HD patients but also higher changes were observed in HD patients (hs-cTnI +37% – -30%; hs-cTnT +25% – -20%) (113) .

1.6.4.4.3 *Etiology of elevations in hemodialysis patient*

A large proportion of HD patients show chronically elevated levels of cardiac troponins, with baseline pre-dialysis elevations in more than 70% of patients above reference range (137). These higher levels also translate to clinically relevant outcomes with considerably increased mortality risk in those patients (138). The cause of elevated baseline troponins in ESKD patients besides acute myocardial infarction, include cardiac pathologies encountered

in the general population such as left ventricular hypertrophy (139) but also ESKD-specific phenomena such as myocardial stunning (140), volume overload (141), and decreased clearance (142). Furthermore, during hemodialysis treatment, patients often sustain intradialytic complications, most commonly hemodynamic alterations with hypotension, but also frequently anginous discomfort or arrythmias (93).
The elevated enzymes seem to be stable with little fluctuation in observational periods over several months in the individual patient, thus annual measurements can be used as some sort of reference points (143).

1.6.4.5 Clearance

1.6.4.5.1 *Extracorporeal*

There is a large heterogenicity in the literature, regarding cTn kinetics during HD and a summary of most available studies of intradialytic troponin kinetics is provided in table 4. Some studies found a decrease in cTnT levels after HD (144-147), while others found an increase (143, 148, 149) or stable levels (146, 150-152).
Regarding cTnI levels, some studies found a decrease (137, 147, 149), some an increase (137, 153) and some found stable levels (145, 150, 152, 154-156).

Most importantly, the majority of these studies did not consider different membrane properties. One study found that high-flux membranes cleared cTn more efficiently than low-flux membranes (147) and another found higher levels of cTnI after low-flux compared to high-flux membranes (157). Some studies used high-flux dialyzers (137, 150, 158) or low-flux dialyzers (153) only and provided no head-to-head comparisons. Most of the studies in the literature provided no statement of the used membranes. Treatment was not standardized and treatment characteristics, such as dialysate and blood flow rate, or ultrafiltration rate, which are main determinants of clearance, were provided in hardly any study. Only one study corrected results for ultrafiltration induced hemoconcentration (143). Some studies were conducted in the previous century and used cTn assays of the past generation and, moreover, cTnI assays, as mentioned in the chapter 1.6.4.3.1 “Assays” differ depending on the monoclonal antibody used and cannot be used interchangeably.
Regarding HDF, data is scarce, but one study found that HDF had a significant effect on cTnT concentrations after 4 hours and 8 hours of HDF and also cTnI was significantly decreased after HDF8 but not HDF4 (150). In another study, cTnT decreased by almost a

fourth after treatment (158). In a recent systematic review, summarizing the available studies on pre to post cTnT levels, low-flux was found to increase the cTnT concentration and HDF was found to decrease the concentration whereas results for high-flux HD were heterogeneous (159).

Study	Year	Population	HD modality	Measurements	Troponin isoform and assay (as described in the study)	Main results
Assa et al.(153)	2013	90 asymptomatic chronic HD patients	4h low-flux HD (F8, Fresenius)	Pre-post HD	- cTnI (ARCHITECT STAT assay)	- cTnI increased significantly after HD
Cardinaels et al.(150)	2015	13 asymptomatic chronic HD patients	4-h HD 8-h HD 4-h online HDF and 8-h online HDF. High-flux FX80 and FX800 dialyzers (Fresenius)	Pre-Post HD	- cTnT (Roche Diagnostics) - cTnI (ARCHITECT hs-cTnI assay, Abbott Diagnostics)	- No significant differences post-dialysis for cTnT and cTnI concentrations after 4 and 8 hours of HD - HDF had a highly significant effect on cTnT and cTnI concentrations especially after 8 hours of HDF.
Castini et al.(154)	2017	30 asymptomatic chronic HD patients	Not reported	Pre-post HD	- cTnI (Vitros ES assay, manufactured by Ortho Clinical Diagnostics, and the Vitros 5,600 System)	- HD did not affect cTnI levels - The diagnostic accuracy of cTnI assays in ESRD patients is not affected
Chen et al.(144)	2017	10 asymptomatic chronic HD patients	Not reported	Pre dialysis, 2 hours after HD start and immediately post HD	- cTnT (Fifth generation immunoassay Roche Diagnostics)	- 2 hours after HD initiation, cTnT decreased by 10.7% - 4 hours after HD initiation 12% decline
Conway et al. (143)	2005	75 asymptomatic chronic HD patients	Not reported	Pre-post HD	- cTnT (Third generation' ECLIA assay on an E170 analyzer Roche Diagnostics)	- Elevated baseline cTnT - Median cTnT concentration was significantly greater post- than pre-dialysis - No significant difference after correction for the effect of haemoconcentration
Deléaval et al.(145)	2006	50 asymptomatic chronic HD patients	Not reported	Pre-post HD	- cTnI (Dimension® RxL "Improved method" assay, Dade Behring) - cTnT (Elecsys® "Third generation" assay, Roche Diagnostics)	- cTnT levels slightly but non-significantly reduced during dialysis - No changes were observed for cTnI
Frankel et al.(151)	1996	16 asymptoamtic chronic HD patients	Not reported	Pre-post HD	- cTnT (ES 300, Boehringer Mannheim)	- 71% of patient with CRF undergoing hemodialysis with no significant differences between pre- and post-dialysis values
Levi et al.(146)	2015	43 asymptomatic chronic HD patients	n.a.	Pre dialysis and after 3 Sessions over a one-week period	- cTnT (Type of assay not available)	- 11.31 pg/mL decrease in hs cTnT - Ten patients (23%) were found to have no decrease or an increase in troponin levels after hemodialysis.
Lippi et al. (147)	2008	34 asymptomatic chronic HD patients	High-flux vs. Low-flux HD.	Pre-post HD	- cTnT (Third-generation ECLIA assay on an E170 analyzer, Roche Diagnostics GmbH, Mannheim, Germany),	- High-flux membranes cleared both troponins more efficiently from circulation than low-flux membranes.

					- cTnI (Dade Behring Dimension chemistry system, Newark, NJ)	
Löwbeer et al.(152)	1999	36 asymptomatic chronic HD patients	Not reported	Pre-post HD	- cTnT (Enzymun-Test Troponin-T on ES 300 system (Boehringer Mannheim GmbH, Mannheim, Germany) - cTnI (Opus, Behring)	- No significant difference from pre to post HD
Šavuk et al. (157)	2021	122 asymptomatic chronic HD patients	Low-flux and High-flux membranes	Pre-post HD	- N.a.	- No significant change of cTnI using high-flux membranes but cTnI levels were higher after HD with low-flux membranes
Tarapan et al. (137)	2019	100 asymptomatic chronic HD patients	HD or online HDF using high-flux dialyzer	Pre-post HD	- cTnI (ARCHITECT STAT High Sensitive Troponin-I assay, Abbott Diagnostics)	- cTnI levels were reduced after HD but in 25% of HD patients there was a significant increase - Hb higher than 11 g/dL dialysate flow more than 500 mL/min were associated with cTnI elevation - No specification which modality affected more than the other
Tun et al. (155)	1998	144 asymptomatic chronic HD patients	Not reported	Pre-post HD	- cTnI (ACCESS Troponin Test)	- No statistically significant differences in serum levels of cardiac troponin I before and after dialysis.
Urso et al. (156)	2004	16 asymptomatic chronic HD patients	Online HDF vs. Standard HD	Pre-post HD	- cTnI (Dimension, Dade Behring)	- Troponin I was not significantly different in pre vs post-dialysis, both in standard HD and on-line HDF
Wayand et al. (149)	2000	59 asymptomatic chronic HD patients	Not reported	Pre-post HD	- cTnT (Enzymun® Troponin T assay on an ES 700 analyzer, Roche) - cTnI (Stra®® II analyzer, Dade Behring)	- Increases of cTnT and decreases cTnI from pre- to post HD
Wolley et al. (158)	2013	78 asymptomatic chronic HD patients	Hemodiafiltration on Fresenius 5008 machines using high-flux membranes	Pre-post HD	- cTnT (Roche Diagnostics, Mannheim, Germany)	- Hemodiafiltration reduced cTnT by a median of 24%
Wongcharoen et al. (148)	2021	200 asymptomatic chronic HD patients	Not reported	Pre-post HD	- cTnT (Roche Diagnostics) - cTnI (ARCHITECT i2000SR system, Abbott Diagnostics)	- cTn T level increased significantly after HD - No significant change of cTnI after hemodialysis.

Table 4: Overview of studies examining intradialytic troponin kinetics.
HDF Hemodiafiltration, HD Hemodialysis, cTnT cardiac troponin T, cTnI cardiac troponin I

A consensus statement from the SONG-HD MI Expert Working group concluded, that as of the writing of this statement, there was insufficient evidence that there is a substantial effect of standard dialysis on cTn to alter the diagnosis of AMI (109).

1.6.4.5.2 *Renal*

Reduced kidney function is often observed with elevated cTn levels, with consistently high levels of cTn in CKD patients on hemodialysis and peritoneal dialysis (138).
In a study, examining over 2000 ambulatory CKD patients with no history of cardiovascular disease, 43% of patients had cTnT levels above the conventional URL and in participants with an eGFR < 30 mL/min/1.73 m^2, 68% had concentrations above the URL. The 99th percentile for cTnT for the overall study population was 126 (95% CI, 100-144) ng/L and with every 15 mL/min/1.73 m^2 decrement in eGFR, there was a more than 40% higher threshold for the 99th percentile cTnT (1.45 [95% CI, 1.31-1.60]) (160).
It is not entirely clear, if reduced clearance or rather increased cardiac injury as part of chronic kidney disease is the underlying mechanism for the elevation. At low levels of cTnT, renal clearance contributes to clearance of cTnT, with declining importance as levels rise (161).

1.6.4.5.3 *Extrarenal (hepatic)*

As previous studies have shown that cTnT is cleared in part by glomerular filtration but only explain a 2-3 fold elevation of cTnT, a subsequent animal study using labelled cTn showed that substantially extrarenal clearance of cTn occurs, and mainly occurs in the liver (162). At high cTnT levels, typically after a myocardial infarction extrarenal clearance appears to be predominant, possibly also due to scavenger receptor-mediated endocytosis (161).

AIMS

In this study we aimed to explore troponin kinetics in patients with end stage kidney disease during hemodialysis sessions with different classes of membranes.

2 Methods

2.1 Study subjects

Patients at least 18 years of age with end stage renal disease undergoing chronic hemodialysis for at least 3 months at first study dialysis treatment were eligible for study participation. Patients were excluded if no informed consent could be obtained, or if female patients were pregnant. Baseline characteristics were collected, including known cardiovascular disease, previous myocardial infarction, history of diabetes mellitus or arterial hypertension, smoking status, previous echocardiography regarding left ventricular hypertrophy as well as residual renal function, as defined as last known residual diuresis.

2.2 Objectives

The primary aim of the trial was to evaluate the kinetics of high sensitivity cTnT and cTnI after 1 hour of dialysis relative to baseline for different dialysis modalities. Secondary outcomes of the trial included comparisons of the relative change of high sensitivity cardiac troponin T from baseline to after completion and the relative change of high sensitivity cardiac troponin I from baseline to after 1 hour and after completion of hemodialysis treatment for different dialysis modalities, to compare the absolute differences of high sensitivity cardiac troponin T and high sensitivity cardiac troponin I from baseline to after 1 hour and after completion of hemodialysis treatment for different dialysis modalities and to determine, whether the rate of IDH is associated with less pronounced changes of troponin T and I values due the possibly increased release of cardiac enzymes.

2.3 Treatments

After informed consent was obtained, patients were randomized to a treatment sequence (see figure 5) with different membranes at 4 consecutive mid-week dialysis sessions. Membranes used in the study included, Theranova 400 (Baxter, Deerfield, Illinois, USA; representing a MCO membrane), FX10 Dialyzer (representing a low-flux Dialyzer) and FxCor Diax 800 (representing a high-flux Dialyzer; both Fresenius Medical Care, Bad Homburg, Germany). A summary of the dialyzer specification is provided in table 5. Dialyzer choice was based on availability and performance on middle-molecule removal compared to other dialyzers in this class (163). All treatments were performed on the Fresenius 5008 or 6008 system.

Dialysis treatment was standardized: dialysate temperature was set 1.0°C below the patient's body temperature, but not below 35.5°C, to achieve better hemodynamic stability, dialysis fluid composition was standardized to a concentration of calcium of 1.25mmol/L, bicarbonate of 30mmol/L, and a variable potassium and sodium concentration, depending on the patients' plasma potassium and sodium levels. Ultrafiltration volume was set according to the patient's prescription. Patients were treated with a total of 4 hemodialysis sessions. Blood flow rate, dialysate flow rate and effective dialysis time were measured. HDF was performed as post-dilution HDF.

Parameter	**Membrane**		
	FX 10*	**FxCor Diax 800***	**Theranova 400§**
Ultrafiltration coefficient (ml/h x mmHg)	14	62	48
K_0A Urea	n.a.	1365	1482
Clearance (mL/min)			
Urea	261	291	282
Creatinine	231	277	269
Phosphate	210	267	261
Vitamin B12	138	217	207
Inulin		156	161
Beta-2-microglobulin (±SD)	n.a.	55.1(3.10)	84.7(3.18)
Effective surface area (m^2)	1.8	2.0	1.7
Membrane material	Polysulfone	Polysulfone	Polyarylethersulfone-polyvinylpyrrolidone blend
Membrane characteristic			
Wall thickness (µm)	n.a.	n.a.	35#
Inner diameter (µm)	185	210	180
Sieving coefficient			
Beta-2-Microglobulin	n.a.	0.9	1.0
Albumin	n.a.	<0.001	0.008

Table 5: Dialyzer characteristics used in the study

Clearance: QB: (300ml/min); The in vitro performance data were obtained with QD = 500ml/min; T=37°C (ISO8637); The ultrafiltration coefficients were maintained using human blood in case of Fresenius products and bovine blood in terms of Baxter products, both manufactures used Hct = 32% and protein content of 6%
*Fresenius' product information (164)
§ Baxter Theranova 400 product information (165)
#Data derived by Kirsch et al.(58)

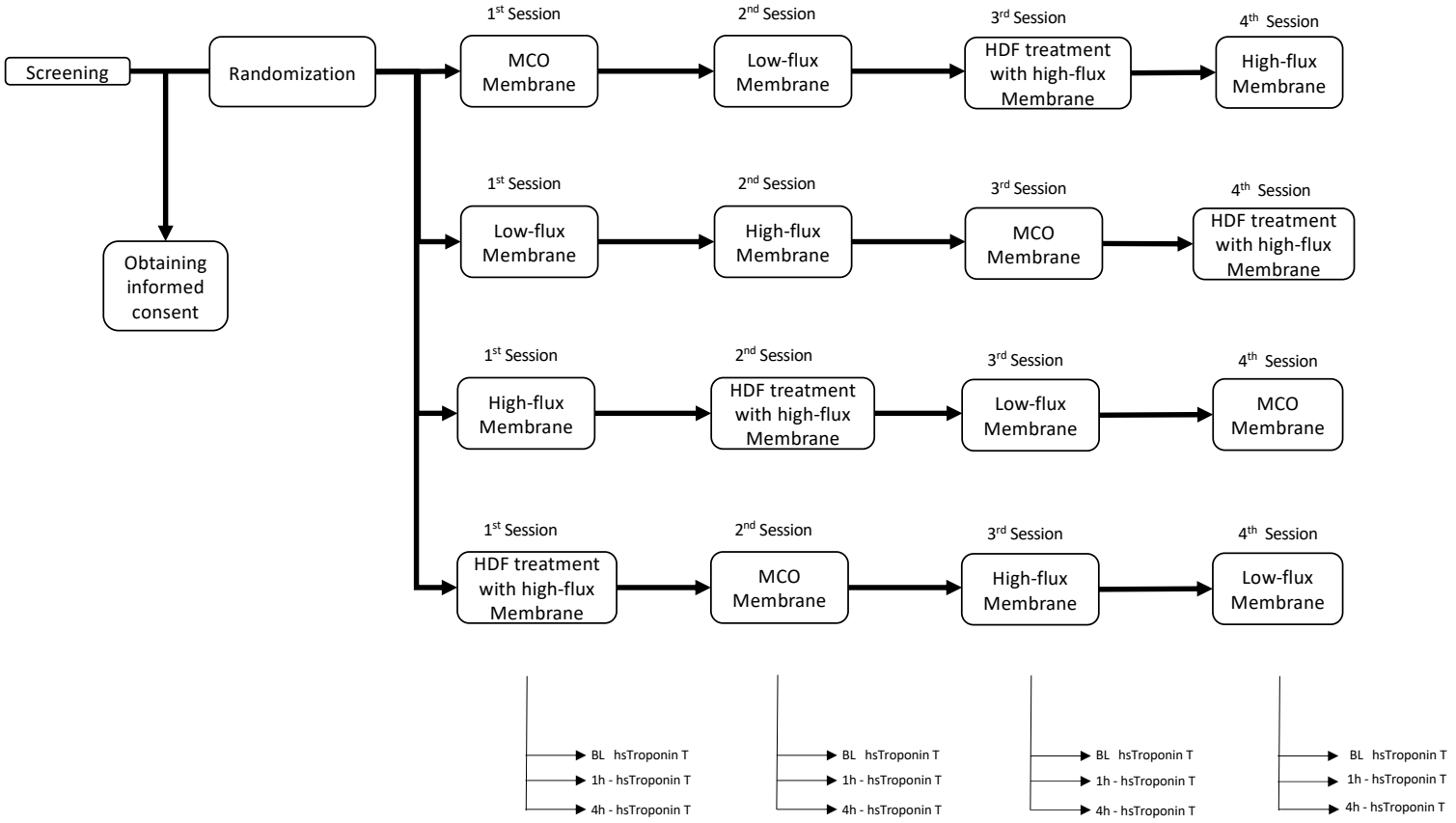

Figure 5: Study Flowchart

HDF Hemodiafiltration, MCO medium cut-off

2.4 Blood samples and measurements

Blood samples were taken before HD treatment, after 1 hour, as well as post-dialysis from the arterial access port of the hemodialysis arteriovenous set. The time period of 1 hour was chosen, because of the commonly used 1-hour rule in or out algorithm in the ACS ESC guidelines (166). We only performed analyses during mid-week session, first, because hemodynamic stability is most often compromised during the first treatment of the week, due to the need of large volumes of ultrafiltration and, second, because we assumed that cTnT levels reach a steady state 48 hours after the last dialysis session. As we only evaluated single mid-week sessions, the total duration of the study for all 4 sessions was 2 weeks. To account for the effect of hemoconcentration, hematocrit was measured at all time points.

Troponin diagnostics were performed using the Elecsys® Troponin T-hs (Roche Diagnostics GmbH, Mannheim, Germany) (with a coefficient of variation <10% at the 99th percentile upper reference limit (URL) (167) and Alinity I STAT High Sensitive Troponin-I Reagent Kit (Abbott Ireland Diagnostics Division, Lisnamuck, Longford, Ireland)(168), both meeting precision requirements according to the Fourth Universal Definition of Myocardial Infarction for high-sensitivity troponin assays) (169).

Information for dialysis personnel was handed out for each study person, which participated in treatment of patients, see supplemental (S1).

Intradialytic hypotension was defined as a drop in blood pressure ≥30 mmHg with the occurrence of symptoms (e.g., nausea, headache, dizziness) or a resulting therapeutic intervention (e.g. stop of UF or leg elevation), as recommended by currently valid guidelines (98) and as this is the routine approach in the dialysis unit in which the study was conducted. Blood pressure drops ≥30mmHg without symptoms or therapeutic intervention were defined as simple blood pressure decreases.

2.5 Randomization

Patients were randomized using the web-based randomization system "Randomizer" (www.randomizer.at) developed at the Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz. Randomization 1:1:1:1 in one of the aforementioned sequences (William's design), see table 6.

	Session 1	Session 2	Session 3	Session 4
Sequence 1	MCO	Low-flux	HDF	High-flux
Sequence 2	Low-flux	High-flux	MCO	HDF
Sequence 3	High-flux	HDF	Low-flux	MCO
Sequence 4	HDF	MCO	High-flux	Low-flux

Table 6: Study Design and Randomization

MCO medium cut-off, HDF hemodiafiltration

2.6 Data analysis

After concentrations were measured, data was collected in password protected excel files and then extracted to the statistical program to perform the statistical analysis, as described below in chapter 2.7.

Reduction was calculated with relative and absolute differences because, in routine clinical practices, these are the most used measures. Absolute changes with either increase or decrease were analysed as both are important for diagnostic algorithms.

The concentrations were further normalized to baseline concentration and ratio was termed reduction, abbreviated by the symbol R=c(t)/c(t=0). The baseline R is 1 by definition, an increase was indicated by R>1, a decrease by R<1.

Endpoints were further corrected for ultrafiltration-induced hemoconcentration (170):

Equation 11: Correction for hemoconcentration

$$hp = \frac{H1}{H0} \times \frac{100 - H0}{100 - H1}$$

Factor hp…hemoconcentration

H0…Hematocrit at baseline

H1… Hematocrit at sampling time points at 1 hour, respectively post HD.

2.7 Statistical analysis

In a recent publication, a relative reduction in YKL-40 for MCO membrane, high-flux membrane and HDF treatment was investigated in 20 patients. For MCO a relative reduction (pre to post treatment session of about 4 hours) of 63.6% (2.2%), for high flux: 29.8% (2.2%) and for HDF: 44.8% (2.2%), were observed (58). The molecular weight of cTnT is similar to the molecular weight of YKL-40 (hs-Troponin T: 36-39kDa and YKL-40: 40kDa).

Therefore, similar results were expected (i.e., difference between MCO and HDF of about 20% after 4 hours). Since, in this study, the difference after one hour was the primary focus, smaller differences between MCO and HDF were assumed (between 5%-10%) with a standard deviation of 5% (summarized below). Based on a sample size calculation with an alpha of 1.67%, a power of 90% and a two-sided paired t-test, 20 subjects needed to be included. Assuming a drop out of 4 patients, we aimed to recruit 24 patients.

The primary endpoint (relative change in cTnT) was analysed using a linear mixed effects model with subject as random effect and sequence (1-4), period (1-4) and treatment (1-4) as fixed effects. The differences between the treatments MCO versus low flux, MCO versus high flux and MCO versus HDF were presented as least square mean difference with the corresponding 95% confidence interval. The least square mean, which is a statistical technique used to estimate the population means of different groups or levels within a dataset and commonly used in linear regression models, was used to improve the handling of unbalanced data, adjustment for covariates and facilitation of post hoc comparisons as it is more robust compared to means.
Following group comparisons as primary aim were be performed: MCO membrane versus low flux membrane, MCO membrane versus high flux membrane and MCO membrane versus HDF treatment with high flux membrane, therefore the significance level was set to alpha=0.0167 (Bonferroni correction).

The primary outcome measure was assessed as the relative change from baseline (pre-treatment) to after 1 hour of hemodialysis in high sensitivity cTnT.
The secondary endpoints (absolute and relative differences for high sensitivity cardiac troponin T and I) were analyzed in the same way as the primary endpoint. A two-sided p-value of <0.05 was considered to indicate statistical significance. Associations of IDH with changes of cTnI and cTnT values were explored descriptively.
Secondary outcome measures were assessed as the relative change of high sensitivity cTnT from baseline to after completion of hemodialysis, the relative change of high sensitivity cTnI from baseline to after 1 hour and after completion of hemodialysis and the absolute differences of high sensitivity cTnT and cTnI from baseline to after 1 hour and after completion of hemodialysis.
The analysis was performed with SAS software version 9.4 (SAS Institute, Cary, NC). The data was presented as summary tables and, where appropriate, as plots. Clinical and

demographic baseline parameters was summarized descriptively. Continuous variables were summarized as means, standard deviation, median, minimum, and maximum or interquartile range, for categorical data frequencies and relative frequencies were used.

3 Results

3.1 Baseline characteristics

In total, 22 patients were recruited for the study, but one patient withdrew informed consent before first study visit and one patient could not participate due to medical reasons. Initially, we included 20 patients in our study, but one patient was excluded from final analysis due to NSTE-ACS during dialysis with substantial distortion on the absolute values of the results, thus a per protocol analysis including 19 patients was conducted, on which the following sections are focused.

The study population included 47.4% female, with a mean age of 65.5± 13.4 years and a median of 19 months (min. 3, max. 165) on dialysis. Sixty-eight percent had a history of coronary artery disease (CAD) and 36.8% had previously suffered an AMI. Most patients had multiple comorbidities present, with arterial hypertension and left ventricular hypertrophy being the most common.
Patients' baseline characteristics are provided in table 7.

Characteristic	All patients (n=19)
Sex (n, %)	
Male	10 (52.6%)
Female	9 (47.4%)
Age (years) (mean±SD)	65.5± 13.4
Dialysis vintage (days) (median, min and max)	19 months (min. 3, max. 165)
Comorbidities (n, %)	
Cardiovascular disease	13 (68%)
Diabetes mellitus	6 (31.6%)
Arterial Hypertension	17 (89.5%)
Left ventricular hypertrophy	14 (73.7%)
Previous myocardial infarction	7 (36.8%)
Smoking	12 (63.2%)
Non-smoker	1 (5.4%)
Present	6 (31.6%)
Former	
Underlying renal disease (n, %)	
Diabetic kidney disease	3 (15.8%)
Hypertensive/Vascular	4 (21.0%)
Glomerulonephritis	2 (10.6%)
Cystic Kidney Disease	3 (15.8%)
Other/Unknown	7 (36.8%)
Type of access (n, %)	
Catheter	16 (84.2%)
Fistula	3 (15.8%)
Residual renal function (n, %)	
≥ 500mL/day	6 (31.6%)
< 500mL/day	13 (68.4%)

Table 7: Patient baseline characteristics

Table adapted from (1) n, number of studies

3.2 Treatment characteristics

Mean ultrafiltration volume, treatment time, blood- and dialysate flow rate were similar in between groups. In total, 4 episodes of IDH occurred and 19 episodes of blood pressure decreases of >20mmHg without any associated symptoms. Treatment characteristics are provided in table 8.

	Modality							
Characteristic	**High-flux**		**Low-flux**		**MCO**		**HDF (high-flux)**	
Ultrafiltration volume (millilitres), [Mean] [SD]	n=19	2657.89 (± 1055.31)	n=19	2405.26 (± 992.46)	n=19	2335.79 (± 993.82)	n=19	2262.11 (± 984.30)
Treatment time (minutes), [Mean] [SD]	n=19	232.79 (± 20.42)	n=19	234.95 (± 22.68)	n=19	240.47 (± 16.28)	n=19	236.63 (± 17.59)
Blood flow rate (ml/min) [Mean] [SD]	n=17	279.41 (± 26.49)	n=19	274.95 (± 27.10)	n=17	276.94 (± 29.66)	n=19	278.11 (± 29.97)
Dialysate flow rate (ml/min) [Mean] [SD]	n=17	488.71 (± 25.96)	n=19	499.21 (± 54.95)	n=17	486.35 (± *20.25*)	n=19	468.58 (± 48.57)
Total convection volume (L)							n=18	20.4 (±*3.4)*
Hematocrit baseline [%], [Mean] [SD]	n=19	30.68 (± 4.49)	n=18	30.94 (±*5.06*)	n=19	31.37 (± *5.13*)	n=17	31.65 (±5.52)
Hematocrit after 1 hour [%], [Mean] [SD]	n=18	32.56 (± 4.72)	n=19	32.00 (±5.17)	n=19	32.89 (± 4.70)	n=18	32.94 (±5.34)
Hematocrit after treatment [%], [Mean] [SD]	n=18	33.94 (± 5.30)	n=18	33.83 (±5.93)	n=19	34.58 (± 5.62)	n=19	34.89 (±5.65)
Intradialytic Hypotension according to K/DOQI [%]	n=0	0	n=1	5.3	n=2	10.5	n=1	5.3
Blood pressure decrease ≥ 20mmHg [%]	n=5	26.3	n=5	26.3	n=5	26.3	n=4	21.1
Symptoms [%]	n=0	0	n=1	5.3	n=2	10.5	n=1	5.3

Table 8: Treatment characteristics

n, number of studies; SD standard deviation; MCO medium cut-off, HDF hemodiafiltration, K/DOQI Kidney Disease Outcomes Quality Initiative

3.3 Cardiac troponin kinetics

3.3.1 Cardiac Troponin T

Descriptive analysis of cTnT kinetics is provided in table 9. Mean relative and absolute cTnT changes were comparable for MCO and HDF and larger for both high- and low-flux HD.

	Modality							
Value	**High-flux**		**Low-flux**		**MCO**		**HDF (high-flux)**	
cTnT (Baseline) [pg/mL], [Mean] [SD]	n=19	101.26 (± *74*.39)	n=19	107.74 (± 82.06)	n=19	105.37 (± *71*.68)	n=19	103.21 (± *67*.08)
Difference cTnT (1 hour) [pg/mL], [Mean] [SD]	n=19	-6.42 (± 5.59)	n=19	+1.84 (± 10.84)	n=19	-21.63 (± *15*.91)	n=18	-20.89 (± 18.53)
Difference cTnT (post HD) [pg/mL], [Mean] [SD]	n=18	-8.39 (± *7.8*9)	n=19	-0.05 (± 22.45)	n=18	-31.67 (± 22.12)	n=19	-27.95 (± 20.46)
CTnT (relative difference 1 hour) [%], [Mean], [SD]	n=19	-7 (± *6*)	n=19	+2 (± *7*)	n=19	-22 (± *16*)	n=18	-21 (± 14)
CTnT (relative difference post HD) [%], [Mean], [SD]	n=18	-9 (± *8*)	n=19	+3 (± *13*)	n=18	-33 (± *19*)	n=19	-29 (±*13*)

Table 9: Descriptive results for cardiac cTnT by treatment modality

cTnT cardiac troponin T, cTnI cardiac troponin I, HD Hemodialysis, MCO medium cut-off, HDF hemodiafiltration, SD standard deviation

Using a linear mixed effects model, for the relative differences in cTnT, no significant sequence and period effects were observed for relative changes from baseline to 1h (sequence: P= 0.45, period: P=0.97) and relative changes from baseline to post HD (sequence: P= 0.59, period: P=0.65). The effect for membrane differed significantly ($p<0.001$): Significantly different relative changes after 1h were observed for MCO compared to low-flux and MCO to high-flux, see table 10 and figure 7.

No difference was observed for MCO versus HDF treatment with high-flux membrane. Similar results were observed post HD, with the most pronounced change during the first hour. For absolute changes, LSM for MCO were -21.2 (95% CI -27.6 to -14.8 pg/mL), -6.4 (95% CI -12.8 to -0.0 pg/mL) for high-flux, -20.2 (95% CI -26.8 to -13.7 pg/mL) for HDF treatment and +2.3 (95% CI -4.1 to 8.6 pg/mL) for low-flux hemodialysis after one hour, see table 10 and figure 6.

			High-flux HD		Low-flux HD		MCO		HDF	
cTnT	**Baseline** [pg/mL], [Mean] [SD]	**0h**	101.3 (± *74*.4)		107.7 (± 82.1)		105.4 (± *71*.7)		103.2 (± *67*.1)	
	Absolute Differences [pg/mL], [LSM] [95% CI]	**1 hour**	-6.41 (-12.8 – 0.0)	p=0.049	2.3 (-4.1 – 8.6)	p=0.48	-21.2 (-27.6 – -14.8)	p=<0.001	-20.2 (-26.8 – -13.7) *	p=<0.001
		post HD	-7.7 (-17.2 – 1.8) *	p=0.11	0.3 (-9.0 – 9.6)	p=0.96	-31.4 (-40.9 – -21.9)	p=<0.001	-27.8 (-37.1 – -18.5) *	p=<0.001
	Relative difference [%], [LSM], [95% CI]	**1 hour**	-6.8 (-12.2 – -1.5)	p=0.013	2.2 (-3.2 – 7.5)	p=0.42	-21.9 (-27.3 – -16.6)	p=<0.001	-21.2 (-26.6 – -15.7)	p=<0.001
		post HD	-8.3 (-15.0 – -1.7) *	p=0.015	3.5 (-3.0 – 9.9)	p=0.28	-33.0 (-39.6 – -26.4)	p=<0.001	-28.9 (-35.3 – -22.4)	p=<0.001

Table 10: Least square mean absolute and relative differences of cardiac Troponin T after 1 hour and after treatments

Adapted from (1). LSM…least square mean, LSMD…least square mean difference, SD…standard deviation, CI…confidence Interval
Least square means (LSMs) derived by linear mixed model analysis. CI as 95% confidence interval. SD standard deviation, HD hemodialysis treatment *=n=17-18 due to missing's; Comparisons and p-values refer to differences to baselines, cTnT cardiac troponin T, HD Hemodialysis, MCO medium cut-off, HDF hemodiafiltration.

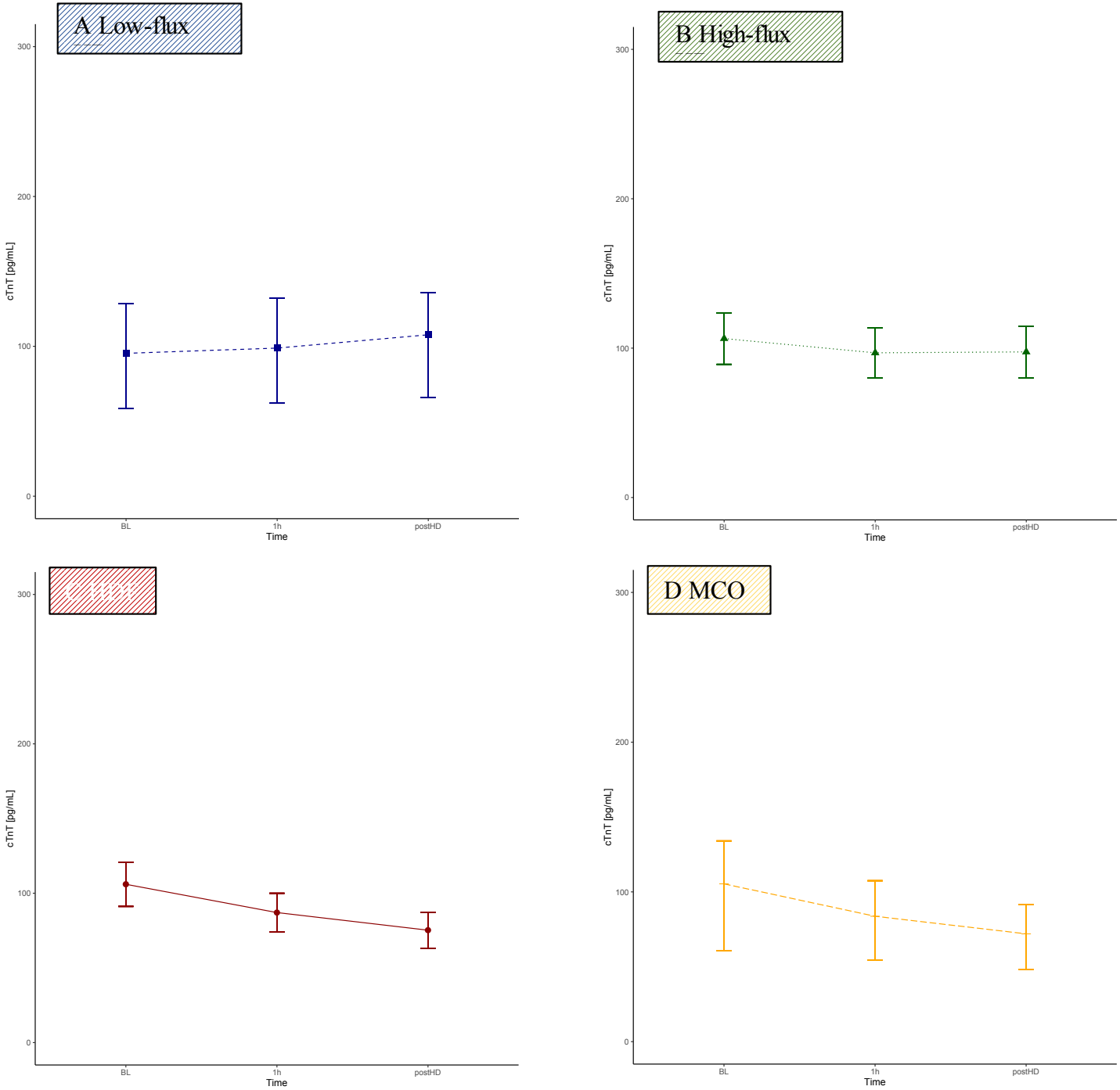
A Low-flux
B High-flux
C HDF
D MCO
cTnT [pg/mL]
300
200
100
0
BL
1h
postHD
Time

Figure 6: cTnT profiles according to modality

Adapted from (1). Panels show absolute solute profiles in pg/mL of cTnT according to treatment modality after 1hour of treatment and post HD presented as LSM±SE.
Legend: BL (baseline), LSM (least square mean), SE (standard error), cTnT (cardiac Troponin T), HD (hemodialysis).

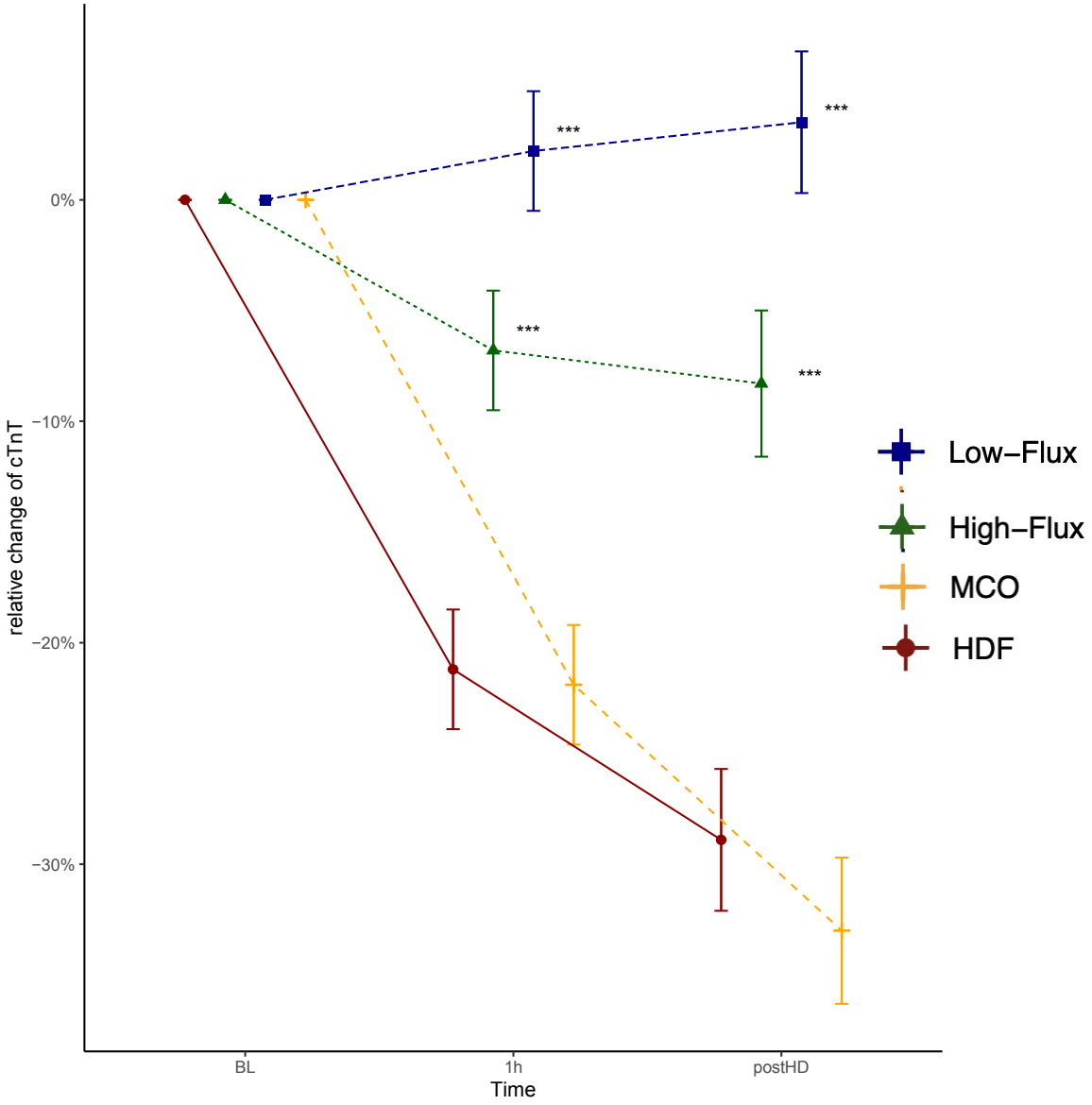

Figure 7: Relative Troponin T profiles according to modality

Adapted from (1). Panel shows relative changes of cardiac Troponin T according to treatment modality after 1 hour of treatment and post HD presented as least square mean ± standard error.
Legend: BL (baseline), HD (hemodialysis); *** p= <0.001 refer to differences to MCO

3.3.2 Cardiac Troponin I

For the relative difference in cTnI, no significant sequence, period and membrane effects were observed for relative changes from baseline to 1h (sequence: P= 0.1369, period: P=0.67, membrane m: P=0.91) and relative changes from baseline to post HD (sequence: P= 0.58, period: P=0.23, membrane m: P=0.41).

Descriptive analysis and linear mixed effects model analysis of cardiac Troponin I kinetics are provided in tables 11 and 12 and figure 8 and showed no clear trend in all treatment modalities.

	Modality							
Value	**High-flux**		**Low-flux**		**MCO**		**HDF (high-flux)**	
Troponin I (Baseline) [pg/mL], [Mean] [SD]	n=19	112.35 (± 159.31)	n=18	78.11 (± 87.23	n=19	73.83 (± *89.88*)	n=18	89.28 (±145.47)
Difference Troponin I (1 hour) [pg/mL], [Mean] [SD]	n=19	-15.31 (± *198.92*)	n=18	+37.71 (± *103.91*)	n=19	+48.56 (± *130.70*)	n=17	+44.23 (± *154.60*)
Difference Troponin I (post HD) [pg/mL], [Mean] [SD]	n=18	+6.51(± *236.53*)	n=18	+100.99 (± *175.42*)	n=19	+46.20 (±*134.74)*	n=18	-10.72 (± *176.31*)
Troponin I (relative difference 1 hour) [%], [Mean], [SD]	n=19	+201(± *8423*)	n=18	+217(± *435*)	n=19	+284 (± *797*)	n=17	+385(± *1347*)
Troponin I (relative difference post HD) [%], [Mean], [SD]	n=18	+135 (± *450*	n=18	+463 (± *1179*)	n=19	+170 (± *499*)	n=18	+124 (± *298*)

Table 11: Descriptive results for cardiac cTnI by treatment modality

SD standard deviation, HD hemodialysis treatment

			High-flux HD		Low-flux HD		MCO		HDF	
	Baseline [pg/mL], [Mean] [SD]	**0h**	112.4 (± 159.3)		78.1 (± 87.2) *		73.8 (± *89.9*)		89.3 (±145.5) *	
Troponin I	**Absolute Differences** [pg/mL], [LSM] [95% CI]	**1 hour**	-10.3 (-81.5 – 60.8)	p=0.77	40.5 (-32.2 – 113.2) *	p=0.27	53.6 (-17.5 – 124.7)	p=0.14	48.8 (-26.9 –124.6) *	p=0.20
		post HD	20.89 (-66.4 – 108.0) *	p=0.63	102.1 (15.4 – 188.8) *	p=0.022	47.7 (-37.1 – 132.4)	p=0.26	-1.0 (-88.8 – 86.8) *	p=0.98
	Relative difference [%], [LSM], [95% CI]	**1 hour**	201.8 (-215.4 – 618.9)	p=0.34	223.6 (-202.9 –650.1) *	p=0.30	295.7 (-121.3 – 712.6)	p=0.16	405.2 (-38.9 – 849.3) *	p=0.07
		post HD	165.3 (-164.6 – 495.2) *	p=0.32	462.0 (133.8 – 790.1) *	p=0.007	149.1 (-171.7 – 469.9)	p=0.35	112.7 (-219.6 – 445.0)	p=0.50

Table 12: Least square mean relative and absolute difference of cardiac Troponin I after 1 hour and after treatment

Adapted from (1). Least square means (LSMs) derived by linear mixed model analysis. CI as 95% confidence interval. SD standard deviation, HD hemodialysis treatment, *=n=17-18 due to missings; Comparisons and p-values refer to differences to baselines

LSM…least square mean, LSMD…least square mean difference, SE…standard error, CI…confidence Interval, cTnI cardiac troponin I, HD Hemodialysis, MCO medium cut-off, HDF hemodiafiltration, SD standard deviation

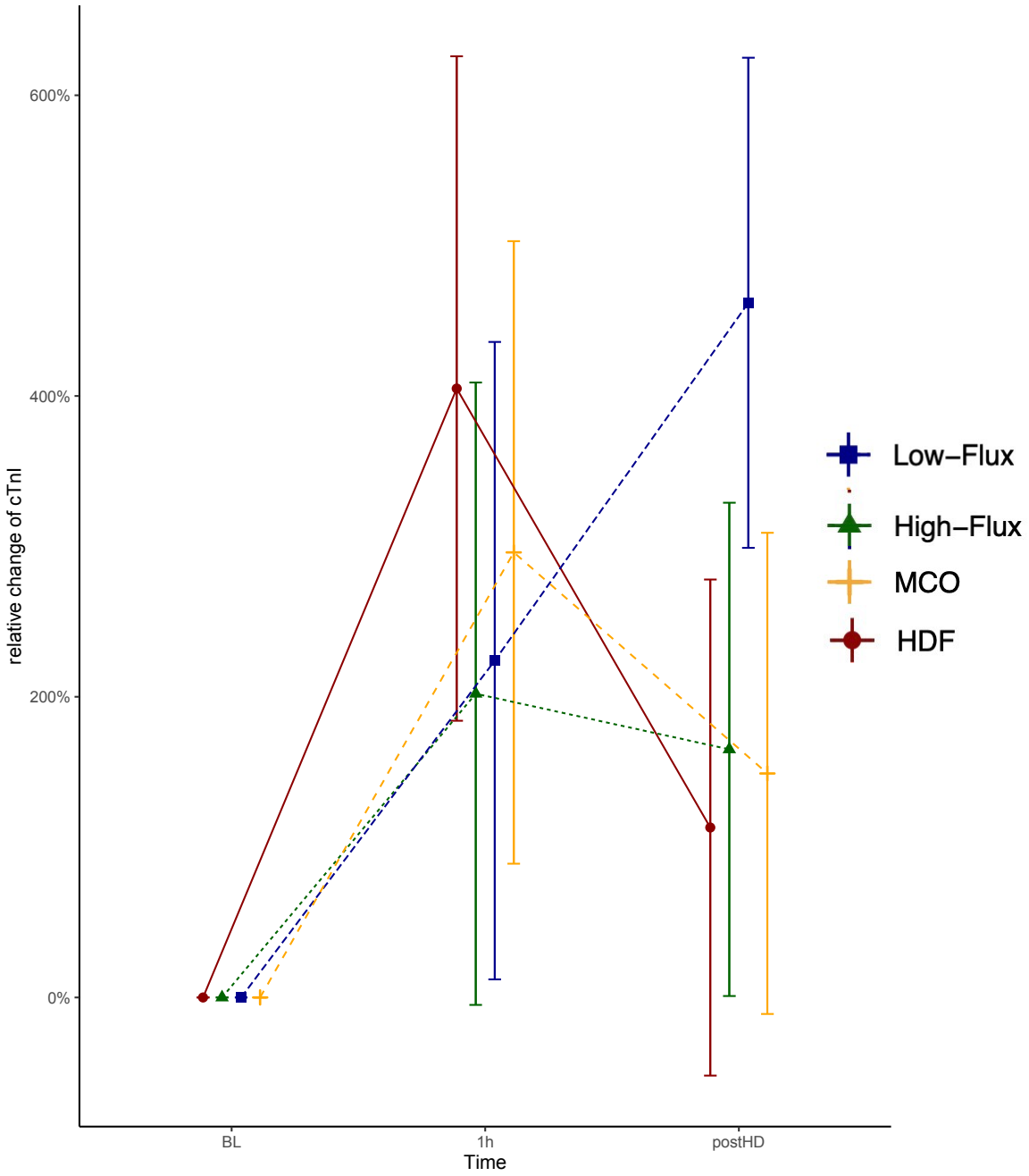

Figure 8: Relative changes of Troponin I according to modality

Adapted from (1). Panel shows relative changes of cardiac Troponin I according to treatment modality after 1hour of treatment and post HD presented as least square mean ± standard error.

Legend: BL (baseline), HD (hemodialysis)

3.3.3 Effect of hemoconcentration

			High-flux HD	Low-flux HD	MCO	HDF
CTnT	**Baseline** [pg/mL], [Mean] [SD]	0 h	101.26 (± *74*.39)	107.74 (± 82.06)	105.37 (± *71*.68)	103.21 (± *67*.08)
	Absolute Differences [pg/mL], [LSM] [95% CI]	1 hour	-16.83 (-26.7 – -6.9) p=0.001	-3.41 (-13.4 – 6.6) p=0.40	-26.42 (-36.1 – -16.7) p=<0.0001	-25.22 (-35.8 – -14.6) * p=<0.0001
		post HD	-23.10 (-37.0 – -9.2) * p=0.002	-10.07 (-24.0 – 3.9) p=0.15	-40.96 (-54.6 – -27.4) p=<0.0001	-35.72 (-49.5 – -21.9) * p=<0.0001
	Relative difference [%], [LSM], [95% CI]	1 hour	-13.98 (-19.7 – -8.2) p=<0.0001	-2.86 (-8.7 – 2.9) p=0.32	-27.11 (-32.7 – -21.5) p=<0.0001	-26.31 (-32.6 – -20.0) p=<0.0001
		post HD	-21.35 (-28.5 – -14.2) * p=<0.0001	-8.35 (-15.5 – -1.2) p=0.02	-41.88 (-48.8 – -35.0) p=<0.0001	-36.87 (-43.9 – -29.8) p=<0.0001
CTnI	**Baseline** [pg/mL], [Mean] [SD]	0h	112.35 (± 159.31)	78.11 (± 87.23) *	73.83 (± *89.88*)	89.28 (±145.47) *
	Absolute Differences [pg/mL], [LSM] [95% CI]	1 hour	-25.51 (-88.6 – 37.6) p=0.42	35.46 (-29.9 – 100.8) * p=0.28	45.59 (-16.1 – 107.3) p=0.14	18.39 (-53.8 –90.5) * p=0.61
		post HD	6.14 (-74.5 – 86.8) * p=0.88	83.10 (0.0 – 166.2) * p=0.05	*28.06* *(-47.6*– 103.8) p=0.46	8.5 (-74.0 – 91.0) * p=0.84
	Relative difference [%], [LSM], [95% CI]	1 hour	208.1 (-86.8 – 503.0) p=0.16	219.37 (-86.0 –524.8) * p=0.15	268.33 (-20 – 556.6) p=0.06	69.62 (-267.7 – 406.9) * p=0.67
		post HD	146.80 (-170.8 – 464.4) * p=0.36	450.2 (123.2 – 777.2) * p=0.008	98.32 (-199.6 – 396.3) p=0.51	110.44 (-214.2 – 435.1) p=0.49

Table 13: Corrected differences for Troponin T and I

Adapted from (1). LSM…least square mean, LSMD…least square mean difference, SD…standard deviation, CI…confidence Interval
Least square means (LSMs) derived by linear mixed model analysis. CI as 95% confidence interval. SD standard deviation, HD he modialysis treatment *=n=17-18 due to missing's; Comparisons and p-values refer to differences to baselines, cTnT cardiac troponin T, cTnI cardiac troponin I, HD Hemodialysis, MCO medium cut-off, HDF hemodiafiltration, SD standard deviation

After correction for hemoconcentration (170), there was a significant difference to non-corrected values with low-flux HD, indicating relevant hemoconcentration in this type of membrane. Furthermore, absolute and relative changes to baseline were more pronounced with MCO, high-flux HD and HDF after correction, see Table 13.

			Low-flux HD	High-flux HD	MCO	HDF
cTnT	Uncorrected	1 hour	1.01	0.93	0.79	0.82
		post HD	0.99	0.95	0.68	0.73
	Corrected for hemoconcentration	1 hour	1.00	0.84	0.74	0.78
		post HD	0.93	0.82	0.59	0.63
cTnI	Uncorrected	1 hour	1.43	0.86	1.66	1.74
		post HD	2.19	1.10	1.63	1.17
	Corrected for hemoconcentration	1 hour	1.35	0.77	1.56	1.32
		post HD	1.99	0.99	1.39	1.18

Table 14: Corrected and uncorrected reduction ratios for cTnT and cTnI
cTnT cardiac troponin T, cTnI cardiac troponin I, HD hemodialysis, MCO medium cut-off, HDF hemodiafiltration.

When describing dialysis kinetics, the concentrations are usually provided as reduction ratios, are shown as corrected and uncorrected reduction ratios for cTn in table 14.
Reduction ratios with an increase are indicated by R>1, a decrease by R<1.

3.3.4 Effect of treatment variables.

Tables 15 and 16 show correlations of cTnT and cTnI with ultrafiltration volume, blood flow rate and dialysate flow rate after 1 hour of treatment.
There was a weak positive correlation of blood flow rate with low-flux membranes for cTnT but a weak negative correlation for cTnI with low-flux membranes and blood flow rate. Otherwise, no significant correlation effects were observed. Similar results were observed post HD, with no relevant effect of ultrafiltration volume, dialysis treatment time, blood flow rate and dialysate flow rate, except for a weak positive correlation (Spearman factor 0.6378, p=0.003) for blood flow rate when using low-flux HD in terms of cTnT. Regardless of treatment modality, there was no correlation of blood flow rate and baseline hematocrit with ΔcTnT and ΔcTnI.

	Spearman correlation coefficient			p-value		
Modality	**Ultrafiltration volume**	**Blood flow rate**	**Dialysate flow rate**	**Ultrafiltration volume**	**Blood flow rate**	**Dialysate flow rate**
MCO HD	0.01717	0.14418	-0.44936	0.94	0.58	0.07
Low-flux HD	-0.07489	**0.58153**	0.12412	0.76	**0.009**	0.61
High-flux HD	-0.03638	-0.18742	-0.15498	0.88	0.47	0.55
HDF	0.3869	0.04607	-0.01552	0.11	0.86	0.95

Table 15: Correlation of absolute differences of cTnT with ultrafiltration volume, dialysate flow rate, blood flow rate and treatment time after 1 hour

cTnT cardiac troponin T, cTnI cardiac troponin I, HD Hemodialysis, MCO medium cut-off, HDF hemodiafiltration, SD standard deviation

	Spearman correlation coefficient			p-value		
Modality	**Ultrafiltration volume**	**Blood flow rate**	**Dialysate flow rate**	**Ultrafiltration volume**	**Blood flow rate**	**Dialysate flow rate**
MCO HD	-0.12044	-0.28044	-0.01471	0.62	0.27	0.95
Low-flux HD	-0.32868	**-0.53113**	0.12803	0.18	**0.02**	0.61
High-flux HD	-0.18037	0.23616	-0.18098	0.46	0.36	0.49
HDF	0.36	-0.31818	-0.12393	0.16	0.21	0.64

Table 16: Correlation of absolute differences of cTnI with ultrafiltration volume, dialysate flow rate and blood flow rate

cTnT cardiac troponin T, cTnI cardiac troponin I, HD Hemodialysis, MCO medium cut-off, HDF hemodiafiltration, SD standard deviation

3.3.5 Effect of residual kidney function

Regardless of membrane used, patients with residual kidney function, defined as urine output above 500mL per day showed significantly lower baseline levels of cTnT, see table 17.

Modality	Residual kidney function (Urine output per day)	Mean baseline cTnT [pg/mL] (SE)	p-value
MCO	>500mL	50.00 (36.18)	
	≤500mL	120.10 (72.22)	**0.02**
Low-flux	>500mL	55.75 (38.00)	
	≤500mL	121.60 (85.85)	**0.04**
High-flux	>500mL	53.00 (34.69)	
	≤500mL	114.10 (77.55)	**0.04**
HDF	>500mL	51.00 (37.13)	
	≤500mL	117.10 (67.11)	**0.03**

Table 17: Correlation of baseline cTnT values with residual kidney function

cTnT cardiac troponin T, cTnI cardiac troponin I, HD Hemodialysis, MCO medium cut-off, HDF hemodiafiltration, SD standard deviation

3.3.6 Influence of IDH and blood pressure decreases on intradialytic cTn changes

Since the patients and study treatments were selected and optimized to avoid the occurrence of IDH and thus there were only 4 episodes of IDH in the whole study period, we were not able to draw conclusions on the influence on troponin kinetics. When taking into account all blood pressure decreases, without occurrence of symptoms, thus, no true IDH, there were no significant differences of cTnT after 1 hour compared to baseline in between groups, see table 18. There were also no effects observed post HD, see table 19 and no effects on cTnI.

Modality	Blood pressure decrease >30mmHg	N	Mean difference of cTnT [pg/mL] (SD)	p-value
MCO	no	14	22.8 (17.2)	
	yes	5	18.4 (12.7)	0.56
Low-flux HD	no	14	-1.8 (11.3)	0.96
	yes	5	-2.0 (7.7)	
High-flux HD	no	14	7.3 (5.5)	0.30
	yes	5	4.0 (5.7)	
HDF	no	14	21.2 (20.4)	0.86
	yes	4	19.8 (12.0)	

Table 18: Influence of blood pressure decreases on cTnT after 1 hour of treatment.
cTnT cardiac troponin T, HD Hemodialysis, MCO medium cut-off, HDF hemodiafiltration, SD standard deviation; SD standard deviation

Modality	Blood pressure decrease >30mmHg	N	Mean difference of cTnT [pg/mL] (SD)	p-value
MCO	no	13	33.1 (24.9)	
	yes	5	28.0 (13.9)	0.59
Low-flux HD	no	14	2.3 (25.3)	0.32
	yes	5	-6.2 (10.8)	
High-flux HD	no	14	9.0 (8.3)	0.52
	yes	4	6.3 (6.7)	
HDF	no	15	27.9 (22.4)	0.96
	yes	4	28.3 (12.7)	

Table 19: Influence of blood pressure decreases on cTnT post HD
cTnT cardiac troponin T, HD Hemodialysis, MCO medium cut-off, HDF hemodiafiltration, SD standard deviation; SD standard deviation

3.3.7 Proportion of patients with a significant intradialytic troponin reduction

A significant reduction of cTnT, defined as a Δ of 5 pg/mL in one hour, was found in 95% of treatment with MCO, 47.3% with low-flux HD, 68.4% with high-flux HD and 94.5% with HDF. Similar results were observed post HD.

4 Discussion

In this randomized controlled cross-over trial, examining troponin profiles in 19 clinically stable HD patients, we found significant differences of cTn levels.
cTnT profiles were heavily dependent on the type of membrane and dialysis modality used. Troponin I showed no consistent time course or trends.

4.1 Comparison of membranes

The difference from baseline to after 1hour and post dialysis was most pronounced in patients treated with MCO-HD and HDF, less pronounced with high-flux HD, while there was a small relative increase with low-flux HD, which was no longer-observable after correction for hemoconcentration. The most pronounced difference in cTnT occurred within the first hour but did not further increase until after dialysis treatment. As expected, the reduction was much more pronounced with MCO and HDF compared to high-flux HD and low-flux HD which can be explained by the increased convective clearance in these two treatment modalities.

Internal filtration is cumbersome to measure but can be estimated by dispersion of a non-diffusible indicator molecule, for example using indocyanine green, which has been previously done using a high-flux dialyzer (171) or can be mathematically modelled (172). The significant amount of internal filtration in MCO was previously supported by a study using a nuclear imaging technique, which utilized a non-diffusible marker molecule, which was injected into the blood compartment and subsequently, nuclear emission was recorded by a gamma camera. Relative variations of the marker molecule's concentration along the length of the filter were used to calculate internal filtration and resulted in 29.7 mL/min for a Q_B of 300 mL/min (45).
In HDF, a convection volume in excess of 20% of the total blood volume processed for the treatment is necessary to achieve levels of middle molecule clearance that were shown to be associated with beneficial outcomes (76). In a previous study using post-dilution HDF, observing reduction ratios of urea, creatinine, β_2M, myoglobin, prolactin, alpha-1-microglobulin, alpha-1-acid glycoprotein and albumin to calculate a global removal score, a minimum of 19.2L with a Q_B of 350mL/min, a Q_{UF} of 80mL/min and a filtration fraction of 23% was needed to achieve superior efficiency compared to MCO membranes (173).

This rate of blood flow was not achieved in our study, probably mostly due to the fact of using mainly CVC as blood access types, which explains a small, but not statistically significant difference of clearance of the larger middle molecule.

In our study we observed blood flow rates of about 280mL/min which translates to a total of 67.2L of blood volume processed in 4 hours. As the mean total convection volume in our study equaled to 20.4 Liters, and only 5 patients achieved a target volume of >23L as recently used in the CONVINCE Trial (174), one can assume that in clinical practice, where patients are usually selected for HDF that are likely to achieve target convective volume the effect of HDF on cTnT clearance will be even more pronounced.

We assumed a difference between MCO and HDF of about 20% after 4 hours, respectively between 5%-10% after 1 hour. In our study we found a decrease in cTnT of 21.9% with MCO and 21.2% with HDF treatment after 1 hour and 33.0% and 28.9%, respectively, thus changes were smaller than expected and differences not significant.
A possible reason why reduction of cTnT was more pronounced with MCO compared to HDF, is that, first, at a low blood flow rates, as observed in our study, MCO seems to be more effective than HDF in terms of larger middle molecule clearances, as previously reported (58) and also because total convective volume was rather low, as discussed above.

Another possible explanation, why the molecules investigated in our study did not have the same reduction as previously reported for molecules of comparable molecular weights (YKL-40 40kDa vs. cTnT 39kDa) (58) is that when characterizing proteins, the Stokes radius has to be taken into account. The Stokes radius, also termed hydrodynamic radius, is the radius of a sphere with the same hydrodynamic properties as the biomolecule which can be determined by size exclusion chromatography (175). For the physical phenomenon of diffusion, not only the atoms of the molecule itself, but also the surrounding solvents, which are bound by electrostatic forces, account for the radius, which can lead to a significant difference of the "real" radius of a molecule. Furthermore, as proteins increase in size, they tend to fold, driven by hydrophobic effects (176). A previous study, examining the hydrodynamic properties of bovine cTnT and cTnI, showed, that cTnT, with a stokes radius of 80Å, forms highly asymmetric aggregates in solution, while cTnI is essentially monomeric (177). In the more recent literature, stokes radius of cTnT was calculated to be 33.7Å (178), which adds to the complexity of interpreting data and underlies, that the

molecular weight, on which our study sample size calculation was based on, does not completely reflect protein properties. We were not able to find a correlation between the molecular weight and stokes radius of cTn in the literature.

4.2 Impact of diagnosis of AMI

As patients on HD are less likely to show typical ischemic symptoms and often have ECG abnormalities at baseline or present nonspecific changes, diagnosis more heavily relies on cardiac biomarkers (109). Thus, suspicion for AMI should be raised also in patients by atypical symptoms such as abdominal pain or nausea, depending on the pretest probability.
Our study showed, in respect to the 0h/1h algorithm of the 2023 ESC Guidelines (166), that a relevant Δ1h of cTnT >5pg/mLof increase or decrease, would be missed in most HD patients or may even be iatrogenic phenomenon, depending on treatment modality. When relying solely on cardiac biomarkers at the threshold of 5pg/mL after 1 hour, in over 90% of treatments with MCO and HDF, almost 70% of treatments with high-flux HD and almost half of treatments with low-flux HD, this threshold would be surpassed. When accounting for hemoconcentration, which is not daily practice, the effect would be even greater. An increase of uncorrected values of cTn during dialysis, except in patients with low-flux HD, would be indicative for a myocardial damage but not necessarily for infarction as other causes, such as IDH are known reason for release of cTn.

The recently published consensus approach by the SONG-HD MI Expert Working group, which proposed using Δ of >20% of either increase of decrease of cTn (109) occurs without evidence of ACS when patients are treated with medium cut-off membranes or hemodiafiltration. Furthermore, this, consensus report does not differentiate between isoforms of cTn, which is of great interest. Thus, standard diagnostic biomarker algorithms cannot be applied in this setting and need to be interpreted cautiously in concert with clinical symptoms, a patient's past medical history and ECG findings.
Accordingly, this may significantly affect diagnosis of acute myocardial infarction, a finding which has not previously been reported. There was no clear trend in cardiac Troponin I kinetics and values varied substantially, which limits the clinical use of this marker in this setting.

4.3 Impact of ultrafiltration volume

We observed no correlation of ultrafiltration with the Δ of cTnT after 1hour and post HD.

4.4 Influence of blood flow rate and baseline hematocrit

With low-flux membranes, there was a weak positive correlation of blood flow rate and cTnT after 1 hour and post HD, but also weak negative correlation for cTnI and blood flow rate. We cannot exclude, that these results might be due to possible outliers, which do not reflect true correlations and can therefore, only cautiously be interpreted.

In our study population, there was a rather low blood flow rate of 280 mL/min, since the most common type of vascular access was CVC, thus, when achieving higher blood flow rates, one might assume even higher clearances of molecules and therefore higher reduction ratios than observed in our study.

4.5 Influence of IDH and blood pressure decreases on Δ troponin

Initially, assuming an occurrence rate of IDH in 10% of sessions in a dialysis population, we wanted to determine the influence of IDH on ΔcTn as IDH is a known reason for myocardial stunning and stunning may lead to myocardial injury with subsequent troponin release in the blood. Thus, one may assume that there is a diminished decrease of cTn in blood samples if troponins get released at the same time as they get cleared by dialysis.
Unfortunately, sample size for analysis of impact of IDH was too small, thus we only reported influence of blood pressure decreases. In this approach, we found no significant differences between groups, but a small numerical trend, which still may be due to the very limited number of events Observed.

4.6 Correction of cTnT and cTnI for hemoconcentration

Our study nicely illustrates how important adequate knowledge about intradialytic kinetics and molecular sizes of molecules of interest are in the study of the effects of dialysis treatment on concentrations. Since the readout of most clinical protein measurements are concentrations, it is important to understand that the concentration is affected by both changes in the numerator, i.e., the amount of molecule present, as well as by changes in the

denominator, i.e., the volume. In hemodialysis, this is of relevance when studying molecules, the sieving coefficient of which lies significantly below 1. These molecules – importantly molecules in the mid-range in terms of size, such as β_2M, κ-FLC, λ-FLC but also cTnT and cTnI – may be cleared by convective transport but their concentration in the filtrate will lie significantly below that in the plasma water. Thus, any net negative filtration (ultrafiltration), i.e., any convection volume that is not substituted will result in an artificially increased concentration that is not reflective of a true increase in the molecule. In the case of molecules that are primarily cleared by convection, such as the ones of interest in the present study, "hemoconcentration" will mask the true decrease in cardiac troponin by artificially increasing the measured concentration. Correction for this hemoconcentration can be done mathematically with parameters that are similarly affected by hemoconcentration, such as hematocrit or total protein content (170). After correcting our cTnT results for hemoconcentration using pre/post hematocrit, the previously observed increase during and after low-flux HD treatment was no longer present, indicating that there is relevant hemoconcentration (170). Furthermore, the "real decreases" observed with the other membranes, were even more pronounced after correction.

4.7 Differences of cTnT and cTnI

Possible reasons for different kinetics of larger middle molecules, i.e. cTn, include physical phenomena such as absorption to the membrane, concentration polarization, membrane fouling, and formation of a so-called protein cake (15). The small increase of cTnT in low-flux hemodialysis is most likely explained by effects of hemoconcentration (179). If hemoglobin concentrations, hematocrit or the relative blood volumes are available at sampling times, the increase can be predicted and corrected for. The effect of hemoconcentration is also present in other treatment modes and our results allow to raise the point that true intradialytic reductions are even larger than derived from uncorrected concentrations. A measurement one hour after dialysis would show the equilibrated concentrations and reveal effects of hemoconcentration as well.

The increase in cTnI can only be partly explained by protein binding and ultrafiltration-induced hemoconcentration (170) and kinetics of cTnI (which is much smaller than cTnT) require further clarification, since we assumed to achieve higher and predictable clearance of cTnI. It has been reported that cTnI is highly phosphorylated (180) leading to a high net

negative charge which results in membrane interactions as the membrane is also negatively charged and subsequently in insignificant clearance.

Recently, it has been shown that cTnI, but not cTnT and the T-I-C-Complex, adheres to polysulfone membranes (181), which is essentially the same material as the membranes FX10 and FXCorDiax800 used in our study. This may lead to membrane fouling and the formation of a secondary membranes, as described in the chapter "1.2.1.1.5.3 Concentration polarization and membrane fouling" which ultimately decreases clearance (39). These proteins can be eluted from the hemodialysis membranes with a hydron bond cleaving agent, an ionic detergent to destabilize hydrophobic interactions and a hydroxylamine solution to release covalently bound fragments and be further analyzed by immunological techniques (22). Thus, whether the different membranes used in our study, exhibit differences in secondary membrane formation can be evaluated using this method.
Also, cardiac Troponin I is proteolytically cleaved into fragments, which are detected by a various extent by different assays, which are not standardized, thus each assay does have a different reference range.

From a biological point of view, after a cardiac insult (non-ST-elevation myocardial infarction), cTnI seems to increase more rapidly than cTnT in a regular population (133). Furthermore, animal studies (135) have shown, that cTnI is degraded and released faster than cTnT from necrotic cardiac tissue, which may be the reason why cTnI reaches higher peak concentrations and returns to normal concentrations faster in patients with AMI. Since myocardial stunning may lead to a troponin release, and we did not assess the occurrence of stunning, one might assume that there might be a release, with faster extrarenal clearance of cTnI than cTnT, which may contribute to the large intraindividual changes during each session.
Taken together, we cannot entirely explain the observations of Troponin I which merit further investigations. Finally, it is important to keep in mind that interferences with testing of cardiac troponin T occurs in hemolyzed blood samples (182), but this did not occur in our study cohort.

4.8 Other results

Additionally, we found that patients with residual kidney function, defined as urine output above 500mL per day showed significantly lower levels of cTnT at baseline. The presence of residual renal function seems to be protective for mortality even after adjustment for presence of cardiovascular disease (183) and as higher baseline troponin levels are predictors for all cause and cardiovascular death (184), cTnT might reflect this relationship. Previously, cTnT has been reported to be associated with a higher risk of death (5-fold) whereas cTnI only has a gradual correlation in hemodialysis patients.

5 Conclusion

The Δ1h in cTnT and Δpost HD in our study of stable HD patients, without any clinical evidence of myocardial ischemia, significantly exceeded the current guideline-recommended diagnostic threshold. Additionally, a patient who would have an increase of >20% in cTnT, the increase would be completely diminished when MCO-HD or HDF are applied. An increase. When patients present with an increase of cTnT on HDF, MCO or high-flux HD, this should raise suspicion for myocardial damage. We found significant variability without any trends in kinetics of cTnI, which strongly questions its usefulness for diagnosis of AMI in this setting.

Taken together, using routinely employed HD modalities and last-generation cTn assays our study provides robust evidence that standard diagnostic AMI-algorithms cannot be applied during HD.

6 Limitations

Despite the strengths of our study, we acknowledge several limitations. First, because only one type of membrane for each class was used, it remains unclear if our results are generalizable to other membranes. Second, we did not document if patients had myocardial stunning or paroxysmal atrial fibrillation during dialysis study sessions, which may mitigate decreases of cTn during treatments. Third, we cannot draw conclusions on the quantity of adsorption since we conducted no elution of the membrane which should be investigated in future trials.

Fourth, but this lies in the down-stream clinical follow-up based on the diagnosis of AMI, the benefit of early revascularization remains controversial since data from the

SWEDEHEART Registry showed no difference in 1-year mortality in NSTEMI patients on dialysis with early revascularization over medical therapy alone (185), thus there is unclear utility of early detection of acute myocardial infarction.

Fifth, we can only speculate whether different profiles of cTnI and cTnT are due to absorption to the membranes, different release kinetics or other factors.

Our sample size calculation was based on previous study findings that there is a significant difference in clearance of middle molecules in MCO and HDF, thus we assumed between 5%-10% of difference after 1 hour with a standard deviation of 5% and included 20 subjects. We did not observe a significant difference between those two groups in our study, which might be due to a small sample size. Furthermore, HD was below the currently recommended threshold of a convection volume of >23L. Also, we did not assess sensitivity and specificity of the diagnostic tests in patients undergoing hemodialysis treatment, which should be evaluated in future trials.

Lastly, removal in intermittent HD essentially depends on blood flow, thus our results must be kept in context to the rather low blood flow in our patients.

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8 Supplemental Material

8.1 Information for Study personnel

TROP-T Studie

Ansprechpersonen:
Kolland/Kirsch/Schuller/Amenitsch/Ginthör

Primär Check welche Membran für die Dialyse verwendet wird:
→ Entweder low flux, high flux oder MCO Membran bzw, High Flux mit HDF (post-dilution) (Membranen: FX10, FXCorDiax800 oder Theranova 400) sowie die Fresenius Machine

Dialyse wird standardmäßig wie folgt eingestellt:

- 35,5°C
- Calcium: 1,25mmol/L
- Bikarbonat: 30mmol
- Natrium und Kalium je nach Werten!
- UF nach Anordnung des Arztes

→ Bitte das Dialyseprotokoll mit „Studienpatient/in" versehen damit der behandelnde Arzt/die Ärztin nicht irrtümlich die Einstellungen verändert.

Während der Dialyse Dokumentation von intradialytischer Hypotension sowie Brustschmerz am Dialyseprotokoll wie gewohnt.

Blutabnahmen (*Die Standard-Röhrchen bitte nur zur Hälfte befüllen*)

Zu Beginn:

- 1x normale aBGA (wie gewohnt, bei uns im POC Gerät analysiert)
    - **Gleichzeitig** dialysatseitig das Natrium Spritze abziehen mit Pickerl vom patienten und Datum versehen und im Kühlschrank einlagern.
- 1x normales Li-Hep Röhrchen **mit** Gel → Biobank Anforderung
- 1x normales Li-Hep Röhrchen **ohne** Gel → KIMCL Anforderung (CAVE hier steht zwar violettes Röhrchen, jedoch wird ebenso ein LiHep Röhrchen verwendet)
- Bzgl. Natrium Abgleich Maschine Voreinstellung notieren und auf Visite warten – nicht selbstständig verändern

Nach 1 Stunde

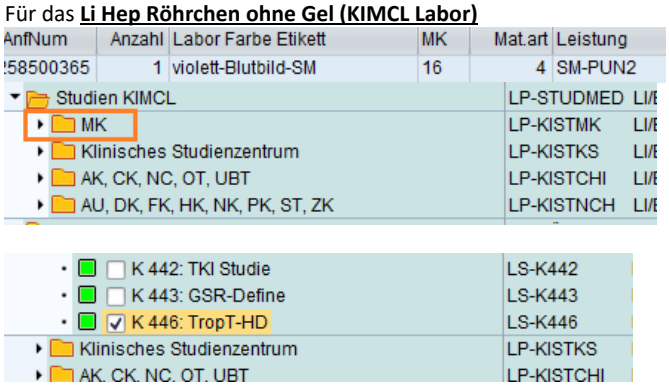
- 1x normales Li-Hep Röhrchen **mit** Gel → Biobank Anforderung
  1x normales Li-Hep Röhrchen **ohne** Gel → KIMCL Anforderung

Unmittelbar nach der Dialyse

- 1x normales Li-Hep Röhrchen **mit** Gel → Biobank Anforderung
  1x normales Li-Hep Röhrchen **ohne** Gel → KIMCL Anforderung

Die Anforderung im Medocs läuft wie folgt ab:

Für das **Li Hep Röhrchen ohne Gel (KIMCL Labor)**



Für das **LiHep Röhrchen mit Gel (Biobank)**