Continuous-Equivalent Urea Clearances
EKR and stdK as Dose Measures in Intermittent Hemodialysis
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EKR and stdK as Dose Measures
in Intermittent Hemodialysis

ACADEMIC DISSERTATION
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Abstract

Continuous-Equivalent Urea Clearances EKR and stdK as Dose Measures in Intermittent Hemodialysis

Background

Survival of hemodialysis patients is associated with the treatment dose in numerous large observational studies, but no statistically significant cause and effect relationship has been confirmed in randomized clinical trials.

How to measure the hemodialysis dose has been debated for decades. Urea is not a good representative of uremic toxins and its concentration does not reflect the severity of uremia.

In the conventional thrice weekly schedule, estimates of the volume cleared in a single hemodialysis session predict survival better than urea concentration, but they cannot be used in comparing dosing in different schedules. Positive outcomes have been reported from frequent (“daily”) hemodialysis, but whether this is due to more efficient toxin removal or other factors remains unknown. In many studies the role of residual renal function (RRF) has been ignored, although it has a profound effect on outcome. Scaling of dose by urea distribution volume may be unsatisfactory.

Methods

In metabolic equilibrium urea removal rate E is equal to its generation rate G. Continuous-equivalent clearance (ECC) is a simple concept based on the definition of clearance:

\[ \text{ECC} = \frac{G}{C}, \]

where C is the reference concentration: time-averaged concentration TAC in EKR, average predialysis concentration PAC in stdK. G, TAC, and PAC are derived from the urea kinetic model (UKM). ECC takes into consideration the schedule and includes RRF.
In the present thesis the characteristics of ECCs were investigated by computer simulations based on data derived from 1,200 urea kinetic modeling sessions among 51 patients. A method to create an optimized dialysis prescription automatically using a computer was also developed and the associations of different ECC values with death risk compared using statistical methods.

Results

1) Residual renal function contributes significantly to urea removal and even more to the removal of true uremic toxins. The ECC concept is a rational way to address RRF. Incremental dialysis relieves the burden of the treatment.

2) Increasing frequency with constant weekly treatment time and dialyzer clearance decreases TAC and PAC and increases EKR and stdK. stdK is more sensitive to frequency and RRF than EKR.

3) With a constant EKR target, increasing frequency decreases PAC. With a constant stdK target, increasing frequency increases TAC.

4) The EKR/V and stdK/V values corresponding to eKt/V 1.20 in a conventional 3 x 4 h/week schedule were 3.44 and 2.40/week.

5) The dialysis dose can be adjusted for protein catabolic rate by reducing high urea concentrations. A prescription fulfilling multiple criteria can be created automatically by a computer. ECCs are required for optimizing frequency, time, and concentrations.

6) EKR is significantly associated with mortality in the present material, while stdK is not. Protein catabolic rate (PCR) and dialysis dose seem to have a synergistic association with survival.

7) Urea and β2-microglobulin react similarly to changes in time and frequency, but differently to changes in blood and dialysate flow (Qb, Qd). Clearance of urea is heavily flow-dependent, that of β2-microglobulin is not. With equal urea clearance (EKR) or concentration (TAC), concentration of β2-microglobulin is lower with more gentle treatment (lower Qb and Qd and longer treatment time).
Conclusions

No single absolutely correct dialysis dose measure can be said to exist. Urea has exceptional kinetics which does not universally describe the behavior of uremic toxins. The outcomes probably cannot be improved by raising urea removal above the current level.

A distinction must be made between dose and effect. The continuous-equivalent clearances EKR/V and stdK/V are patient-dependent measures of the effect of dialysis on urea concentrations. They handle treatment frequency and RRF appropriately, but are not ideal determinants of treatment adequacy when based solely on urea kinetics.

The delivered dialysis dose can be defined technically as weekly dialyzer urea clearance normalized with body surface area (nKt_{urea}), e.g. 180 L/week/1.73 m^2 corresponding to about 14 mL/min of EKR, 3.6/week of EKR/V and 2.4/week of stdK/V in a 3 x 4 h/week schedule. This guarantees sufficient removal of easily dialyzable retention solutes. The target can be safely reduced by the normalized renal urea clearance (nKr_{urea}, L/week/1.73 m^2). Kt can be easily measured with an online ionic dialysance monitor, but weekly nKt is not equal to continuous clearance. Dialyzer clearance and weekly treatment time determine the delivered dose, reflecting consumption of resources. Blood samples, UKM and computers are not needed. ECC, Kt/V and URR are indirect measures of delivered dose.

Future investigations with constant dose (weekly nKt) will hopefully reveal the best strategies (time, frequency or convection) to control the long-term effects of uremic toxins. Dialyzer urea clearance multiplied by treatment time is not enough to define dialysis dosing. It cannot be described with only one number; at least four are required: weekly dose, convection volume, duration and frequency. Dose, dosing and adequacy are different things.
Urean vakiopuhdistumat EKR ja stdK jaksoittaisen keinomunuais-hoidon annosmittoina

Keinomunuaishoidolla tarkoitetaan menetelmiä, joilla verestä poistetaan ulkoisen laitteen (artificial kidney) avulla munuaisten toiminnanvajauksessa kertyviä haitallisia aineita (uremic toxins). Yleisesti käytettyä luontevaa englanninkielistä vastinetta keinomunauishoitot-sanaan ei ole. Useimmiten käytetään sanoja hemodialysis tai blood purification.

Vakiopuhdistuma (continuous-equivalent clearance, ECC) ja mallinnushoito (urea kinetic modeling session) eivät ole vakiointuneita suomen kielen sanoja.

Tausta

Laajoissa havainnoivissa tutkimuksissa keinomunuaispotilaiden menestymisellä on yhteys hoitoannokseen, mutta satunnaistetuissa klinisissä hoitokokeissa syysseuraussuhdetta ei ole kyettä varmistamaan.

Keinomunuaishoidon annoksen mittaamisesta on kiistelty vuosikymmeniä. Virtsa-aine (urea) ei ole sopiva edustamaan munuaisten toiminnanvajauksessa kertyviä haitallisia aineita (ureemisia toksiineja) eikä sen pitoisuus kuvasta munuaisten toiminnanvajauksen vaikeusastetta.

Tavanomaisessa hoitokaaviossa yksittäisessä keinomunuaishoidossa puhdistunut nestemäärä ennakoi potilaan menestymistä paremmin kuin ureapitoisuus, mutta sitä ei voi käyttää erilaisten hoitokaavioiden vertailussa. Tiheällä (“päivittäisellä”) hoitolla on saavutettu myönteisiä tuloksia, mutta on epäselvä, johtuvatko ne ureemisten toksiinien tehokkaammassa poistamisesta vai muista tekijöistä. Monissa tutkimuksissa jäljellä oleva munuaistoiminta (RRF) on jätetty huomiotta, vaikka se vaikuttaa merkittävästi hoitotuloksii. Puhdistuman suhteuttaminen urean jakautumis-tilavuuteen on epätyydyttävä normalisointimenetelmä, josta kärsivät erityisesti naiset ja lapset.
Menetelmät

Aineenvaihdunnossa ollessa tasapainossa urean poistumisnopeus $E$ on yhtä suuri kuin sen syntymisnopeus $G$. Vakiopuhdistuma (ECC) perustuu puhdistuman määritelmään:

$$ECC = G / C,$$


Väitöskirjatyössä selvitetettiin vakiopuhdistumien ominaisuuksia tietokonemallilla perustuen 51 potilaan 1200 mallinnushoitoon (urea kinetic modeling sessions), joista oli käytettävissä hoitotiedot ja laboratoriokokeitten tulokset. Kehitettiin myös menetelmä dialyysihoitomääryyksen laatimisesti automaattisesti tietokoneen avulla ja verrattiin eri tavalla laskettujen vakiopuhdistumien yhteyttä kuolleisuuteen.

Tulokset

1) Keinomunuaispotilaalla oman munuaistoiminnan osuus urean poistamisesta voi olla jopa 40-50 %. Se alentaa pitoisuksia ja suurentaa EKR- ja stdK-arvoja ja voi korvata viikossa useita tunteja keinomunuaihoitoa. Vakiopuhdistuma on kännyköllinen tapa ottaa huomioon jäljellä oleva munuaistoiminta, mikä keventää hoidosta aiheutuvaa taakkaa.

2) Hoitotiheyden lisääminen pidentää viikottaista hoitoa laskee TAC- ja PAC- ja nostaa EKR- ja stdK-arvoja. stdK on herkempi tiheydelle ja RRF:lle kuin EKR.


4) Tavanomaisessa $3 \times 4$ h/viikko hoitokaavioissa $eKt/V$-arvoja 1.2 vastaavat $EKR/V$- ja stdK/V-lukemat olivat 3.44 ja 2.40 /viikko.

5) Keinomunuaihoitogon annos voidaan sopeuttaa valkuisen hajoamisnopeuteen (PCR) rajoittamalla ureapitoisuksia. Tietokoneella voidaan luoda automaattisesti hoitosuunnitelia, joka ottaa huomioon useita rajauksia ja tavoitteita. Vakiopuhdistumia tarvitaan, koska hoitotiheys saattaa muuttua.

7) Urean ja β2-mikroglobuliinin pitoisuudet reagoivat samalla tavalla hoitoajan ja -tiheyden, mutta eri tavalla virtausnopeuksien muutoksia. Ureapuhdistuma riippuu voimakkaasti veren ja ulkonesteen virtauksesta, β2-mikroglobuliinin puhdistuma vähemmän. Samalla urean vakiopuhdistumalla tai keskipitoisuudella β2-mikroglobuliinin pitoisuudet ovat matalammat lempeämmässä hoidossa (pienemmät virtaukset, pitempi hoitoaika).

**Johtopäätökset**

Yhtä ehdottomasti oikeaa keinomunuaishoidon annosmittaa ei ole. Urean kinetikka on poikkeuksellista eikä kuva yleisesti ureemisten toksiinien käyttäytymistä. Hoitotulokset tuskin paranevat urean poistamista tehostamista.

Annos ja vaikutus on sytyt erottaa toisistaan. Ureakineettiseen malliin perustuvat vakiopuhdistumat EKR and stdK ovat potilaasta riippuvia lukuja, jotka kuvavat hoidon vaikutusta veren ureapitoisuuteen. Ne ottavat huomioon hoitotiheyden ja jäljellä olevan munuaistoiminnan, mutta eivät sittenkään ole – pelkästään ureasta laskettuina – ihanteellisia keinomunuaishoidon annosmittoja.

Keinomunuaishoidon annos voidaan määritellä viikkottaisena urean dialysaattoripuhdistumana suhteutettuna ijon pinta-alaan (nKt<sub>urea</sub>), esim 180 L/viikko/1.73 m<sup>2</sup>, mikä vastaa suunnilleen EKR-arvoa 14 mL/min, EKR/V-arvoa 3.6/viikko ja stdK/V-arvoa 2.4/viikko tavanomaisessa 3 x 4 h/viikko hoitokaaviossa. Se takaa helposti dialysaattovien aineitten riittävän puhdistuman, vaikka ei vastaa samansuuruista jatkuva puhdistumaa. Kt (puhdistuma x hoitoaika) voidaan mitata keinomunuaiskoneen lisälaitteen avulla. Ei tarvita verinäytteitä, ureakineettista mallia eikä tietokoneita. Dialysaattoripuhdistuma ja hoitoaika määrittelevät annetun annoksen ja heijastavat voimavarojen kulutusta. ECC, Kt/V ja URR ovat epäsuoria mittoja.

Tulevat tutkimukset, joissa annos (viikon nKt) on vakioitu, toivottavasti paljastavat parhaat keinot (aika, tiheys vai konvektio) ureemisten toksiinien haittainhayttavaikutusten vähentämiseen. Annostelua ei voi kuvata yhdellä luvulla, tarvitaan ainakin neljä: viikon nKt, konvektiovolyymi, kesto ja tiheys. Annos, annostelu, riittävyys ja laatu ovat eri asioita.
I FREQUENCY

II INCREMENTAL

III EQUIVALENCY

IV AUTOMATION

V ADEQUACY

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**ABBREVIATIONS AND DEFINITIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSA</td>
<td>body surface area</td>
</tr>
<tr>
<td>C</td>
<td>concentration in blood or plasma</td>
</tr>
<tr>
<td>C0</td>
<td>concentration at the beginning of dialysis session</td>
</tr>
<tr>
<td>Ct</td>
<td>concentration at the end of dialysis session</td>
</tr>
<tr>
<td>Cu</td>
<td>concentration in urine</td>
</tr>
<tr>
<td>CAPD</td>
<td>continuous ambulatory peritoneal dialysis</td>
</tr>
<tr>
<td>CKD</td>
<td>chronic kidney disease</td>
</tr>
<tr>
<td>DDQ</td>
<td>direct dialysis quantification</td>
</tr>
<tr>
<td>DPI</td>
<td>dietary protein intake</td>
</tr>
<tr>
<td>E</td>
<td>excretion or removal rate</td>
</tr>
<tr>
<td>EBPG</td>
<td>European Best Practice Guidelines</td>
</tr>
<tr>
<td>ECC</td>
<td>equivalent renal clearance = G / TAC</td>
</tr>
<tr>
<td>EKR</td>
<td>equivalent renal clearance = K / TAC</td>
</tr>
<tr>
<td>EKRc</td>
<td>EKR normalized with distribution volume (mL/min/40 L)</td>
</tr>
<tr>
<td>EKR/V</td>
<td>EKR scaled by V (= stdEKR, /week)</td>
</tr>
<tr>
<td>eKt/V</td>
<td>equilibrated Kt/V</td>
</tr>
<tr>
<td>ESRD</td>
<td>end-stage renal disease, CKD stage 5</td>
</tr>
<tr>
<td>fr</td>
<td>dialysis session frequency</td>
</tr>
<tr>
<td>FSR</td>
<td>fractional solute removal</td>
</tr>
<tr>
<td>G</td>
<td>generation rate</td>
</tr>
<tr>
<td>HD</td>
<td>hemodialysis</td>
</tr>
<tr>
<td>HDF</td>
<td>hemodiafiltration</td>
</tr>
<tr>
<td>HF</td>
<td>hemofiltration</td>
</tr>
<tr>
<td>IDM</td>
<td>ionic dialysance monitoring</td>
</tr>
<tr>
<td>K</td>
<td>clearance</td>
</tr>
<tr>
<td>KDOQI</td>
<td>Kidney Disease Outcomes Quality Initiative</td>
</tr>
<tr>
<td>Kd</td>
<td>dialyzer clearance</td>
</tr>
<tr>
<td>KdA</td>
<td>dialyzer mass area coefficient</td>
</tr>
<tr>
<td>Kr</td>
<td>renal clearance</td>
</tr>
<tr>
<td>Kt</td>
<td>Kt * td, “urea product” (L)</td>
</tr>
<tr>
<td>Kt/V</td>
<td>Kt scaled to distribution volume (Kd * td / Vt)</td>
</tr>
<tr>
<td>LVH</td>
<td>left ventricular hypertrophy</td>
</tr>
<tr>
<td>NBW</td>
<td>normal body weight = Vt / 0.58 (kg)</td>
</tr>
</tbody>
</table>
nEKR EKR normalized with BSA (mL/min/1.73m²)
nEKRant EKR normalized with BSA and Vant (mL/min/1.73m²)
nKr Kr normalized with BSA (mL/min/1.73m²)
nKt Kt normalized with BSA (L/1.73m²)
nsdk normalized with BSA (mL/min/1.73m²)
nsdkant stdK normalized with BSA and Vant (mL/min/1.73m²)
nPCR PCR scaled to NBW
PAC average predialysis concentration, peak average concentration
PCR protein catabolic rate
Qb dialyzer blood flow
Qd dialyzer dialysate flow
HRQOL health-related quality of life
RCT randomized clinical trial
rFC renal fractional clearance Kr/V
rFSR renal fractional solute removal = Vu * Cu / (C0 * V0)
rFSRR renal fractional solute removal rate = rFSR / (td + ti)
RRF residual renal function
spKt/V single pool Kt/V
spvvUKM single pool variable volume UKM
SRI solute removal index
stdEKR EKR scaled by V (= EKR/V, /week)
stdK standard clearance E / PAC
stdK/V stdK scaled by V (/week)
TAC time-averaged concentration
TBW anthropometric total body water (Watson) = Vant
td dialysis time, duration
ti interval time
UF ultrafiltration volume (positive, if fluid is removed)
UKM urea kinetic model
URR urea reduction ratio
V distribution volume
V0 predialysis V
V1 single-pool V
Vant = TBW
Ve “extracellular” pool V
Vi “intracellular” pool V
Vt postdialysis V
Vu dialysis cycle urine volume ≈ interdialysis urine volume
The success of dialysis in sustaining life shows that the short-term mortality associated with renal failure is mainly due to accumulation of dialyzable toxic substances, including water, normally excreted by the kidneys. However, amelioration of immediately life-threatening disturbances is not enough. The goal is satisfactory quality and length of life.

Mortality among hemodialysis patients is much higher than that among general population, in USA 188 vs 8/1000 years at risk in 2012 [US Renal Data System 2015, Centers for Disease Control and Prevention; National Center for Health Statistics 2015]. Quality and length of life are poorer than in many malignant diseases [McFarlane 2009] and threatened by the residual syndrome [Depner 2001b], inconvenience, shortcomings, and complications of the treatment and persistence or progression of the disease which has destroyed the kidneys. It is difficult to separate the long-term side effects from inadequacy of the treatment [Depner 1991a]. Encephalopathy due to aluminium accumulation from dialysate was a serious adverse effect of hemodialysis in the 1970's. The exposure of blood to artificial surfaces may result in activation of harmful biologic pathways [Aucella et al. 2013]. Are acceleration of atherosclerosis, left ventricular hypertrophy or amyloidosis due to treatment or its deficiencies? The effectiveness of hemodialysis in uremic toxin removal is far inferior to that of healthy kidneys, and tubular secretion and metabolic functions cannot be replaced by dialysis even in theory.

Hemodialysis efficiency can be quantified by changes in blood solute concentrations resulting from the therapy [Gotch 1975]. Urea has been used for that purpose, but it is not a good representative of uremic toxins.

Dosing of dialysis is one of the factors affecting outcome, but “adequacy” is not simply equal to Kt/V_{urea}, and no randomized clinical trial shows a significant causal relationship between dialysis dose and survival [Oreopoulos 2002].
Moving of solutes across the dialyzer membrane can be described by the clearance concept:

\[ E = K \times C \]  \hspace{1cm} (1a) \\
\[ K = \frac{E}{C} \]  \hspace{1cm} (1b) \\
\[ C = \frac{E}{K} \]  \hspace{1cm} (1c)

where \( E \) = removal rate, \( K \) = clearance and \( C \) = concentration. Equation 1a states that the removal rate of a solute is directly proportional to its concentration. The slope is referred to as clearance. In metabolic equilibrium removal rate equals generation rate (\( G \)), thus

\[ G = K \times C \]  \hspace{1cm} (2a) \\
\[ K = \frac{G}{C} \]  \hspace{1cm} (2b) \\
\[ C = \frac{G}{K} \]  \hspace{1cm} (2c)

Concentration reflects the balance between generation rate and clearance.

Kt/V and other measures of a single dialysis session can be used in comparing dialysis dosing only if the treatment frequency is equal. Nonconventional schedules have become more popular in recent years, but reports correlating outcome with dose are inconsistent. Continuous-equivalent measures EKR [Casino and Lopez 1996] and stdK [Gotch 1998, Gotch et al. 2000] – based on the definition of clearance – take the treatment frequency and residual renal function (RRF) into consideration and were intended for use in comparing dialysis doses in different schedules and to continuous dialysis and renal function. In this thesis I describe the main characteristics of these measures, report the equivalency of them to eKt/V in conventional dialysis, use them for automating the dialysis prescription and finally attempt to correlate mortality with them in a small patient population.
2  REVIEW OF THE LITERATURE

2.1  Uremic syndrome

2.1.1  Water and sodium

When 269 chronic hemodialysis patients were divided into two groups according to predialysis water overload (above or below 15% of extracellular water) measured by bioimpedance, the mortality risk was twofold in the higher group [Wizemann et al. 2009]. Dry weight is a moving target, which, however, is worth aiming at. Overhydration is associated with hypertension, heart failure, LVH, and intradialysis blood pressure drops due to excessive ultrafiltration rate [Scribner et al. 1960] and with death. The Tassin group in France has the best treatment results in the world, summarized by [Charra et al. 2003]. Twenty-year survival was 43% despite conservative practice [Charra et al. 1992b]. These authorities postulate that it is mainly due to sodium restriction and long dialysis time, which allows slow ultrafiltration and achieving the real dry weight and normal blood pressure slowly, during a period of months. They have no control group and no randomized clinical trials. Patient selection may have affected the results: a decreasing number of patients are able or willing to go on eight-hour dialysis.

With volume control and salt restriction in 19 incident HD patients, blood pressure and left ventricular mass decreased more than with antihypertensive medication, but RRF also decreased more rapidly [Gunal et al. 2004].

Blood pressure control and other outcome measures have also been proved excellent in slow nocturnal (home) HD in uncontrolled studies [Pierratos 1999, Walsh et al. 2005] and randomized trials [Culleton et al. 2007, Rocco et al. 2011]. Long treatment time usually means high dose. The real dry weight is difficult to achieve with short treatment without very strict dietary salt and fluid restriction.

Water balance is an essential element in renal replacement therapy and an art form all of its own, but is addressed in the present thesis only in connection with treatment time.
2.1.2 Acidosis

End-stage renal disease is commonly accompanied by metabolic acidosis [Teehan et al. 1983]. Acidosis is a strong catabolic factor [Bergstrom 1995]. It can be corrected efficiently by adjusting dialysate bicarbonate concentration. In the first decades of hemodialysis history, acetate was used instead of bicarbonate for technical reasons, but it had some degree of immediate toxicity. Lactate is better tolerated and commonly used in CAPD and also in some special home hemodialysis machines.

2.1.3 Anemia and endocrine disturbances

The most obvious cause of anemia in CKD is impaired production of erythropoietin by the sick kidneys. Disturbances of renin, parathyroid hormone, vitamin D and sex hormone metabolism are common in uremia, but can be corrected only minimally by modifying the dialysis dose. They are not addressed in this thesis.

2.1.4 Urea

Adding urea (CH₄N₂O, molecular weight 60 Da) to dialysate in uremic concentrations caused only mild harmful short-term effects [Johnson et al. 1972, Merrill et al. 1953]. In the NCDS trial the outcome was worse in the high TACₜurea groups [Laird et al. 1983].

Urea concentration reflects the balance between generation and clearance, both of which have a positive correlation with survival [Ravel et al. 2013]. In contrast to the NCDS, in some studies – where DPI, PCR and Kt/V were not fully controlled – higher urea concentrations were associated with better outcome [Shapiro et al. 1983]. In observational studies the correlation of mortality with predialysis urea concentration is J- or U-shaped [Lowrie and Lew 1990, Stosovic et al. 2009]. With equal clearance, urea concentrations are high if nPCR is high. High mortality associated with low urea concentration [Degoulet et al. 1982] may be due to malnutrition and wasting caused by comorbidity, and that associated with high concentrations, to underdialysis.
2.1.5 Uremic toxins

Over 140 compounds which accumulate in renal failure and have harmful effects have been identified [Duranton et al. 2012, Glorieux and Tattersall 2015, Glorieux and Vanholder 2011, Lisowska-Myjak 2014, Neiryck et al. 2013b]. Uremic toxins have different generation rates and removal kinetics, some are “middle” or big molecules (500-40,000 Da) and dialyze poorly, some are bound to plasma proteins or tissues and have peculiar dialysis kinetics despite their small molecular weight [Dobre et al. 2013, Eloot et al. 2009, Glorieux and Vanholder 2011, Henderson et al. 2001, Neiryck et al. 2013a]. Some uremic toxins are almost nondialyzable, but are adsorbed to specific membranes [Piroddi et al. 2013]. Uremic toxins are usually classified according to their dialyzability (Table 1, modified from [Glorieux and Tattersall 2015], Creative Commons Attribution Non-Commercial License and with permission of the publishers of Kidney Int and J Am Soc Nephrol).

Table 1. Key uremic retention solutes

<table>
<thead>
<tr>
<th>Uremic retention solutes</th>
<th>MW (Da)</th>
<th>Normal concentration mean</th>
<th>Normal concentration SD</th>
<th>Uremic concentration mean</th>
<th>Uremic concentration SD</th>
<th>Ratio U/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small water-soluble</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea (g/L)</td>
<td>60</td>
<td>&lt;0.4</td>
<td>2.3</td>
<td>1.1</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>ADMA (µg/L)</td>
<td>202</td>
<td>&lt;60.6</td>
<td>878.7</td>
<td>38.4</td>
<td>14.5</td>
<td></td>
</tr>
<tr>
<td>SDMA (µg/L)</td>
<td>202</td>
<td>76.1</td>
<td>646.4</td>
<td>606.0</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td>Middle molecules</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β2m (mg/L)</td>
<td>11,818</td>
<td>1.9</td>
<td>43.1</td>
<td>18.0</td>
<td>22.7</td>
<td></td>
</tr>
<tr>
<td>IL-6 (ng/L)</td>
<td>24,500</td>
<td>4.0</td>
<td>8.6</td>
<td>3.7</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>TNF-α (ng/L)</td>
<td>26,000</td>
<td>7.0</td>
<td>57.8</td>
<td>10.8</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>Protein-bound</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pCS (mg/L)</td>
<td>188</td>
<td>1.9</td>
<td>41.0</td>
<td>13.3</td>
<td>21.6</td>
<td></td>
</tr>
<tr>
<td>IS (mg/L)</td>
<td>212</td>
<td>0.5</td>
<td>44.5</td>
<td>15.3</td>
<td>84.0</td>
<td></td>
</tr>
<tr>
<td>IAA (mg/L)</td>
<td>175</td>
<td>0.5</td>
<td>2.4</td>
<td>2.2</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>HA (mg/L)</td>
<td>179</td>
<td>3.0</td>
<td>87.2</td>
<td>61.7</td>
<td>29.1</td>
<td></td>
</tr>
<tr>
<td>p-OHHA (mg/L)</td>
<td>195</td>
<td>NA</td>
<td>18.3</td>
<td>6.6</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

NA, not available; ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine; β2m, beta2-microglobulin; IL-6, interleukin-6; TNF-α, tumour necrosis factor-alpha; pCS, para-cresyl sulfate; IS, indoxyl sulfate; IAA, indole acetic acid; HA hippuric acid; p-OHHA, para-hydroxyhippuric acid.
Water and potassium in excess may kill rapidly. Poorly dialyzed uremic retention solutes, e.g. β2-microglobulin, kill slowly [Cheung et al. 2006, Davenport 2011, Depner 1991a]. Kinetics of potassium resembles that of urea [Vanholder et al. 1992]. Phosphate behaves differently [Debowska et al. 2015]. We know something about the correlation of specific uremic toxins with morbidity and mortality, summarized by [Dobre et al. 2013, Liabeuf et al. 2014 and Neirynck et al. 2013b], but have no effective means to eliminate most of them separately – which is not necessary given that uremia is not caused by retention of a few substances, but is rather a disturbance of the biochemical milieu, homeostasis, interaction of subtoxic concentrations of many substances [Depner 2001b]. Thus, unspecific removal is an acceptable strategy [Baurmeister et al. 2009].

Concentrations of some uremic toxins correlate with PCR [Eloot et al. 2013], but – paradoxically – dialysis patients with high PCR fare better than those with low PCR [Ravel et al. 2013].

Clearance by diffusion is important in the removal of small molecules, such as urea and potassium. Convection has only a small added value in removing these, but plays a major role in the removal of larger uremic toxins. Increasing convection expedites their removal relatively more than removal of urea [Daugirdas 2015]. Although many uremic toxins behave differently from urea [Eloot et al. 2005, Eloot et al. 2007], increasing dialysis dose measured by urea clearance usually enhances their removal and lowers their concentrations [Depner 1991b, Depner 1991c, Depner 2001b, Glorieux and Vanholder 2011, Gotch 1980, Neirynck et al. 2013a], but not in proportion to urea [Meyer et al. 2011, Sirich et al. 2012]. Increasing the session dose inevitably exacerbates technical problems, fluctuation of volumes and concentrations and disequilibrium between body compartments limiting this approach [Schneditz and Daugirdas 2001]. The intracorporeal rather than extracorporeal solute transport may be a major limiting factor in the removal of some uremic toxins [Eloot et al. 2014]. Increasing time and convection and preservation of RRF are the main means to increase middle molecule removal.

β2-microglobulin (molecular weight 11,818 Da) is a marker of middle molecules, but its dialysis kinetics is not as straightforward as that of urea and may differ from other middle molecules [Vanholder et al. 2008].

Blood purification is not the only means to control the concentrations of uremic toxins [Glorieux and Tattersall 2015]. Several protein-bound uremic toxins are produced by degradation of amino acids by colonic bacteria [Lisowska-Myjak 2014, Neirynck et al. 2013a]. One approach to decrease uremic toxicity is by
absorbing from the gut and by affecting the intestinal flora [Liabeuf et al. 2014, Schulman et al. 2006, Ueda et al. 2008]. In kidneys many uremic toxins are excreted by specific tubular mechanisms in addition to glomerular filtration. RRF is important in their removal [Marquez et al. 2011].

2.1.6 Causes of death

Cardiovascular events (40%) and infections (10%) are the most common causes of death of hemodialysis patients [US Renal Data System 2015]. Water retention, hypertension, left ventricular hypertrophy and hyperkalemia are obvious mechanisms related to dialysis dosing, but the association may be more complex, involving a chronic inflammatory state and several retention solutes. Blood access is a remarkable source of infections.

2.2 Blood purification techniques

Only extracorporeal techniques circulating blood through an external device are addressed. They include diffusion, convection, adsorption, and ion exchange, used separately or concomitantly.

2.2.1 Diffusion and convection

In hemodialysis, blood and dialysate flow on opposite sides of a semipermeable membrane. Solute are driven through the membrane by concentration gradient (diffusion) and by pressure gradient with the solvent drag (convection). The contribution of convection to urea clearance is about 5% in low-flux hemodialysis [Depner 1991a]. Large molecules are removed better by convection than by pure diffusion [Eloot et al. 2014]. The glomeruli function by convection.

In hemofiltration (HF), all solute removal takes place by convection; no dialysate is used, but replacement fluid is needed to achieve sufficient filtrate flow. One randomized controlled trial shows better outcome, including survival, with HF than with low-flux HD [Santoro et al. 2008].

In hemodiafiltration (HDF) both replacement fluid and dialysate are used. Some internal hemodiafiltration without separate replacement fluid may take place in
high-flux dialyzers, when dialysate flows into blood in the dialysate inlet end (backfiltration) and out at the other end.

2.2.2 Adsorption and ion exchange

Some solutes are adsorbed to the dialysis membrane in conventional dialysis [Aucella et al. 2013, Eloot et al. 2014, Piroddi et al. 2013]. Hemoperfusion is a technique based solely on adsorption; no extra fluid is used. Adsorption has been utilized in intoxications, in replacing hepatic function and in regenerating the dialysate [Ash 2009]. The low-flux membranes do not permeate β2-microglobulin at all [Eloot et al. 2014]. With polysulfone membranes the majority of β2-microglobulin removal occurs by diffusion and convection, with PMMA membranes by adsorption [Aucella et al. 2013]. Adsorption and ion exchange techniques alone do not suffice to sustain life in ESRD, but attempts have been made to combine them with hemodialysis [Aucella et al. 2013].

2.3 Hemodialysis prescription

2.3.1 Dialysate composition and temperature

The concentrations of components of the dialysate, e.g. sodium, chloride, bicarbonate, and calcium, are an essential part of the prescription, but do not affect the removal of uremic toxins. Temperature likewise has nothing to do with the dose, but lowering it may improve the hemodynamic stability. The positive effects of HDF have sometimes been explained by that mechanism [Daugirdas 2015].

2.3.2 Filter and convection technique

Selection of the dialyzer determines the filtering characteristics and maximum instantaneous clearance (mass transfer area coefficient $K_{0A}$). Many modern dialyzers combine biocompatibility, high efficiency (high $K_{0A}$), high flux (high permeability to water), and large pore size (high permeability to large molecules permitting high clearance, especially with enhanced convection techniques). HDF combines high clearance of small molecules by diffusion and high clearance of big
molecules by convection. There are also differences in the adsorptive capacity of the membranes [Aucella et al. 2013, Perego 2013].

In the HEMO trial [Eknoyan et al. 2002], high flux correlated with better outcome in patients with long dialysis history, with probably negligible RRF. Later observational studies ([Canaud et al. 2006a, Canaud et al. 2015, Davenport et al. 2015]) and RCTs ([Santoro et al. 2008, Schiff 2007], MPO [Locatelli et al. 2009], CONTRAST [Grooteman et al. 2012], Turkish [Ok et al. 2013] and ESHOL [Maduell et al. 2013a]) have also reported positive effects of convection. In MPO, only patients with S-Alb < 40 g/L benefited significantly from high-flux dialysis [Locatelli et al. 2009]. Mortality reduction was significant only in high-volume HDF (filtration >23 L, ESHOL trial) and HF, but not in high-flux HD and low-volume HDF. In high-flux HD, the convective transport is <10 L/session [Mostovaya et al. 2014].

In one heavily criticized meta-analysis [Rabindranath et al. 2005] survival was better with HD than with HDF. In one of the recent four meta-analyses HDF was significantly better [Mostovaya et al. 2014], in three the benefit remained unproven [Nistor et al. 2014, Susantitaphong et al. 2013, Wang et al. 2014]. [Locatelli et al. 2015] interpret these results as inconclusive. [Mostovaya et al. 2015] come to a different conclusion. In their opinion, high-volume (>20 L) online post-dilution HDF is an effective therapy and the convection volume is the most practical measure of the dose of HDF. EBPG have recently been updated to favor high-flux membranes [Tattersall et al. 2010], but probably their use is beneficial only in high-volume HDF. Obviously the added value of increased convection is rather small because it has been so difficult to demonstrate.

### 2.3.3 Blood, dialysate, and filtrate flow

Michaels’ equation [Daugirdas and Van Stone 2001, Ward et al. 2011] (36 on page 93) describes the dependence of dialyzer diffusive clearance (Kd) on blood and dialysate flow (Qb and Qd) and dialyzer K0A. With low permeability (low K0A, middle molecules) the effect of flows on clearance is small. Convective transport does not depend on dialysate flow. In RCTs a significant reduction in mortality has been achieved by HDF only with high filtration volumes (>23 L/session) [Maduell et al. 2013a]. Dialysate and replacement fluid cost, blood is free, but the access may restrict its flow. For optimal urea removal blood and dialysate flows should be in balance (1:1.5-2). In lengthy treatment sessions lower flows may be sufficient, but
dialysate consumption is still substantial. With modern dialyzers the effect of Qd on Kd\textsubscript{area} may differ from that calculated by Michaels’ equation [Hauk et al. 2000, Leypoldt et al. 1997, Ward et al. 2011]. Ultrapure water is a prerequisite for convective techniques. In post-dilution HDF, high filtrate flow also requires high blood flow (Qb).

### 2.3.4 Duration and frequency

Treatment duration, frequency, and symmetry of the schedule are essential elements of the prescription and have a decisive effect on solute removal, survival, and HRQOL (sections 2.6.2 and 2.6.3). The interval between treatments is also important. The odd number of days in a week causes difficulties for hemodialysis patients in the conventional 3 x/week schedule. Mortality is highest on Mondays and Tuesdays [Bleyer et al. 1999, Foley et al. 2011, Fotheringham et al. 2015]. Splitting the weekly treatment time into smaller fractions corrects this problem and lowers concentrations, but may increase blood access complications [Jun et al. 2013, The FHN Trial Group 2010, Weinhandl et al. 2015].

### 2.3.5 Water removal

Fluid accumulation is a common problem in dialysis patients. Technically its removal is simple, but the patients do not always tolerate it. Antihypertensive medication may exacerbate blood pressure drops during dialysis and hamper ultrafiltration leading to volume load, blood pressure rise, and a vicious circle. Water removal is not addressed in this thesis.

### 2.3.6 Prescribed and delivered dose

Dialyzer clearance multiplied by treatment time (Kt) is based on dialyzer characteristics, Qb, Qd, and td. It is a patient-independent, external measure of delivered dialysis dose and often scaled to patient urea distribution volume V (Kt/V). Traditionally the delivered dose has been estimated from its effects on the patient’s blood urea concentrations because measurement of true Kd was difficult before the advent of ionic dialysance monitoring (IDM) devices. Modeled Kt/V is
insensitive to errors of Kd, but V is not an ideal scaling factor (sections 2.6.4, 6.1 and 6.3).

In the USA the single pool Kt/V_{urea} is the primary measure of dialysis dose [National Kidney Foundation 2015], obviously because it can be easily prescribed. Even some observational registry studies are based on the prescribed dose reflecting the intention-to-treat concept.

The KDOQI guidelines recommend a higher prescribed target Kt/V (1.4) to guarantee a minimum delivered Kt/V (1.2) for all [National Kidney Foundation 2015]. In Europe, Qb, Qd, and td are often corrected arbitrarily if the delivered dose target has not been achieved. The resulting new prescribed Kt/V is ignored and forgotten and the focus is in the delivered dose.

If the Kt/V target is A (e.g. 1.2), then the required dialyzer clearance is

\[ K = \frac{A \cdot V}{t} \]  \hspace{1cm} (3)

and the required treatment time

\[ t = \frac{A \cdot V}{K}, \]  \hspace{1cm} (4)

where K is dialyzer clearance in mL/min, V is in mL and t in min.

V can be estimated from anthropometric equations [Hume and Weyers 1971, Watson et al. 1980] and K from Michaels’ equation or nomograms published by the dialyzer manufacturer.

We can choose the dialyzer, set K, t, and Qd and determine the required Qb from a nomogram. Or we can set Qb and Qd and calculate Kd from Michaels’ equation and td from Equation 4.

Online monitors based on ionic dialysance or UV light absorption help in delivering exactly the prescribed dose.

Taking into consideration the compartment effects and prescribing the required Qb, Qd, and td to achieve a continuous-equivalent clearance target is more complex and among the topics addressed in Study IV.
2.4 Delivered dose

2.4.1 Marker solutes

In the first decades the dialysis dose was calculated by the square meter-hour concept [Babb et al. 1971, Charra et al. 1992a, Shinaberger 2001]. Currently the delivered dose is estimated from the patient using marker solutes. Removal rate is not a measure of dialysis efficiency because in metabolic equilibrium it is equal to generation rate regardless of the intensity of dialysis. Urea has exceptional dialysis kinetics and is not a good representative of uremic toxins, but has several advantages as a marker: it is the main metabolite of ingested protein – over 90% of nitrogen is excreted as urea –, abundant, easy to measure, distributed evenly in body water, permeates cell membranes without difficulty, is not bound to plasma proteins, and dialyzes well [Depner 1991a]. Survival correlates with urea-based dose measures (section 2.6.1).

Formerly vitamin B12 (mw 1,355 Da) was as a marker of “middle molecules” [Vanholder et al. 1995]. This is not a uremic toxin, but the corresponding measure “dialysis index” correlated with signs of uremic neuropathy [Babb et al. 1975, Babb et al. 1977, Babb et al. 1981, Milutinovic et al. 1978]. Later, β2-microglobulin has been used as a representative of middle molecules. It fits with the concept of the square meter-hour hypothesis [Babb et al. 1971]. The original aim of the NCDS trial was to ascertain whether it was more important to eliminate small or middle-sized molecules [Lowrie et al. 1976]. Dialysis time was a representative of removal of middle molecules. Outcome correlated with it, but the association was not significant and the middle molecules were forgotten for decades.

In the HEMO trial two markers were used: urea and β2-microglobulin [Eknoyan et al. 2002]. The importance of middle molecules and other poorly dialyzable uremic toxins and controversy about the relative importance of small and large molecules has once again arisen [Vanholder et al. 2008], in association with dialysis frequency, duration, and membrane [Daugirdas 2015]. Kt/Vur ea does not describe the clearance of middle molecules. Their removal depends mainly on convection and weekly treatment time. Practices and devices which yield good middle molecule clearance usually also yield sufficient urea clearance, in the range where the effect of urea clearance on outcome levels out and the differences are of little significance.
2.4.2 Concentration and clearance

Clearance reflects the removal rate and concentration changes during the dialysis cycle, but uremic toxicity is more dependent on concentration levels [Sargent and Gotch 1975]. In the National Cooperative Dialysis Study (NCDS) patients with high time-averaged urea concentrations (TAC) fared worse than those with low ones [Laird et al. 1983, Lowrie and Sargent 1980, Lowrie et al. 1981, Sargent 1983]. However, in a reanalysis of the NCDS material [Gotch and Sargent 1985] the clearance-based variable $Kt/V_{\text{urea}}$ was a better measure of dialysis dose than urea concentration, because

1) urea concentration also depends on its generation rate
2) $Kt$ is a patient-independent measure of delivered dialysis dose
3) scaling by urea distribution volume ($V$) is based directly on urea kinetics
4) approximate $Kt/V$ can be derived from only two blood urea concentration values (Equation 6)
5) $Kt/V$ correlates with outcome more closely than urea concentration (section 2.6.1.)

Urea clearance is a useful descriptor of the treatment method, but the severity of uremia depends on concentrations of true uremic toxins. In determining dialysis dosing we must separate the dose – expressed as dialyzer clearance and treatment time – from its effect and accept that other factors, too, affect the outcome.

2.4.3 Single-pool UKM

The intermittency of conventional hemodialysis entails some special problems and solutions for measuring the dialysis dose delivered at one session [Farrell and Gotch 1977, Gotch et al. 1974, Sargent and Gotch 1980].

Urea removal ratio (URR) describes the effect of dialysis on the patient. It has been used widely in large epidemiological studies. It ignores RRF and UF.

$$\text{URR} = \frac{(C_0 - C_t)}{C_0}.$$  \hspace{1cm} (5)

Solute removal index (SRI) or fractional solute removal (FSR) is a more sophisticated version of URR [Keshaviah 1995, Keshaviah and Star 1994, Verrina et al. 1998]. It takes UF into account and is often used in direct dialysis quantification (DDQ).
Equation

\[ \frac{Kt}{V} = \ln\left(\frac{C_0}{C_t}\right), \]  

(6)

where \( \ln \) is the natural logarithm and \( C_0 \) and \( C_t \) the pre- and postdialysis concentrations, is the simplest urea kinetic model [Lowrie and Teehan 1983], derived by mathematical integration from the clearance definition. The concentration \( C_t \) after dialysis time \( t \) is

\[ C_t = C_0 \cdot e^{-\frac{Kt}{V}}, \]  

(7)

where \( e \) is the base of the natural logarithm. \( \frac{Kt}{V} \) is a descriptor of the effect of dialysis on blood urea concentration, scaled automatically— but perhaps not optimally—to patient size and derived from only two blood urea concentration measurements. URR and the approximate \( \frac{Kt}{V} \) (Equation 6) are mathematically linked:

\[ \frac{Kt}{V} = \ln\left(\frac{1}{1 - \text{URR}}\right). \]  

(8)

Equation 6 is valid if

1) removal of urea by dialysis obeys the clearance equation 1a (on page 19)
2) urea is not removed via other pathways during dialysis
3) urea is not generated during dialysis
4) the whole mass of urea is evenly distributed in only one compartment
5) the size of the compartment remains constant during dialysis.

None of these conditions is true. The classic single pool variable volume urea kinetic model (spvvUKM) [Sargent and Gotch 1980] corrects the inaccuracy of Equation 6 due to ultrafiltration, urea generation, and water accumulation and removal during the dialysis cycle. It outputs \( V_t \) and \( G \). The equations (33 and 34 on page 92) must be solved iteratively, because \( V_t \) and \( G \) appear in both. \( \frac{Kt}{V} \) is calculated from \( V_t \) and the input variables \( Kd \) and \( td \). The calculated \( V_t \) and \( G \) depend heavily on \( Kd \). Error in \( Kd \) causes a nearly proportional error in \( V_t \), but a 50% error in \( Kd \) causes only 2% error in \( \frac{Kt}{V} \) [Buur 1991]. Ionic dialysance from IDM can be used as \( Kd \) in UKM.

Several simple equations have been proposed for estimating session dose [Prado et al. 2005]. The best validated is Daugirdas’ “second generation” logarithmic equation for sp\( Kt/V \) [Daugirdas 1993, Daugirdas 1995]:

\[ \text{Equation} \]

\[ \text{Kt/V} = \ln\left(\frac{C_0}{C_t}\right), \]  

where \( \ln \) is the natural logarithm and \( C_0 \) and \( C_t \) the pre- and postdialysis concentrations, is the simplest urea kinetic model [Lowrie and Teehan 1983], derived by mathematical integration from the clearance definition. The concentration \( C_t \) after dialysis time \( t \) is

\[ C_t = C_0 \cdot e^{-\frac{Kt}{V}}, \]  

where \( e \) is the base of the natural logarithm. \( \frac{Kt}{V} \) is a descriptor of the effect of dialysis on blood urea concentration, scaled automatically— but perhaps not optimally—to patient size and derived from only two blood urea concentration measurements. URR and the approximate \( \frac{Kt}{V} \) (Equation 6) are mathematically linked:

\[ \frac{Kt}{V} = \ln\left(\frac{1}{1 - \text{URR}}\right). \]  

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Several simple equations have been proposed for estimating session dose [Prado et al. 2005]. The best validated is Daugirdas’ “second generation” logarithmic equation for sp\( Kt/V \) [Daugirdas 1993, Daugirdas 1995]:
\[ \text{Kt/V} = -\ln \left( \frac{C_t}{C_0} - 0.008 \cdot T \right) + \left( 4 - 3.5 \cdot \frac{C_t}{C_0} \right) \cdot \frac{UF}{W}, \tag{9} \]

where \( T \) is treatment time (h), \( UF \) ultrafiltration volume (L) and \( W \) postdialysis weight (Kg). Daugirdas’ Kt/V has no assumptions regarding \( K_d \) and \( V \), but is based on the logarithmic decrease of concentration during the dialysis session (Equation 6), with corrections for \( UF \) and \( G \). \( K_d \) is not needed as an input parameter. Garred’s logarithmic equation has been validated in a smaller population [Garred et al. 1994a]. Both have good concordance with the classic spvvUKM.

The single pool UKM ignores the compartment effect, which appears e.g. as the disequilibrium syndrome and a rapid rise in blood urea concentration (rebound) after termination of the dialysis session, when urea from the sequestered body compartments flows into the blood [Depner 1992, Gabriel et al. 1994].

[Depner and Bhat 2004] present a variable weekly nKt/V, which emphasizes the frequency:

\[
\text{weekly nKt/V} = 0.92 \cdot N \cdot \left( 1 - e^{-1.1 \cdot \text{spKt/V}} \right), \tag{10}\]

where \( N \) is the number of sessions per week and \( e \) the base of the natural logarithm.

All the abovementioned methods are based on urea. Scribner and Oreopoulos emphasize the importance of time and frequency by introducing the “hemodialysis product” (HDP) as the measure of dose [Scribner and Oreopoulos 2002]:

\[
\text{HDP} = \text{td} \cdot \text{fr}^2. \tag{11}\]

It is totally patient-independent like Kt. Equations 10 or 11 have not become popular.

### 2.4.4 Double-pool UKM

During a hemodialysis session blood and extracellular fluid in highly perfused organs are cleared efficiently, but solutes may remain sequestered in other tissues and intracellularly. Dialysis rapidly reduces the plasma concentrations of such solutes but removes only a small fraction of the total body content. After termination of the session the concentrations equilibrate. Whole-body clearance is lower than dialyzer clearance. A serial two-compartment (double pool) model, developed in the 1970s [Abbrecht and Prodany 1971, Canaud et al. 2000,
Dombeck et al. 1975, Frost and Kerr 1977], describes urea concentrations during a dialysis cycle fairly accurately. It gives urea generation rate G and the “intracellular” and “extracellular” pool distribution volumes, which are needed in simulations. The compartments are functional rather than anatomical entities. The “extracellular” pool is that being dialyzed (blood and interstitial space), the “intracellular” pool the peripheral poorly perfused tissues.

Correct G and V are essential prerequisites in simulations. Renal urea clearance must be included as an input variable in UKM to obtain correct G, which is needed for calculating ECC and PCR. PCR reflects DPI, is an important prognostic factor [Ravel et al. 2013] and has interesting relationships to dialysis dosing (section 6.4).

Both single-pool and double-pool UKM require as input variables two or three blood urea concentration values, dialyzer clearance Kd, renal urea clearance Kr, and the usual dialysis cycle data. Alternatively, one can input V and compute Kd.

The double-pool urea kinetic model can also be applied to other substances if the required parameters (generation rate, distribution volumes, dialyzer clearance, and intercompartment transfer coefficient) are known. β2-microglobulin removal has been described with a triple pool model [Odell et al. 1991]. Quadruple-pool models for phosphate have been presented [Spalding et al. 2002].

[Daugirdas et al. 2009] have published a downloadable double-pool UKM program Solute-Solver with source code. It includes assumptions and approximations regarding the compartment volumes and intercompartment transfer coefficients and can as such be applied only for urea. The overt strength of Solute-Solver is that it has been published – and used e.g. by [Ramirez et al. 2012]. Unfortunately it has not been updated since July 2010 and has problems with newer browsers and operating systems.

Downloadable computer programs for double pool UKM:


The mathematical models have been criticized [Lowrie 1996, Roa and Prado 2004]. “This is indeed a powerful analytic technique, and allows the physician to take emotional distance from the disturbing uncertainties of dialysis” [Barth 1989, page 209]. “Dialysis cannot be dosed” [Meyer et al. 2011, title].
2.4.5 eKt/V

Special attention must be paid to post-dialysis blood sampling to control access and cardiopulmonary recirculation and post-dialysis rebound [Daugirdas and Schneditz 1995, Pedrini et al. 1988, Schneditz et al. 1992, Sherman and Kapoian 1997, Tattersall et al. 1993].

Immediate post-dialysis plasma urea concentration (taken preferably immediately before terminating the treatment session) is used in computing spKt/V. Due to the compartment effect it overestimates patient clearance [Kaufman et al. 1995]. At 30 min. post-dialysis the rebound is over, but the effect of urea generation on its plasma concentration is still negligible or can be estimated. This is the equilibrated post-dialysis concentration.

Waiting 30 min. for an equilibrated blood sample is inconvenient for both patient and personnel. The equilibrated post-dialysis urea concentration can be estimated from the immediate post-dialysis sample [Tattersall et al. 1996, Smye et al. 1992] or by taking the sample 30 min. before termination of the session [Bhaskaran et al. 1997, Ing et al. 2000, Canaud et al. 1995, Canaud et al. 1997, Pflederer et al. 1995]. Equilibrated Kt/V (eKt/V) can be estimated directly, without estimating first the equilibrated post-dialysis concentration, from spKt/V and td with the “rate equation” [Daugirdas 1995, Daugirdas and Schneditz 1994]:

\[
eKt/V = spKt/V - a \times spKt/V / T + b,
\]

where \( a \) and \( b \) are constants depending on the blood access (0.60 and 0.03 for AV and 0.46 and 0.02 for VV) and \( T \) is td in hours. The equation was further modified for the HEMO trial [Daugirdas et al. 2004].

spKt/V overestimates dialysis efficiency especially in short high-efficiency treatments, which in the USA led to underdialysis and high mortality in the 1980's [Barth 1989, Berger and Lowrie 1991, Parker TF 1994, Roa and Prado 2004, Shinaberger 2001, US Renal Data System 2015]. EBPG recommend eKt/V as the primary dose measure. This makes the short and long sessions more commensurable.

With spKt/V = 1.20, eKt/V calculated with Equation 12 (AV access) is:

<table>
<thead>
<tr>
<th>td (h)</th>
<th>2.5</th>
<th>4.0</th>
<th>6.0</th>
<th>8.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>eKt/V</td>
<td>0.94</td>
<td>1.05</td>
<td>1.11</td>
<td>1.14</td>
</tr>
</tbody>
</table>
The eKt/V concept does not replace the true double pool UKM. It cannot be used in simulations and in calculating V, G and PCR.

2.4.6 Direct dialysis quantification (DDQ)


2.4.7 Online monitoring

With a urea monitor the urea concentration of effluent dialysate is measured at short intervals, the double-pool constants determined with curve-fitting techniques, and all essential double-pool UKM values computed during the dialysis session [Bosticardo et al. 1994, Depner et al. 1996, Depner et al. 1999, Garred 1995, Sternby 1998]. The method is accurate, but impractical and expensive.

Online ionic dialysance monitor (IDM; Fresenius OCM, Baxter Diascan) increases the dialysate concentration momentarily, monitors the conductivity change in the dialysate outlet, and calculates the ionic dialysance (conductivity clearance), which is near to urea clearance [Di Filippo et al. 1998a, Di Filippo et al. 2001, Gotch 2002, Gotch et al. 2004, Lowrie et al. 2006, Manzoni et al. 1996, Polaschegg 1993]. It can do this several times during every dialysis session at almost no cost. IDM does not replace UKM but complements it by providing the most problematic UKM input parameter Kd [Di Filippo et al. 2004, Wuepper et al. 2003]. Ionic dialysance corresponds to effective clearance, taking access and cardiopulmonary recirculation into account but not the compartment effects.

Devices monitoring the concentrations of uremic retention solutes in the effluent dialysate by UV light absorption have been developed for estimating dialysis efficiency online – unfortunately using Kt/Vurea as the reference –
[Castellarnau et al. 2010, Donadio et al. 2014, Uhlin et al. 2003] and implemented in dialysis machines (Braun Adimea). They estimate K/V from the logarithmic absorbance versus time curve; K and V cannot be determined separately. Reports on experiences with these are rarer than with ionic dialysance devices.

Guidelines recommend monthly checking of the delivered dose. With online monitoring of ionic dialysance or UV absorption it can be done at every session.

2.4.8 Residual renal function

Creatinine clearance is commonly used as a measure of renal function in nondialysis patients. It is higher than urea clearance, because urea is reabsorbed, but creatinine is excreted in the tubules. EBPG 2007 recommend the average of urea and creatinine clearance as the measure of RRF of dialysis patients [Tattersall et al. 2007]. KDOQI recommends urea clearance [National Kidney Foundation 2015]. It conforms better to the practice of using urea kinetics in dialysis dosing because one of the parameters in UKM is renal urea clearance. Expressing RRF as urea clearance permits calculation of correct G and PCR and is a safe way to sum RRF and dialysis. Continuous-equivalent measures derived from true UKM include renal urea clearance automatically.

Renal clearance can be assessed using radiolabeled solutes $^{51}$Cr-EDTA, $^{99}$mTc-DTPA or $^{125}$I-iothalamate [Krediet 2006], but the guidelines [National Kidney Foundation 2015, Tattersall et al. 2007] recommend calculation from urine collection and the average of corresponding post- and predialysis urea concentrations. The concentration profile during the interval is curvilinear, flattening out towards the end of the period. Thus the average concentration (denominator) calculated this way is lower than the time-averaged value, and renal urea clearance is overestimated. [Gotch and Keen 1991] have presented formulae emphasizing the higher predialysis concentration:

$$Kr = Vu \times Cu / (t \times (0.25 \times Ct1 + 0.75 \times C02)) \quad (3 \times \text{week})$$  \hspace{1cm} (13)

$$Kr = Vu \times Cu / (t \times (0.16 \times Ct1 + 0.84 \times C02)) \quad (2 \times \text{week}),$$  \hspace{1cm} (14)

where $Kr =$ renal urea clearance, $Vu =$ collected urine volume, $Cu =$ urine urea concentration, $Ct1 =$ postdialysis plasma urea concentration of the preceding dialysis session and $C02 =$ predialysis plasma urea concentration at the end of urine
collection. Gotch and Keen recommend collecting urine for only 24 h before dialysis. They also describe a formula for “adding” RRF to dialysis session $Kt/V$:

$$Kt/V_{\text{adj}} = Kt/V + b \times Kr / V,$$

(15)

where $Kr$ is renal urea clearance in mL/min, $V$ is in mL and $b$ is 4,500 in 3 x/week schedule and 9,500 in 2 x/week.

### 2.5 Continuous-equivalent clearance (ECC)

#### 2.5.1 Aiming at a universal dose measure

Dialyzer urea clearance may be several times greater than that of healthy kidneys, but conventionally it is in effect only during less than ten percent of the time. The fluid shifts and concentration fluctuations restrict the usefulness of intermittent hemodialysis.

$Kt/V$ and other measures of a single dialysis session can be used in comparing dialysis dosing only if the treatment frequency is equal [Depner 2001a]. Clearance $K$ ($K_d$) and duration $t$ ($t_d$) have equal weight in $Kt$ and $Kt/V$: four hours with $K = 200$ mL/min is equal to two hours with $K = 400$ mL/min, but $K_d$ and $t_d$ may not have the same impact on solute removal, due at least in part to the compartment effects [Basile et al. 2011, David et al. 1998, Eloot et al. 2008]. Prescribed weekly $Kt/V$ is equal whether the patient is dialyzed six hours two times per week or two hours six times with equal dialyzer clearance, but solute concentrations and treatment outcomes are not equal.

The promising outcomes achieved recently with frequent HD accentuate the need of a universal dose measure in investigating the relationship between dose and outcome. It is not clear whether these are due to higher clearance or lesser fluctuation in volumes and concentrations or other factors. In most investigations the weekly dose has been higher in the frequent group or it has not been appropriately reported.

#### 2.5.2 Definitions based on UKM

$EKR$ ($ECC_{TA}$) and $stdK$ ($ECC_{PA}$) are based on the definition of clearance:
$K = \frac{E}{C}$ \hspace{1cm} (1b on page 19)

In steady state the removal rate $E$ equals the generation rate $G$, thus

$K = \frac{G}{C}$ \hspace{1cm} (2b on page 19)

Urea concentrations fluctuate in intermittent dialysis. If $C$ is the time-averaged concentration (TAC) during the dialysis cycle, then the equation can be said to describe the average clearance (dialysis + RRF), if $G$ is constant [Depner 1991a] and equal to removal rate $E$. Casino and Lopez named this expression equivalent renal clearance (EKR, time-average clearance) [Casino 1999, Casino and Lopez 1996]:

$EKR = \frac{G}{TAC}$ \hspace{1cm} (16)

In conventional intermittent hemodialysis EKR is typically 12-15 mL/min or 120-150 L/week, significantly higher than in CAPD or the renal clearance in ESRD patients without dialysis. The inferior efficiency of hemodialysis may be due to the intermittency, including compartment disequilibrium or differences in the solute transport profile of kidneys, peritoneum, and dialyzer membrane or other factors. Gotch tried to resolve the discrepancy by implementing the stdK concept [Gotch 1998, Gotch 1999, Gotch et al. 2000], based on the “peak concentration hypothesis”, which assumes that high concentration peaks are especially harmful [Clark and Ronco 2001, Keshaviah et al. 1989]. With comparable outcomes the weekly average peak concentration (PAC) in conventional hemodialysis and the constant concentration in CAPD are about equal.

$stdK = \frac{G}{PAC}$ \hspace{1cm} (17)

The unit of EKR and stdK is e.g. mL/min or L/week. Both may be scaled to body size by dividing by urea distribution volume $V$ and expressed as EKR/V and stdK/V:

$EKR/V = \frac{EKR}{V}$ \hspace{1cm} (18)

$stdK/V = \frac{stdK}{V}$. \hspace{1cm} (19)

The most practical unit of EKR/V and stdK/V is /week. $G$, $V$, TAC and PAC can be determined by kinetic modeling. Because $Kr$ is an input variable in computing $G$ by UKM, these variables are not pure dialysis measures but also include RRF.

EKR/V and stdK/V are equivalent continuous clearances scaled by distribution volume $V$. Unfortunately expressions with operators are used as variable names,
such as Kt/V, EKR/V and stdK/V. This may cause confusion in equations like 18, 19 and 29. In Studies I-IV of the present thesis EKR/V is called stdEKR. stdKt/V is a dimensionless misnomer, not an ECC. In Studies II-V stdK/V is used instead of stdKt/V. With equal treatment stdK < EKR.

For full conformity with the peak concentration hypothesis, the predialysis concentration after the longest interval should be substituted for C in Equation 2b on page 19. EBPG 2007 recommend this approach and call the variable SRI [Keshaviah 1995, Tattersall et al. 2007], but it is poorly documented and has not been used in outcome studies. Of course, the actual peak concentration is simpler to determine than PAC or TAC.

The peak concentration hypothesis has not been confirmed empirically. In the old NCDS trial TAC correlated more closely with outcome than PAC [Laird et al. 1983]. The stdK/V concept may be an artificial attempt to render continuous and intermittent therapies commensurable. According to Daugirdas, stdK/V is not a true continuous urea clearance, but a clearance “compressed” by about 1/3 and is extremely sensitive to dialysis frequency. It may also reflect the impact of sequestered small molecular weight solutes [Daugirdas 2014]. There are no studies demonstrating which is more closely associated with outcome, EKR/V or stdK/V. EKR/V is more sensitive to schedule asymmetry than stdK/V [Daugirdas and Tattersall 2010]. Schedule asymmetry is not addressed in the present thesis. Comprehensive analyses concerning the relationships between EKR, stdK and SRI have been presented by [Waniewski et al. 2006, 2010] and [Debowska et al. 2011].

2.5.3 Simple equations

Ideally G, V, TAC, and PAC in the above equations should be from double-pool UKM for greater accuracy, especially in simulations. Gotch and Leypoldt have developed equations for estimating stdK/V without UKM [Gotch 2004, Leypoldt 2004, Leypoldt et al. 2004]. They do not take RRF and convection into consideration, but are pure diffusive dialysis measures [Diaz-Buxo and Loredo 2006a, Diaz-Buxo and Loredo 2006b]. [Daugirdas et al. 2010a] have proposed a complex calculation method involving fluid removal and residual kidney clearance. Weekly URR is an approximation of stdK/V. FSR, SRI and URR are “kinetically” additive, Kt/V is not [Waniewski and Lindholm 2004].
2.5.4 Guidelines

The KDOQI guidelines for hemodialysis adequacy have recently been updated to take RRF and UF into consideration in stdK/V and recommend 2.3/week as the target for schedules other than thrice weekly [National Kidney Foundation 2015]. The EBPG 2002 guidelines recommended 13 - 15 mL/min as the minimum adequate EKR if the patient has significant RRF [Kessler et al. 2002], but the 2007 version includes no recommendations for EKR [Tattersall et al. 2007]. Instead, a solute removal index SRI of 2.0/week is recommended as a minimum for patients with RRF or with other than a 3 x/week schedule.

2.6 Dependence of outcome on dose (adequacy)

2.6.1 Session dose

Abundant information on the association of better outcome with higher dose in conventional 3 x/week schedule is available from large observational studies before HEMO (>10,000 patients: [Li et al. 2000, Lowrie et al. 2002, Owen et al. 1993, Owen et al. 1998, Port et al. 2002, Shinzato et al. 1996, Shinzato et al. 1997]). Most studies on the association of outcome with dialysis dose are based on urea clearance. In some studies no correlation between Kt/V or URR and survival was found [Bleyer et al. 1996, Charra 2001, Charra et al. 1992a, Combe et al. 2001, Panaput et al. 2014, Salahudeen et al. 2003]. The mortality curve levels out or is J-shaped, probably due to malnutrition in the high dose groups [Chertow et al. 1999, Miller et al. 2010]. In some cross-sectional studies the correlation of Kt with survival was stronger than that of Kt/V [Li et al. 2000, Lowrie et al. 1999, Lowrie et al. 2005].

No significant positive correlation between dose and survival was found in the randomized controlled HEMO trial. However, in subgroup analyses the higher dose resulted in better survival among women. HEMO may be confounded by the “dose-targeting bias” [Greene et al. 2005]. It has been criticized for using V as the scaling factor [Lowrie et al. 2005] and for improper extensions to more frequent therapies [Roa and Prado 2004].

After HEMO only few reports on association between dose and survival have been presented [Depner et al. 2004, Termorshuizen et al. 2004]. In a large material
(84,936 patients) high dialysis dose was associated with lower mortality among women but not among men [Port et al. 2004].

There are no RCTs reporting an unequivocal cause and effect relationship between dialysis dose and outcome [Oreopoulos 2002]. Some outcome studies are summarized by [National Kidney Foundation 2006].

Some factors cause dissociation between dialysis adequacy and Kt/V [Vanholder et al. 2002]. The most important are the large-pore membranes, nonconventional schedules and changed patient population. The survival curve levels out with increasing dose, but has shifted over the decades [Honkanen et al. 2014, Szczech et al. 2001]. The limits have been reached in the conventional in-center 3 x/week schedule. Dose measurement methods based on urea clearance are not optimal.

### 2.6.2 Treatment duration

In the early studies urea concentration was adjusted to a constant level with UKM. No difference in outcome was detected when the patients were divided into four groups according to treatment duration [Gotch et al. 1976]. In the randomized NCDS trial the positive effect of time was considerable, but not statistically significant (P = 0.06) [Laird et al. 1983, Lowrie et al. 1981, Parker et al. 1983], which led to shortening of treatments, especially in the USA [Gotch and Uehlinger 1991]. In Tassin the normal treatment duration was eight hours with excellent survival [Charra et al. 2003]. The association between session length and survival is strong in Japan, weaker in Europe and almost nonexistent in the USA in sessions longer than 3.5 hours [Daugirdas 2014].

Removal of solutes with large distribution volume or low dialyzer clearance or impaired inter-compartment mass transfer benefits more from time than urea [David et al. 1998, Eloot et al. 2008, Glorieux and Vanholder 2011], review [Eloot et al. 2012].

Increasing treatment duration is the simplest way to increase session Kt and Kt/V. In many investigations the effect of time has not been separated from the dose and environmental factors (institution or home, day or night) [Lacson et al. 2012, Nesrallah et al. 2012, Ok et al. 2011], reviews [Diaz-Buxo et al. 2013, Hakim and Saha 2014, Walsh et al. 2005]. In some studies the material has been adjusted for Kt/V_{urea} [Brunelli et al. 2010, Flythe et al. 2013, Lockridge and Kjellstrand]

Several uncontrolled enthusiastic reports on long nocturnal HD in small patient populations have appeared, but in the frequent long nocturnal arm of the controlled FHN trial [Rocco et al. 2011] the outcome was not essentially better than in conventional 3 x/week treatment and long-term mortality was even higher [Jardine and Perkovic 2015, Rocco et al. 2015]. There were severe recruitment difficulties in the FHN trial. Patients indifferent as to whether they will be randomized to conventional in-center or frequent nocturnal home hemodialysis form a small and special group and are not a representative sample of the dialysis population as a whole. In a recent nonrandomized controlled study of 494 patients, survival and many soft endpoints were significantly better with longer treatment time [Ok et al. 2011].

Time has an essential role in ultrafiltration and fluid balance. Increased dialysis time leads to better control of volume excess, to reduced occurrence of intradialysis hypotension, and to better control of serum phosphorus [Daugirdas 2013].

Sometimes the patient demands that the session be curtailed [Sehgal et al. 1998] or occasional interruptions are included in the treatment time (“the wall clock syndrome” [Depner 1994]). Patients may be happy to extend their total time on dialysis provided they feel better between treatments [Eloot et al. 2014, Honkanen et al. 2014].

The role of treatment time has not been conclusively determined; investigation continues (the TiME trial, https://clinicaltrials.gov/ct2/show/NCT02019225, accessed November 12, 2015).

2.6.3 Treatment frequency

Deaths are more frequent on the day after the long interval [Bleyer et al. 1999, Foley et al. 2011, Fotheringham et al. 2015]. The alternate-day schedule corrects this drawback [Georgianos and Sarafidis 2015]. Excellent results have been reported from eight-hour alternate day nocturnal home dialysis [Jun et al. 2013].
In a Chinese nonrandomized study survival was better in the 2 x/week group than in the 3 x/week, also in a subgroup on dialysis for over five years [Lin et al. 2012]. In another Chinese study, quality of life scores did not differ between the twice and thrice weekly groups [Bieber et al. 2014].

In several small observational studies with or without historical or registry controls many advantages of high frequency have been reported. These include blood pressure, LVH, phosphorus control, anemia, and HRQOL. On the other hand, the frequency of blood access complications has commonly increased [Jun et al. 2013, Weinhandl et al. 2015]. Some reviews criticize the observational studies on frequent dialysis: the results are good, but the studies poor [Lacson and Diaz-Buxo 2001, Perl and Chan 2009, Suri et al. 2006, Walsh et al. 2005]. In one observational study [Suri et al. 2013] outcomes of short daily in-center treatment were poorer than in conventional treatment. An excellent review has been presented by [Diaz-Buxo et al. 2013].

In a small RCT (52 patients) [Culleton et al. 2007] frequent nocturnal hemodialysis had positive effects on left ventricular mass, blood pressure, mineral metabolism, and quality of life.

In the randomized controlled short daily FHN trial “frequent hemodialysis, as compared with conventional hemodialysis, was associated with favorable results with respect to the composite outcomes of death or change in left ventricular mass and death or change in a physical-health composite score but prompted more frequent interventions related to vascular access”, and “the net effects of frequent hemodialysis will need to be balanced against the added burden for the patient and societal cost” [The FHN Trial Group 2010, pages 2287 and 2299].

In the frequent nocturnal FHN trial patients had improved control of hyperphosphatemia and hypertension, but no significant benefit in survival or left ventricular mass [Rocco et al. 2011]. Long-term mortality was higher than in the conventional group [Rocco et al. 2015]. A cohort study also suggests that 5-7 weekly sessions are associated with poorer survival [Suri et al. 2013].

Average weekly treatment time and stdK/V were in the frequent FHN groups considerably higher than in the 3 x/week groups. Thus the effects of frequency, duration, and dose cannot be differentiated.

No meta-analyses of the RCTs concerned on duration and frequency have been presented. A comprehensive review is presented by [Eloot et al. 2014]. Another recent review prefers conventional 3 x/week dialysis but with longer treatment times than is currently recommended [Hakim and Saha 2014]. According to EBPG
2007 Guideline 1.1, dialysis should be delivered at least 3 x/week and the total duration should be at least 12 h/week [Tattersall et al. 2007]. KDOQI 2015 does not set absolute limits. Daugirdas' recent opinion is that 2 x/week may suffice if the patient has considerable RRF [Daugirdas 2015]. stdK/V is affected by frequency more than EKR/V.

Increasing frequency often means increasing weekly treatment time and enables higher weekly dose, but stdK/V and EKR/V may be increased and concentrations decreased also by increasing frequency with equal Kd and weekly td [Clark et al. 1997, Depner 1998, Galland et al. 1999, Goldfarb-Rumyantzev et al. 2002, Leypoldt 2005].

2.6.4 Scaling

Dialyzer clearance K and treatment time t are input parameters in UKM. Only the scaling factor V is computed by kinetic calculations. V is also an independent prognostic factor: Physically large patients (with high V) have a survival advantage in hemodialysis with equal Kt/V [Lowrie et al. 2004, Owen et al. 1998, Owen et al. 2001, Wolfe et al. 2000]. Obese persons likewise have a survival advantage despite lower V/weight [Abbott et al. 2004, Port et al. 2002, Wolfe et al. 2000]. On the other hand, high modeled V and its rise over time reflect overhydration and predict poor outcome [Daugirdas et al. 2011]. Anthropometrically estimated total body water is greater than modeled urea volume [Daugirdas et al. 2003].

Kt (urea product) is a patient-independent measure of dialysis session dose, and recommended by [Chertow et al. 1997, Li et al. 2000, Lowrie et al. 1999, Lowrie et al. 2002, and Maduell et al. 2013b]. Kt omits the compartment effects and other patient-dependent tasks. Obviously scaling is needed. Outside dialysis, clearances are commonly scaled to BSA. With equal Kt/V, women and small people have poorer outcome and a smaller V/BSA ratio than men and large individuals [Daugirdas et al. 2003, Daugirdas et al. 2010b, Depner et al. 2004, Hume and Weyers 1971, Miller et al. 2010, Spalding et al. 2008]. [Greene et al. 2009] have proposed a corrected V(n) = 3.271 * V^{2/3} to be used in stdK/V. Some investigators have proposed adjusting Kt and stdK/V to BSA [Daugirdas 2014, Daugirdas 2015, Daugirdas and Greene 2005, Daugirdas et al. 2008a, Daugirdas et al. 2008b, Daugirdas et al. 2010c, Lowrie et al. 2005, Lowrie et al. 2006, Ramirez et al. 2012]. This enhances the dose to women and children. Bioelectrical resistance has also been presented as a scaling factor [Basile et al. 2010a, Basile et al. 2010b].
Which V – predialysis, postdialysis or time-averaged – should be used in the continuous-equivalent clearance equations (18-19 on page 38) as the reference has not been clearly defined. Postdialysis urea distribution volume (Vt) has been used in the Solute-Solver program [Daugirdas et al. 2009] and in the present thesis.

2.6.5 Residual renal function

The renal excretion profile of uremic solutes is different from that of dialysis. Renal function is “qualitatively” superior to dialysis with equal urea clearance [Marquez et al. 2011, Suda et al. 2000, Vilar and Farrington 2011, Vilar et al. 2009].


Renal urea clearance may justify marked reductions in dialysis dose [Daugirdas 2014]. There are no reports showing that full-dose dialysis for patients with RRF is better than the incremental approach [Kalantar-Zadeh et al. 2014, Vilar et al. 2009]. In incident HD patients, mortality during the first six months is very high [Kalantar-Zadeh et al. 2014].

In incremental dialysis RRF must be controlled regularly and the prescription corrected if RRF decreases.

2.6.6 Continuous-equivalent clearance

If correctly calculated, ECC combines RRF and dialysis and makes different treatment schedules commensurable. Few reports correlate outcome directly with continuous-equivalent clearance.

[Barreneche et al. 1999] correlate mortality with EKR. Death risk was 2.17 when EKRc was below the median 14.2 mL/min/40 L.

[Manotham et al. 2006] studied EKRc in twice-weekly hemodialysis. Serum albumin was used as the outcome measure. EKRc above 13 mL/min/40 L had
respectively 90% and 100% probabilities of maintaining monthly and 12-month serum albumin levels above 40 g/L. For this, Kt/V should exceed 2.2.

In daily home HD of 191 patients, survival was independently associated with stdK/V (HR 0.29, P<0.001). Survival was highest in the group where stdK/V exceeded 5.1/week [Lockridge et al. 2012]. stdK/V was calculated with the Leypoldt equation.

In the FHN short arm, total stdK/V$_{urea}$ was significantly higher in the frequent group than in the conventional group (3.60 vs. 2.57/week). Frequent hemodialysis was associated with significant benefits [The FHN Trial Group 2010]. In the FHN nocturnal arm the difference in stdK/V was even greater (5.03 vs. 2.91/week) [Rocco et al. 2011]. No definitive benefit of more frequent nocturnal hemodialysis could be demonstrated.

It is not possible to deduce the significance of higher stdK/V in the FHN trials. “Alternatively, the benefit of frequent hemodialysis in the short daily arm may result from improved control of other metabolic by-products, such as phosphate or other retained uremic solutes, more physiologic removal of solutes (yielding lower and less variable time-averaged solute concentrations), or improved control of extracellular volume excess (reducing the time-averaged fluid load)” [The FHN Trial Group 2010, page 2295].

### 2.6.7 Overdialysis

Increasing dialysis intensity without clear benefits is overdialysis, but the limit has been difficult to determine. According to [Gotch et al. 1997] it is spKt/V 1.1 and according to HEMO spKt/V 1.32 or eKt/V 1.16 in the 3 x/week schedule, but several studies report clear benefits from higher doses, at least in selected cases [Szczech et al. 2001]. In the cohort of [Salahudeen et al. 2003] the mortality in the highest Kt/V quintile (>1.68) was higher than in the lower quintile. These authors suspect that efficient dialysis would be harmful for sick and malnourished patients. The frequent nocturnal hemodialysis with slightly reduced flows (Qb 262±62, Qd 354±106 mL/min) and total weekly stdK/V$_{urea}$ 5.03±1.23/week may be an example of overdialysis with higher long-term mortality than in conventional treatment [Rocco et al. 2015]. In high frequency schedules access complications are more common [Jun et al. 2013, Weinhandl et al. 2015].
Phosphate depletion has been observed in nocturnal HD. Some other nutrients, e.g. amino acids and vitamins may also be dialyzed out of the patient and need to be replaced [Dobre et al. 2013, Hawley et al. 2008].

Several possible threats or complications of intensive HD have been presented: increased risk of blood access events, accelerated loss of residual function, intravascular volume depletion resulting in organ hypoperfusion, burnout in home HD and exposure to harmful substances and surfaces present in the dialyzer circuit which may cause platelet activation and microbubbles [Daugirdas 2014, Rocco et al. 2015]. The quality-adjusted life years and their unit costs must also be considered. Health care resources need to be prioritized for interventions of proven efficacy.

2.6.8 Soft endpoints

Significant improvements in soft endpoints have been reported in many RCTs where the effect of the dosing intervention on survival has been positive, but not statistically significant. These include blood pressure, intradialytic hypotension, LVH, hospitalization, nutritional status, and several laboratory values. Few reports associate HRQOL with dialysis dose [Hornberger 1993]. Most experiences concern on frequent dialysis [Mohr et al. 2001, Williams et al. 2004]. The treatment environment (home or center) and timing (day or night) are not essential factors in dosing, but may affect acceptance, compliance, survival and HRQOL.
3 AIMS OF THE STUDY

The purpose of this thesis was to search for answers to following questions:

3.1 Is high mortality in hemodialysis due to low dose?

Mortality among hemodialysis patients is unacceptably high. Reviewing the literature revealed too low dialysis dose as one possible explanation. Is the association between dose and mortality valid in our patient population?

3.2 How should the dialysis dose be measured?

Doses must be measured before they can be convincingly compared and increased. Session doses cannot be used as uniform measures in different schedules. Several reports describe favorable results from long or frequent hemodialysis, but it is not clear whether the benefits are due to more efficient toxin removal or other factors. The recommendations in common guidelines on measuring the dose are inconsistent and confusing with considerable RRF and in schedules other than 3 x/week.

3.3 How could dosing be improved?

How should treatment duration, frequency, blood flow, dialysate flow, and convection volume be adjusted for optimal outcome?
4 SUBJECTS AND METHODS

4.1 Patients

4.1.1 Hemodialysis treatment periods and modeling sessions

This thesis is a collection of observations from a small hospital providing adult dialysis services for a district of about 50,000 inhabitants in Eastern Finland. The observation time was nine years, from January 1, 1998 to December 31, 2006. The material comprises 57 in-center hemodialysis treatment periods of 51 patients, together 114.3 patient years. Short intervals as visitors to other dialysis centers do not interrupt the treatment period and are included in the treatment years. The patient characteristics are summarized in Table 2.

Table 2. Patient characteristics of the hemodialysis treatment periods (N = 57)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>38.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetics</td>
<td>42.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>61.7</td>
<td>15.5</td>
<td>16.6</td>
<td>91.6</td>
</tr>
<tr>
<td>Height</td>
<td>169</td>
<td>11</td>
<td>145</td>
<td>187</td>
</tr>
<tr>
<td>Weight</td>
<td>75.1</td>
<td>18.2</td>
<td>44.2</td>
<td>123.6</td>
</tr>
<tr>
<td>BMI</td>
<td>26.1</td>
<td>5.5</td>
<td>16.3</td>
<td>43.7</td>
</tr>
<tr>
<td>Vt</td>
<td>31.9</td>
<td>6.8</td>
<td>20.5</td>
<td>50.3</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>1.9</td>
<td>1.5</td>
<td>0.0</td>
<td>7.2</td>
</tr>
<tr>
<td>nPCR</td>
<td>1.15</td>
<td>0.24</td>
<td>0.73</td>
<td>1.74</td>
</tr>
</tbody>
</table>

The number of individual patients is 51.
The total material comprises different overlapping groups of urea kinetic modeling (UKM) sessions:

- **Study I FREQUENCY**: 588 sessions of 35 patients 2004-2006
- **Study II INCREMENTAL**: 225 sessions of 30 patients with RRF 2004-2006
- **Study III EQUIVALENCY**: 619 sessions of 35 patients 2004-2006
- **Study IV AUTOMATION**: 205 IDM sessions of 33 patients 2004-2006
- **Study V ADEQUACY**: 1,200 sessions of 51 patients 1998-2006

The individual studies are referred to in the text by their Roman numbers, equivalent to the original communications.

Table 3 shows the causes of discontinuation of the dialysis treatment periods. Nineteen periods were still ongoing at the end of the observation period. “Decision” refers to a unanimous decision by patient and physician to discontinue renal replacement therapy.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuing</td>
<td>19</td>
<td>33.3</td>
<td>2.5</td>
<td>1.7</td>
<td>0.4</td>
<td>5.8</td>
</tr>
<tr>
<td>Death</td>
<td>16</td>
<td>28.1</td>
<td>2.3</td>
<td>1.6</td>
<td>0.6</td>
<td>6.9</td>
</tr>
<tr>
<td>Transplantation</td>
<td>8</td>
<td>14.0</td>
<td>1.4</td>
<td>1.3</td>
<td>0.6</td>
<td>4.6</td>
</tr>
<tr>
<td>Transfer to other unit</td>
<td>8</td>
<td>14.0</td>
<td>1.3</td>
<td>1.2</td>
<td>0.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Transfer to peritoneal dialysis</td>
<td>3</td>
<td>5.3</td>
<td>2.1</td>
<td>1.4</td>
<td>0.7</td>
<td>3.5</td>
</tr>
<tr>
<td>Decision</td>
<td>3</td>
<td>5.3</td>
<td>0.8</td>
<td>0.3</td>
<td>0.6</td>
<td>1.1</td>
</tr>
</tbody>
</table>

The numbers include hemodialysis treatment periods ongoing on January 1, 1998 (from that date on) and incident periods during the nine-year observation time until December 31, 2006 (unless terminated earlier).

Some patients had more than one hemodialysis treatment period, occasionally separated by several years. Study V (ADEQUACY) is based on average values of the treatment periods. The other studies are based on individual UKM sessions.
4.1.2 Dialysis prescriptions

Dosing of dialysis, including treatment frequency, was prescribed by the author on the basis of multiple criteria (weight, hydration status, predialysis blood urea concentration and other laboratory values, eKt/V and stdK/V targets, and patient's preferences). Renal diagnosis, comorbidity, functional status, waiting for transplantation, age, nPCR or anticipated survival time were not used as dosing criteria.

The patients were encouraged by a dietician to maintain a diet containing protein 1.2 g/kg/day, but the actual dietary protein intake was not controlled. nPCR – reflecting DPI – varied quite widely (Table 2).

4.1.3 Data collection

Dialysis data were collected in the routine care of hemodialysis patients automatically online from dialysis machines, scales, and blood pressure meters by the Finesse® dialysis information system (Fresenius) and stored in a Microsoft Access® database. Another kidney patient information system developed by the author combined data from the Finesse database and the Effica® hospital laboratory system (Tieto Oyj), performed the UKM computations and created monthly treatment summary reports.

4.2 Calculations

4.2.1 Urea kinetic modeling

Urea kinetic modeling with three blood samples and interdialysis urine collection was performed routinely once per month (modeling session). Postdialysis blood samples were taken at the termination of the session with a modified KDOQI 2006 slow-blood-flow technique [National Kidney Foundation 2006].

In Studies I-III the dialyzer urea clearance (Kd) of each treatment was calculated with Michaels’ equation (36 on page 93) from the actual blood and dialysate flow (Qb, Qd) and mass transfer area coefficient (K0A) of the dialyzer model, based on several own blood side clearance measurements. In Study V K0A
values provided by the manufacturers were utilized. In Study IV readings from the IDM device were used as Kd.

In the first study (I), computations were performed using the classic single pool variable volume iterative urea kinetic model (spvUKM, equations 33-35 on page 92) [Farrell and Gotch 1977, Gotch FA 1995b] with equilibrated postdialysis urea concentration values calculated by the Tattersall method [Tattersall et al. 1996].

In Studies II-IV the iterative double-pool UKM model was used, modified from the Solute-Solver program code version 1.97 with the Runge-Kutta numeric integration procedure [Daugirdas et al. 2009]. The constants were the same as in Solute-Solver:

blood water = 0.86 * blood volume
plasma water = 0.93 * plasma volume

“intracellular” compartment volume = 2/3 of total postdialysis volume; does not change during the dialysis cycle

“extracellular” compartment postdialysis volume = 1/3 of total postdialysis volume

intercompartment transfer coefficient (Kc, L/min) = 0.016 (L/min) * total postdialysis volume (L)

Plasma concentrations were converted into plasma water concentrations before calculations and back to plasma concentrations in the tables and figures. In Studies I-IV TAC and PAC used in calculating EKR/V and stdK/V are expressed as “extracellular” pool water concentrations converted into plasma concentrations, in Study V EKR/V and stdK/V are calculated from whole body water concentrations.

UKM assumes that the patient is in a metabolic steady state, which was not confirmed. The Borah equation [Borah et al. 1978] with Sargent’s modification [Sargent 1983] was used in nPCR calculation.

In Studies I-IV calculation of the renal urea clearance Kr from interdialysis urine volume and urea concentration was included in the V and G iteration loops. To obtain the time-averaged concentration (TAC) and average predialysis concentration (PAC), needed for calculating EKR and stdK, treatment parameters – including frequency – were averaged over four weeks preceding and including the modeling session. Treatments were then equalized by iterating the single or double pool UKM concentration equation (single pool: 35 on page 92) sequentially over average treatment time and average interval time until stabilizing of the
predialysis concentration. This procedure modifies an asymmetric schedule to an evenly distributed one, but has no influence on the patient-specific values V, G, and Kr. The effect of schedule asymmetry was not investigated in this thesis.

In Study V the Solute-Solver program was used as such and Kr was calculated from dialysis cycle urine urea removal by using the average of post- and predialysis urea concentrations.

4.2.2 Simulation and automation

The thesis is based on computer simulations of hemodialysis treatment. V, G, Kr and weekly fluid removal requirement are the patient data needed to create the dialysis prescription. They were derived from actual dialysis sessions by UKM. Kd, td, and fr can be varied in simulated treatments, and concentrations, EKR/V, and stdK/V calculated, assuming that variations in dialysis do not affect urea generation rate. By numeric solution of the UKM equations it is also possible to compute the required Kd or td to achieve desired concentrations, EKR/V and stdK/V.

In Study IV, dialyzer mass area coefficient (K0A) was calculated at each session from dialysate flow (Qd), blood flow (Qb) and online Kd by Michaels’ equation [Daugirdas and Van Stone 2001, Ward et al. 2011]. The average K0A of each dialyzer model was then used in simulations to compute the Qb and Qd to achieve the required Kd. By successive simulations the computer generated a prescription fulfilling multiple criteria based on the quality standards of care.

4.2.3 HEMO-equivalent EKR/V and stdK/V

In the standard-dose group of the HEMO trial [Eknoyan et al. 2002] the average delivered eKt/V was 1.16. One third of the patients had RRF. To ensure a safety margin for anuric patients, EKR/V and stdK/V values corresponding to eKt/V 1.20 in a conventional four-hour dialysis given three times per week (3 x 4 h/week) schedule without RRF were calculated for each session as follows:

Single pool urea distribution volume (V1) was computed with the classic single pool variable volume urea kinetic model (spvvUKM). Then Kd was solved from Daugirdas’ eKt/V rate equation:
\[ eKt/V = (Kd \times td / V1) - a \times (Kd \times td / V1) / td + b \]  \hspace{1cm} (20) \\
\[ Kd = (eKt/V - b) \times V1 / (td - a). \]  \hspace{1cm} (21)

1.20 was assigned to eKt/V and 240 min to td. In sessions with arteriovenous blood access \( a \) was 36 min and \( b \) 0.03, with venovenous access 28 min and 0.02 [Daugirdas 1993, Daugirdas 1995]. Dialysis treatment 3 x 4 h/week was simulated for each modeling session with this \( Kd \) and \( Kr = 0 \). EKR/V and stdK/V were then calculated in each simulated session.

### 4.2.4 Anthropometric normalization of ECC

In Study V \( nEKR \) and \( nstdK \) are ECC values normalized with body surface area analogically to glomerular filtration rate or renal clearance, with mL/min/1.73m\(^2\) as the unit:

\[ nEKR = EKR / BSA \times 1.73 \]  \hspace{1cm} (22) \\
\[ nstdK = stdK / BSA \times 1.73. \]  \hspace{1cm} (23)

Daugirdas et al. have developed a method to obtain a BSA-normalized stdKt/V [Daugirdas et al. 2008a, Daugirdas et al. 2010b]:

\[ SAn-stdKt/V = stdKt/V \times Vant / BSA / 20, \]  \hspace{1cm} (24)

where \( Vant \) is anthropometric TBW in liters, BSA in m\(^2\) and the constant 20 the mean of \( V/BSA \) (L/m\(^2\)) in their material. Similarly, \( nEKRant \) and \( nstdKant \) can be calculated using an anthropometric scaling factor \( Vant/BSA \):

\[ nEKRant = EKR/V \times Vant / BSA \times 1.73 \]  \hspace{1cm} (25) \\
\[ nstdKant = stdK/V \times Vant / BSA \times 1.73 \]  \hspace{1cm} (26)

with appropriate unit conversion factors. \( Vant/BSA \) takes gender into consideration. The unit of the anthropometrically normalized ECCs is mL/min/1.73m\(^2\).

### 4.3 Computer applications

In Study V the double-pool computations were performed with a noncommercial software Solute-Solver [Daugirdas et al. 2009], in the other studies with programs.
written in the Basic programming language included in Microsoft Office Access® 2007 SP3. Microsoft Office Excel® 2007 SP3 was used to create the graphs. The demonstration program HDOptimizer.exe was written in Microsoft Visual Basic® 2010.

4.4 Statistical methods

Continuous variables are expressed as means with standard deviations (SD) and minimum and maximum values. Categorical variables are expressed as percentages. Mortality is the number of deaths per 1,000 patient years of hemodialysis. Survival times and Kaplan-Meyer curves are not presented.

In Study V, univariate and multivariable binary logistic regression analyses were performed to identify variables associated with death. Variables with a univariate p-value <0.10 were entered into the multivariable models. Odds ratios (ORs) and 95% confidence intervals (CIs) are reported. SPSS 22.0 and STATA 13.1 were used in statistical calculations.

4.5 Ethical aspects

The thesis was performed with the permission of the medical director of the hospital and is based on a retrospective analysis of register data collected and utilized in the routine care of patients. There was no control group nor randomization and no intervention. The patient data were anonymized and deidentified prior to analysis. The author participated in the care of all patients.
5 RESULTS

EKR/V and stdK/V are continuous-equivalent clearances scaled by urea distribution volume V. In Studies I-IV EKR/V was referred to as stdEKR. In Study I stdK/V was referred to as stdKt/V.

5.1 Effect of frequency (I FREQUENCY)

The figures are based on a simulated patient with the average characteristics of 588 modeling sessions of 35 patients. In this population the values of stdEKR and stdKt/V corresponding to eKt/V 1.20 – close to the standard dose in the HEMO trial – were 3.34/week and 2.23/week respectively. Figures 1-4 represent the patient dialyzed (simulated) with the HEMO standard dose-equivalent doses. weKt/V is the sum of eKt/Vs in one week.

5.1.1 Effect on measures of dialysis dose

Figure 1 describes the effect of frequency on different measures of dialysis dose. stdEKR and stdK/V can be increased by increasing frequency – without increasing weekly treatment time or Kd. PAC and stdK/V are more sensitive to frequency than TAC and stdEKR. Doubling the treatment frequency from 3 to 6 x/week with equal weekly treatment time decreases PAC by 20%, but TAC only by 6%.
Figure 1. (not included in the original publication). Effect of treatment frequency on concentrations and measures of dialysis dose. Weekly treatment time 12 h, Kd 200 ml/min, double pool, no RRF, no UF.

5.1.2 Effect on required treatment time

Figure 2 describes the effect of frequency on the weekly treatment time required to achieve the HEMO standard dose equivalent ECCs with constant Kd. Much more time is needed to achieve the stdKt/V target on a twice-weekly schedule than on a thrice-weekly schedule. The effect of frequency is less steep with stdEKR as the target. Weekly Kt/V is by definition not dependent on frequency.

With frequencies greater than 3 x/week, using stdKt/V as the target results in shorter treatment times and higher concentrations than stdEKR (Figures 2-4).
5.1.3 Effect on concentrations

With constant stdEKR, increasing frequency lowers PAC values (Figure 3). With constant stdKt/V, TAC is considerably higher with higher frequency (Figure 4).

Figure 2. Effect of treatment frequency on weekly treatment time required to achieve HEMO standard dose equivalent targets. Kd 200 ml/min.
Figure 3. Effect of treatment frequency on predialysis concentration (C0 or PAC) with different HEMO standard dose equivalent targets. Kd 200 ml/min, dose adjusted by treatment time.

Figure 4. Effect of treatment frequency on time-averaged concentration (TAC) with different HEMO standard dose equivalent targets. Kd 200 ml/min, dose adjusted by treatment time.
5.2 Effect of residual renal function (II INCREMENTAL)

Figures 5-9 are based on a simulated patient with the average characteristics of 225 modeling sessions of 30 patients. Only sessions with RRF were included. stdEKR = EKR/V.

In this cohort the values of stdEKR and stdKt/V corresponding to eKt/V 1.20 – close to the standard dose in the HEMO trial – were 3.48/week and 2.29/week respectively. eKt/V 1.20 was achieved with an average of 187 mL/min dialyzer clearance in a 3 x 4 h/week schedule (conventional dialysis). Additional measures of RRF and both stdEKR and stdK/V increase linearly with renal urea clearance (Kr). stdEKR increases in parallel with renal fractional clearance (rFC = Kr/V), stdK/V in parallel with renal fractional solute removal rate (rFSRR) (Figure 5).

![Figure 5. Effect of Kr on measures of RRF and dialysis dose. Standard dialysis (3 x 4 h/week, Kd 187 mL/min, eKt/V 1.20, UF 2.24 L).](image)

5.2.1 Effect on required treatment time

The required treatment time to achieve the HEMO equivalent targets has a linear inverse relationship to Kr (Figure 6). If the HEMO standard dose equivalent
stdEKR or stdK/V is used as the target, RRF may replace several hours of weekly dialysis treatment time. stdK/V is affected by RRF more than stdEKR. In incremental dialysis, with Kr = 4 mL/min the target stdK/V is achieved in one half of the weekly treatment time required without RRF. Somewhat longer treatment time is required to achieve the stdEKR target.

Figure 6. Dependence of required weekly treatment time on RRF. Frequency 3 x/week, Kd 187 mL/min.

5.2.2 Effect on concentrations

With constant stdEKR target, PAC decreases with increasing Kr; with a constant stdK/V target, TAC increases with increasing Kr (Figures 7 and 8).

In Figures 6-9 the dialysis dose is varied incrementally by adjusting the treatment time to achieve the HEMO standard dose equivalent stdEKR and stdK/V targets.
Figure 7. Dependence of predialysis urea concentration PAC on RRF. Frequency 3 x/week, Kd 187 mL/min, dose adjusted by treatment time.

Figure 8. Dependence of TAC on RRF. Frequency 3 x/week, Kd 187 mL/min, dose adjusted by treatment time.
5.2.3 Contribution to urea removal

Figure 9 presents the fraction (%) of total urea removal excreted by the kidneys. With $Kr = 4 \text{ mL/min}$, using the HEMO-equivalent stdK/V as target, almost one half of the total urea excretion takes place through the kidneys. Dialysis and the kidneys compete for solutes.

Ignoring RRF in UKM does not affect $V$ or $eKt/V$, but leads to underestimation of stdEKR, stdK/V, G and PCR. RRF lowers concentrations and increases stdEKR and stdK/V. The average renal urea clearance of 2 mL/min corresponds to 0.25-0.36 units of eKt/V.
5.3 Equivalent doses (III EQUIVALENCY)

The study is based on 619 modeling sessions of 35 patients with urea distribution volumes of 14.4-57.5 L and nPCR values of 0.48-2.34 g/kg/day. \( \text{stdEKR} = \text{EKR/V} \).

5.3.1 ECC corresponding to HEMO standard dose

In the HEMO trial [Eknoyan et al. 2002] the mean eKt/V in the standard dose group was 1.16±0.08 /session. In the present study the patients were “dialyzed” (simulated) 3 * 4 h/week to eKt/V 1.2 by adjusting Kd. Kr was set at zero and weekly ultrafiltration was equal to that in the actual sessions. The mean Kd was 189 mL/min. The mean HEMO standard dose equivalent stdEKR was 3.44/week and stdK/V 2.40/week with moderate variation. Instead, TAC and PAC varied 6.8-6.5-fold parallel to variations in G and nPCR (Table 4). The mean HEMO-equivalent TAC 17.7 mmol/L was equal to the lower target in the NCDS.

| Table 4. HEMO standard dose-equivalent TAC, PAC, stdEKR and stdK/V |
|-----------------------------|-----------|--------|------|--------|
| Unit                        | Mean      | SD     | Min  | Max    |
| renal urea clearance        | mL/min    | 0.00   | 0.00 | 0.00   |
| urine output                | L/day     | 0.00   | 0.00 | 0.00   |
| ultrafiltration             | L/week    | 8.33   | 2.97 | 0.55   | 18.66 |
| dialyzer urea clearance     | mL/min    | 189    | 37   | 93     | 315   |
| dialysis frequency          | /week     | 3.00   | 0.00 | 3.00   | 3.00  |
| dialysis duration           | min       | 240    | 0    | 240    | 240   |
| weekly dialysis time        | h         | 12.0   | 0.0  | 12.0   | 12.0  |
| equilibrated Kt/V           | /session  | 1.20   | 0.00 | 1.20   | 1.20  |
| time-averaged urea concentration | mmol/L | 17.7   | 5.2  | 5.9    | 40.2  |
| average predialysis urea concentration | mmol/L | 25.4   | 7.3  | 8.6    | 55.8  |
| stdEKR                      | /week     | 3.44   | 0.08 | 3.23   | 3.92  |
| stdK/V                      | /week     | 2.40   | 0.07 | 2.21   | 2.83  |

3 * 4 h/week, eKt/V 1.2 /session, Kd adjusted.
Dependence of stdEKR and stdK/V on eKt/V is not linear (Figure 10). With increasing eKt/V, stdEKR increases more steeply than stdK/V. A 100-percent increase in eKt/V from 0.80 to 1.60 results in a mere 43-percent increase in stdK/V from 1.91 to 2.73/week. stdEKR is lower than weekly Kt/V and eKt/V. ECCs behave differently from weekly Kt/V and eKt/V (Figures 2-9).

Figure 10. (not included in the original publication). Dependence of urea stdEKR and stdK/V on eKt/V. Kr = 0, schedule 3 x 4 h/week, eKt/V adjusted by Kd.

5.3.2 Dialyzing to HEMO-equivalent ECC

Mean TAC and PAC were higher in women than in men when dialyzed to a constant eKt/V, stdEKR or stdK/V corresponding to the HEMO standard dose (Table 5).
Table 5. Mean TAC and PAC of urea in women and men dialyzed to HEMO-equivalent clearance targets.

<table>
<thead>
<tr>
<th>Dialysed to</th>
<th>Gender</th>
<th>TAC mmol/L</th>
<th>PAC mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>eKt/V 1.2 (without RRF)</td>
<td>Women</td>
<td>18.7</td>
<td>26.8</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>17.2</td>
<td>24.6</td>
</tr>
<tr>
<td>stdEKR 3.44/week</td>
<td>Women</td>
<td>18.9</td>
<td>26.3</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>17.0</td>
<td>23.8</td>
</tr>
<tr>
<td>stdK/V 2.40/week</td>
<td>Women</td>
<td>19.8</td>
<td>27.1</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>17.8</td>
<td>24.4</td>
</tr>
</tbody>
</table>

Dialysing to a constant TAC (17.7 mmol/L, the mean of HEMO standard dose equivalent and equal to the NCDS lower target) results in a 7.1-fold variation in stdEKR (1.15-8.12/week).

5.3.3 Solutes with different kinetics

“Extracellular” and “intracellular” distribution volumes of 13 and 26 L for urea and 3 and 9 L for β2-microglobulin and intercompartment transfer coefficients of 600 mL/min for urea and 40 mL/min for β2-microglobulin were used in two-compartment simulations for Figures 11-13 and Tables 6 and 7. Generation rates were 200 µmol/min and 200 µg/min. The TAC units are correspondingly mmol/L and mg/L. The generation rate has only a negligible effect on percent changes of TAC and EKR.

Kt/V is linearly proportional to td, but concentrations and ECCs are not (Figure 11). Concentrations can be decreased by increasing the frequency without increasing the weekly treatment time (Figure 12).
Figure 11. (not included in the original publication). Dependence of concentrations on treatment time. \(fr = 3 \times \text{week}, K_{d_{\text{urea}}} = 200 \text{ mL/min}, K_{d_{\beta2M}} = 30 \text{ mL/min}. \) No RRF, no UF.

Figure 12. (not included in the original publication). Dependence of concentrations on treatment frequency with constant weekly treatment time 12 h. \(K_{d_{\text{urea}}} = 200 \text{ mL/min}, K_{d_{\beta2M}} = 30 \text{ mL/min}. \) No RRF, no UF.
Table 6. Effect of blood and dialysate flow on Kd, TAC and EKR of solutes with different kinetics (not included in the original publication)

<table>
<thead>
<tr>
<th></th>
<th>K_0A</th>
<th>Qb</th>
<th>Qd</th>
<th>Kd</th>
<th>TAC</th>
<th>EKR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mL/min</td>
<td>mL/min</td>
<td>mL/min</td>
<td>mL/min</td>
<td>Δ %</td>
<td>units/L</td>
</tr>
<tr>
<td>urea</td>
<td>1000</td>
<td>300</td>
<td>500</td>
<td>262</td>
<td>14.3</td>
<td>14.0</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>300</td>
<td>100</td>
<td>100</td>
<td>-62</td>
<td>30.6</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>100</td>
<td>500</td>
<td>100</td>
<td>-62</td>
<td>30.6</td>
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<td></td>
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<td>100</td>
<td>100</td>
<td>91</td>
<td>-65</td>
<td>33.3</td>
</tr>
<tr>
<td>β2M</td>
<td>40</td>
<td>300</td>
<td>500</td>
<td>36</td>
<td>110.2</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>300</td>
<td>100</td>
<td>31</td>
<td>-13</td>
<td>121.3</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>100</td>
<td>500</td>
<td>32</td>
<td>-11</td>
<td>119.7</td>
</tr>
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<td></td>
<td>40</td>
<td>100</td>
<td>100</td>
<td>29</td>
<td>-21</td>
<td>129.7</td>
</tr>
</tbody>
</table>

Schedule 3 x 4 h/week, no RRF, no UF. Δ % is the difference from the first row of urea and β2M data.

According to Michaels’ equation, clearance of urea is more flow-dependent than that of β2-microglobulin with low K_0A. Reducing Qb from 300 to 100 mL/min or Qd from 500 to 100 mL/min has an almost equal relative effect, but much greater on urea than on β2-microglobulin (Table 6).

Table 7. Effect of dialysate flow and treatment time (not included in the original publication)

<table>
<thead>
<tr>
<th></th>
<th>K_0A</th>
<th>Qb</th>
<th>Qd</th>
<th>td</th>
<th>Kd</th>
<th>TAC</th>
<th>EKR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mL/min</td>
<td>mL/min</td>
<td>mL/min</td>
<td>min</td>
<td>mL/min</td>
<td>Δ %</td>
<td>units/L</td>
</tr>
<tr>
<td>urea</td>
<td>1000</td>
<td>300</td>
<td>500</td>
<td>240</td>
<td>262</td>
<td>14.2</td>
<td>14.0</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>300</td>
<td>100</td>
<td>551</td>
<td>100</td>
<td>-62</td>
<td>14.2</td>
</tr>
<tr>
<td></td>
<td>1000</td>
<td>300</td>
<td>100</td>
<td>480</td>
<td>100</td>
<td>-62</td>
<td>16.1</td>
</tr>
<tr>
<td>β2M</td>
<td>40</td>
<td>300</td>
<td>500</td>
<td>240</td>
<td>36</td>
<td>110.2</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>300</td>
<td>100</td>
<td>551</td>
<td>31</td>
<td>-13</td>
<td>55.9</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>300</td>
<td>100</td>
<td>480</td>
<td>31</td>
<td>-13</td>
<td>63.6</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>300</td>
<td>500</td>
<td>480</td>
<td>36</td>
<td>58.3</td>
<td>-47</td>
</tr>
</tbody>
</table>

Treatment frequency 3 x/week, no RRF, no UF. Δ % is the difference from the first row of urea and β2M data.

The first and fourth rows of Table 7 describe the conventional 3 x 4 h/week treatment with usual blood and dialysate flows as the references. If Qd is reduced
to 100 mL/min, treatment time has to be increased to 551 min to achieve the same TAC\textsubscript{urea} and EKR\textsubscript{urea}. With these changes in Qd and td, β2-microglobulin concentration is halved and its EKR doubled. In the 8 h treatment with reduced Qd TAC\textsubscript{urea} increases 13% from the reference, but TAC of β2-microglobulin decreases 42%, only slightly less than with full Qd (last row).

Kt is a patient-independent measure of the delivered dialysis dose. It can be easily monitored with an IDM device. Figure 13 shows that increasing treatment duration lowers β2-microglobulin concentration more than increasing frequency with equal weekly Kt.

![Figure 13](image)

Figure 13. (not included in the original publication). Effect of frequency and time on concentrations with equal weekly Kt (180 L). Dialyzer KoA 1000 mL/min for urea and 40 mL/min for β2-microglobulin, Qb=350 mL/min, no RRF, no UF. A: weekly treatment time 12 h. B: frequency 3 x/week, td adjusted by Qd (125-800 mL/min). 100% TAC\textsubscript{urea}=14.7 mmol/L and TAC\textsubscript{β2M}=111 mg/L.
5.4 Creating the prescription (IV AUTOMATION)

The study is based on 205 UKM sessions of 33 patients with ionic dialysance data. Readings from the IDM device were used as Kd in UKM. stdEKR = EKR/V.

5.4.1 Prescribed and delivered dose

If the prescribed and delivered Kd are equal, the delivered spKt/V (measured by classic spvvUKM or Daugirdas’ equation) is higher than the prescribed one because V calculated by spvvUKM is smaller than the anthropometric total body water used in the prescription [Daugirdas et al. 2003, Depner et al. 1992, Kloppenburg et al. 2001]. It is easy to achieve the prescribed dose (Table 8).

Table 8. Mean Kd, td, anthropometric TBW, modeled V and prescribed and measured Kt/V (not included in the original publication)

<table>
<thead>
<tr>
<th>Kd</th>
<th>td</th>
<th>TBW</th>
<th>V</th>
<th>Kt/VPre</th>
<th>Kt/VDau</th>
<th>spKt/V</th>
<th>eKt/V</th>
</tr>
</thead>
<tbody>
<tr>
<td>mL/min</td>
<td>min</td>
<td>L</td>
<td>L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>202</td>
<td>297</td>
<td>40.1</td>
<td>33.4</td>
<td>1.54</td>
<td>1.80</td>
<td>1.83</td>
<td>1.47</td>
</tr>
</tbody>
</table>

On-line ionic clearance from the IDM device has been used as Kd in calculating the prescribed Kt/V (Kt/VPre) from anthropometric TBW (Watson) and actual td.

5.4.2 Optimization procedure

V, G, Kr, and weekly fluid removal requirement are the patient data needed to create the dialysis prescription. They were derived from the actual dialysis sessions by double-pool UKM. The goal of the optimization procedure was to generate from each dataset a prescription fulfilling 12 criteria (Table 9).

Qb and td were continuous variables. The frequency values were 2, 3, 3.5 (alternate day), 4, 5, 6 and 7 x/week and dialysate flow 300, 500 and 800 mL/min. Prescription generation started with simulations with minimum fr, Qb, Qd, and td. If more dialysis was needed, Qb was increased first, then Qd to 500 mL/min, then td, then Qd to maximum, and finally treatment frequency. Weekly UF volume and the dialyzer (K0A) were held constant within each simulation. RRF (Kr) was taken into account.
Table 9. Optimization criteria

<table>
<thead>
<tr>
<th>Parameter</th>
<th>min</th>
<th>max</th>
</tr>
</thead>
<tbody>
<tr>
<td>treatment frequency</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>treatment time</td>
<td>240</td>
<td>300</td>
</tr>
<tr>
<td>dialysate flow</td>
<td>300</td>
<td>800</td>
</tr>
<tr>
<td>blood flow</td>
<td>50</td>
<td>a287</td>
</tr>
<tr>
<td>stdEKR</td>
<td>b3.44</td>
<td></td>
</tr>
<tr>
<td>stdK/V</td>
<td>b2.35</td>
<td></td>
</tr>
<tr>
<td>TAC</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>PAC</td>
<td>30.0</td>
<td></td>
</tr>
</tbody>
</table>

*Average value. The blood flow upper limit used in each optimized session was 90% of the patient's maximum blood flow during the previous four weeks.

**Average value. The minimum stdEKR and stdK/V were defined individually for each session to correspond to eKt/V 1.2 in a 3 x 4 h/week schedule without RRF.

5.4.3 Automatic prescriptions

A computer program for creating a dialysis prescription based on patient data (V, G, Kr, weekly UF) from previous actual sessions and on 12 freely definable criteria was developed. A simplified version of the program can be downloaded from [http://www.verkkomunuainen.net/optimize.html](http://www.verkkomunuainen.net/optimize.html), accessed November 12, 2015. It has not been validated clinically and is intended to be used only for demonstrating and testing the optimization method, not for treating patients.

The simulated optimized treatments differed considerably from both the conventionally prescribed actual and the simulated HEMO-equivalent ones (Tables 10 and 11). By optimization, 173 (84%) of the sessions fell into the 3 x/week schedule, 15 (7%) needed more; in 17 (8%) 2 x/week was sufficient (Table 10). These proportions of course depend on the optimization criteria (Table 9).

In 43 sessions (21%) the optimized dialysis dose was determined by the concentration limits. The HEMO-equivalent clearance was not enough to keep TAC and PAC below the defined upper limits (20 and 30 mmol/L) if nPCR was greater than 1.3 g/kg/day. Figure 14 summarizes the results.
Table 10. Optimized sessions: frequency distribution and values by frequency (average ± SD)

<table>
<thead>
<tr>
<th>fr /week</th>
<th>Sessions</th>
<th>Kr /week</th>
<th>nPCR /g/kg/day</th>
<th>stdEKR /week</th>
<th>stdK/V /week</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>17</td>
<td>3.2 ± 1.3</td>
<td>1.09 ± 0.22</td>
<td>3.52 ± 0.23</td>
<td>2.35 ± 0.18</td>
</tr>
<tr>
<td>3</td>
<td>173</td>
<td>0.6 ± 1.1</td>
<td>1.06 ± 0.24</td>
<td>3.51 ± 0.19</td>
<td>2.44 ± 0.14</td>
</tr>
<tr>
<td>3.5</td>
<td>12</td>
<td>0.6 ± 0.9</td>
<td>1.35 ± 0.28</td>
<td>3.91 ± 0.44</td>
<td>2.74 ± 0.24</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>2.1 ± 1.1</td>
<td>1.74 ± 0.12</td>
<td>4.87 ± 0.40</td>
<td>3.37 ± 0.11</td>
</tr>
<tr>
<td>sum</td>
<td>205</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: fr, treatment frequency; Sessions, number of sessions in each frequency category; Kr, renal blood water urea clearance; nPCR, normalized protein catabolic rate. With the new scheduling the number of sessions decreased to 202.

Table 10 may be interpreted as follows: With normal nPCR two sessions per week is sufficient only if the patient has moderate RRF, but with high nPCR high frequency is required to achieve the TAC and PAC targets despite RRF, and this is reflected in high clearances.

Figure 14. TAC, PAC, stdEKR and stdK/V plotted against nPCR in the optimized sessions.
## Table 11. Actual and simulated sessions

<table>
<thead>
<tr>
<th></th>
<th>Actual</th>
<th>HEMO</th>
<th>Optimized</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>treatment frequency</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>average /week</td>
<td>3.11</td>
<td>3.00</td>
<td>2.96</td>
</tr>
<tr>
<td>minimum /week</td>
<td>2.00</td>
<td>3.00</td>
<td>2.00</td>
</tr>
<tr>
<td>maximum /week</td>
<td>4.45</td>
<td>3.00</td>
<td>4.00</td>
</tr>
<tr>
<td>SD /week</td>
<td>0.33</td>
<td>0.00</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>treatment duration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>average min</td>
<td>297</td>
<td>240</td>
<td>250</td>
</tr>
<tr>
<td>minimum min</td>
<td>243</td>
<td>240</td>
<td>240</td>
</tr>
<tr>
<td>maximum min</td>
<td>485</td>
<td>240</td>
<td>299</td>
</tr>
<tr>
<td>SD min</td>
<td>40</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td><strong>eKt/V</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>average /week</td>
<td>1.47</td>
<td>1.20</td>
<td>1.18</td>
</tr>
<tr>
<td>minimum /week</td>
<td>0.93</td>
<td>1.20</td>
<td>0.76</td>
</tr>
<tr>
<td>maximum /week</td>
<td>2.39</td>
<td>1.20</td>
<td>2.03</td>
</tr>
<tr>
<td>SD /week</td>
<td>0.26</td>
<td>0.00</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>stdEKR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>average /week</td>
<td>4.65</td>
<td>3.44</td>
<td>3.56</td>
</tr>
<tr>
<td>minimum /week</td>
<td>3.08</td>
<td>3.23</td>
<td>3.23</td>
</tr>
<tr>
<td>maximum /week</td>
<td>6.31</td>
<td>3.61</td>
<td>5.29</td>
</tr>
<tr>
<td>SD /week</td>
<td>0.61</td>
<td>0.08</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>stdK/V</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>average /week</td>
<td>2.96</td>
<td>2.35</td>
<td>2.47</td>
</tr>
<tr>
<td>minimum /week</td>
<td>2.12</td>
<td>2.15</td>
<td>2.17</td>
</tr>
<tr>
<td>maximum /week</td>
<td>3.78</td>
<td>2.53</td>
<td>3.47</td>
</tr>
<tr>
<td>SD /week</td>
<td>0.32</td>
<td>0.07</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>TAC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>average mmol/L</td>
<td>12.4</td>
<td>16.5</td>
<td>15.8</td>
</tr>
<tr>
<td>minimum mmol/L</td>
<td>4.7</td>
<td>6.8</td>
<td>6.8</td>
</tr>
<tr>
<td>maximum mmol/L</td>
<td>25.7</td>
<td>30.0</td>
<td>20.1</td>
</tr>
<tr>
<td>SD mmol/L</td>
<td>3.6</td>
<td>4.6</td>
<td>3.6</td>
</tr>
<tr>
<td><strong>PAC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>average mmol/L</td>
<td>19.3</td>
<td>24.2</td>
<td>22.8</td>
</tr>
<tr>
<td>minimum mmol/L</td>
<td>7.5</td>
<td>9.8</td>
<td>9.8</td>
</tr>
<tr>
<td>maximum mmol/L</td>
<td>36.3</td>
<td>44.7</td>
<td>30.0</td>
</tr>
<tr>
<td>SD mmol/L</td>
<td>5.5</td>
<td>6.7</td>
<td>5.2</td>
</tr>
<tr>
<td><strong>weekly treatment time</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>average h</td>
<td>15.4</td>
<td>12.0</td>
<td>12.3</td>
</tr>
<tr>
<td>SD h</td>
<td>2.4</td>
<td>0.0</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>weekly dialysate consumption</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>average L</td>
<td>459</td>
<td>360</td>
<td>302</td>
</tr>
<tr>
<td>SD L</td>
<td>65</td>
<td>0</td>
<td>95</td>
</tr>
</tbody>
</table>
5.5 Prognostic value (V ADEQUACY)

The study is based on 57 hemodialysis treatment periods of 51 patients. EKR/V and stdK/V are continuous-equivalent clearances scaled to urea distribution volume. nEKR and nstdK are continuous-equivalent clearances normalized with BSA, nEKRant and nstdKant in addition with Vant.

5.5.1 Association of ECC with death risk

Equivalent renal urea clearance (EKR) [Casino and Lopez 1996] and standard clearance (stdK) [Gotch 1996, Gotch et al. 2000] take treatment frequency and residual renal function (RRF) into account and were intended for use in comparing dialysis doses in different schedules and to continuous dialysis and renal function.

Table 12. Association of patient characteristics and dialysis dose measures with death risk in 57 hemodialysis treatment periods of 51 patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
<th>p</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.6</td>
<td>15.5</td>
<td>16.7</td>
<td>91.6</td>
<td>0.103</td>
<td>1.038</td>
<td>0.993 - 1.085</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.1</td>
<td>18.2</td>
<td>44.2</td>
<td>123.6</td>
<td>0.525</td>
<td>0.989</td>
<td>0.957 - 1.023</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.1</td>
<td>5.5</td>
<td>16.3</td>
<td>43.7</td>
<td>0.198</td>
<td>0.924</td>
<td>0.819 - 1.042</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.84</td>
<td>0.25</td>
<td>1.31</td>
<td>2.34</td>
<td>0.872</td>
<td>0.823</td>
<td>0.078 - 8.727</td>
</tr>
<tr>
<td>V (L)</td>
<td>31.8</td>
<td>6.7</td>
<td>20.5</td>
<td>50.3</td>
<td>0.637</td>
<td>1.021</td>
<td>0.936 - 1.113</td>
</tr>
<tr>
<td>nPCR (g/kg/day)</td>
<td>1.15</td>
<td>0.24</td>
<td>0.73</td>
<td>1.74</td>
<td>0.058</td>
<td>0.065</td>
<td>0.004 - 1.095</td>
</tr>
<tr>
<td>nKr (mL/min/1.73 m²)</td>
<td>1.7</td>
<td>1.4</td>
<td>0.0</td>
<td>6.0</td>
<td>0.861</td>
<td>0.963</td>
<td>0.631 - 1.469</td>
</tr>
<tr>
<td>nEKR (mL/min/1.73 m²)</td>
<td>12.5</td>
<td>1.3</td>
<td>8.4</td>
<td>16.4</td>
<td>0.044</td>
<td>0.611</td>
<td>0.379 - 0.988</td>
</tr>
<tr>
<td>nstdK (mL/min/1.73 m²)</td>
<td>8.5</td>
<td>1.0</td>
<td>6.2</td>
<td>12.2</td>
<td>0.183</td>
<td>0.638</td>
<td>0.330 - 1.235</td>
</tr>
<tr>
<td>nEKRant (mL/min/1.73 m²)</td>
<td>15.1</td>
<td>2.3</td>
<td>8.3</td>
<td>20.3</td>
<td>0.113</td>
<td>0.806</td>
<td>0.617 - 1.053</td>
</tr>
<tr>
<td>nstdKant (mL/min/1.73 m²)</td>
<td>10.2</td>
<td>1.6</td>
<td>6.1</td>
<td>14.3</td>
<td>0.232</td>
<td>0.785</td>
<td>0.527 - 1.168</td>
</tr>
<tr>
<td>EKR/V (mL/min/1.73 m²/week)</td>
<td>4.35</td>
<td>0.64</td>
<td>2.36</td>
<td>5.82</td>
<td>0.033</td>
<td>0.326</td>
<td>0.117 - 0.912</td>
</tr>
<tr>
<td>stdK/V (mL/min/1.73 m²/week)</td>
<td>2.93</td>
<td>0.39</td>
<td>1.73</td>
<td>3.88</td>
<td>0.059</td>
<td>0.205</td>
<td>0.040 - 1.060</td>
</tr>
<tr>
<td>fr (h/week)</td>
<td>2.9</td>
<td>0.3</td>
<td>2.0</td>
<td>3.7</td>
<td>0.413</td>
<td>0.503</td>
<td>0.097 - 2.606</td>
</tr>
<tr>
<td>td (h/week)</td>
<td>13.5</td>
<td>2.3</td>
<td>7.7</td>
<td>18.4</td>
<td>0.077</td>
<td>0.786</td>
<td>0.602 - 1.027</td>
</tr>
</tbody>
</table>
Mortality was significantly associated with EKR/V and nEKR but not with stdK/V or nstdK (Table 12). In multivariable analysis, EKR/V was the only variable having an association with death risk (OR=0.326, CI=0.117-0.912, p=0.033).

### 5.5.2 Interaction between nPCR and ECC

By definition (Equations 16-19 on page 38)

\[
G = \text{EKR/V} \times \text{TAC} \times V \\
G = \text{stdK/V} \times \text{PAC} \times V \\
(EKR/V) / (stdK/V) = \text{PAC} / \text{TAC}. 
\]

In hemodialysis nPCR is generally calculated as also in the present study by the Borah equation [Borah et al. 1978] with Sargent's modification [Sargent 1983]:

\[
n\text{PCR} = (9.35 \times G + 0.294 \times V) / (V / 0.58),
\]

where nPCR is expressed in g/kg/day, G in milligrams of urea-N/min and V in L. By substituting G from Equations 27 and 28 and using appropriate unit conversion factors we obtain

\[
n\text{PCR} = 0.0151 \times \text{EKR/V} \times \text{TAC} + 0.171 \\
n\text{PCR} = 0.0151 \times \text{stdK/V} \times \text{PAC} + 0.171,
\]

where nPCR is in g/kg/day, EKR/V and stdK/V in /week and TAC and PAC in mmol/L. V will be eliminated. nPCR is high if urea concentration is high despite high or normal clearance. Mathematical linking inevitably contributes to the correlations between nPCR and EKR/V and stdK/V (Table 13).

Figure 15 describes the linear regression between nPCR and EKR/V in the present material. To eliminate the confounding effect of nPCR on the dose-mortality relationship, the material was split to two groups with roughly equal mean nPCR but different mean EKR/V. The line separating the groups appears in Figure 15. Table 14 shows that the difference in mortality between the low and high dose groups is still significant.
Figure 15. Linear regression between nPCR and dialysis dose (EKR/V) and the line separating the groups of Table 14.

Table 13. Spearman’s correlations, significant at the 0.01 level (2-tailed)

<table>
<thead>
<tr>
<th></th>
<th>Weight</th>
<th>BMI</th>
<th>BSA</th>
<th>V</th>
<th>nPCR</th>
<th>nEKR</th>
<th>nstdK</th>
<th>nEKRant</th>
<th>nstdKant</th>
<th>EKR/V</th>
<th>stdK/V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>1</td>
<td>0.854</td>
<td>0.950</td>
<td>0.748</td>
<td>0.352</td>
<td>0.453</td>
<td>0.530</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.854</td>
<td>1</td>
<td>0.658</td>
<td>0.455</td>
<td>0.393</td>
<td>0.427</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSA</td>
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<td>0.658</td>
<td>1</td>
<td>0.817</td>
<td>0.364</td>
<td>0.430</td>
<td>0.521</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>0.748</td>
<td>0.455</td>
<td>0.817</td>
<td>1</td>
<td>0.436</td>
<td></td>
<td>-0.475</td>
<td>-0.354</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nPCR</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>0.493</td>
<td>0.519</td>
<td>0.535</td>
<td>0.609</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nEKR</td>
<td></td>
<td>1</td>
<td></td>
<td>0.929</td>
<td>0.694</td>
<td>0.711</td>
<td>0.566</td>
<td>0.631</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nstdK</td>
<td>0.352</td>
<td>0.364</td>
<td>0.436</td>
<td>0.929</td>
<td>1</td>
<td>0.569</td>
<td>0.686</td>
<td>0.351</td>
<td>0.509</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nEKRant</td>
<td>0.453</td>
<td>0.393</td>
<td>0.430</td>
<td>0.493</td>
<td>0.694</td>
<td>0.569</td>
<td>1</td>
<td>0.962</td>
<td>0.821</td>
<td>0.850</td>
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</tr>
<tr>
<td>nstdKant</td>
<td>0.530</td>
<td>0.427</td>
<td>0.521</td>
<td>0.519</td>
<td>0.711</td>
<td>0.686</td>
<td>0.962</td>
<td>1</td>
<td>0.706</td>
<td>0.809</td>
<td></td>
</tr>
<tr>
<td>EKR/V</td>
<td>-0.475</td>
<td>0.535</td>
<td>0.566</td>
<td>0.351</td>
<td>0.821</td>
<td>0.706</td>
<td>1</td>
<td>0.961</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>stdK/V</td>
<td>-0.354</td>
<td>0.609</td>
<td>0.631</td>
<td>0.509</td>
<td>0.850</td>
<td>0.809</td>
<td>0.961</td>
<td>1</td>
<td></td>
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Table 14. Dialysis treatment periods divided into two groups with roughly equal mean nPCR

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>High</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EKR/V</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>Mean</td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>Age</td>
<td>60.8</td>
<td>13.2</td>
<td>62.5</td>
</tr>
<tr>
<td>Weight</td>
<td>77.1</td>
<td>21.2</td>
<td>72.9</td>
</tr>
<tr>
<td>BMI</td>
<td>26.5</td>
<td>6.5</td>
<td>25.7</td>
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<tr>
<td>BSA</td>
<td>1.86</td>
<td>0.27</td>
<td>1.81</td>
</tr>
<tr>
<td>V</td>
<td>33.7</td>
<td>7.5</td>
<td>29.8</td>
</tr>
<tr>
<td>nPCR</td>
<td>1.19</td>
<td>0.28</td>
<td>1.12</td>
</tr>
<tr>
<td>nKr</td>
<td>2.0</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>nEKR</td>
<td>12.1</td>
<td>1.5</td>
<td>13.0</td>
</tr>
<tr>
<td>nstdK</td>
<td>8.3</td>
<td>1.1</td>
<td>8.7</td>
</tr>
<tr>
<td>nEKRant</td>
<td>14.2</td>
<td>2.4</td>
<td>16.2</td>
</tr>
<tr>
<td>nstdKant</td>
<td>9.8</td>
<td>1.7</td>
<td>10.7</td>
</tr>
<tr>
<td>EKR/V</td>
<td>3.99</td>
<td>0.59</td>
<td>4.72</td>
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<td>stdK/V</td>
<td>2.75</td>
<td>0.38</td>
<td>3.12</td>
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<tr>
<td>Treatment frequency</td>
<td>2.8</td>
<td>0.4</td>
<td>3.1</td>
</tr>
<tr>
<td>Treatment time</td>
<td>12.6</td>
<td>2.5</td>
<td>14.4</td>
</tr>
<tr>
<td>Treatment periods</td>
<td>n</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>Females</td>
<td>%</td>
<td>31.0</td>
<td>46.4</td>
</tr>
<tr>
<td>Diabetics</td>
<td>%</td>
<td>37.9</td>
<td>46.4</td>
</tr>
<tr>
<td>ending to death</td>
<td>%</td>
<td>37.9</td>
<td>17.9</td>
</tr>
<tr>
<td>Patient years</td>
<td>n</td>
<td>49.8</td>
<td>64.5</td>
</tr>
<tr>
<td>Deaths</td>
<td>n</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Mortality</td>
<td>/1000 py</td>
<td>221</td>
<td>78</td>
</tr>
</tbody>
</table>
5.5.3 Association of ECC and mortality with gender

Women had significantly higher nPCR, EKR/V and stdK/V and lower mortality than men, but differences in BSA-based ECCs were not significant (Table 15).

Table 15. Dialysis treatment periods by gender

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Age years</td>
<td>63.3</td>
<td>14.5</td>
<td>60.6</td>
<td>16.1</td>
<td>0.529</td>
</tr>
<tr>
<td>Weight kg</td>
<td>65.2</td>
<td>15.3</td>
<td>81.2</td>
<td>17.4</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>25.7</td>
<td>5.9</td>
<td>26.3</td>
<td>5.3</td>
<td>0.694</td>
</tr>
<tr>
<td>BSA m²</td>
<td>1.66</td>
<td>0.17</td>
<td>1.95</td>
<td>0.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>V L</td>
<td>26.1</td>
<td>3.6</td>
<td>35.3</td>
<td>5.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>nPCR g/kg/day</td>
<td>1.23</td>
<td>0.23</td>
<td>1.10</td>
<td>0.24</td>
<td>0.043</td>
</tr>
<tr>
<td>nKr mL/min/1.73 m²</td>
<td>1.9</td>
<td>1.4</td>
<td>1.6</td>
<td>1.4</td>
<td>0.467</td>
</tr>
<tr>
<td>nEKR mL/min/1.73 m²</td>
<td>12.4</td>
<td>1.1</td>
<td>12.7</td>
<td>1.5</td>
<td>0.401</td>
</tr>
<tr>
<td>nstdK mL/min/1.73 m²</td>
<td>8.2</td>
<td>0.7</td>
<td>8.7</td>
<td>1.1</td>
<td>0.066</td>
</tr>
<tr>
<td>nEKRant mL/min/1.73 m²</td>
<td>14.8</td>
<td>1.9</td>
<td>15.4</td>
<td>2.6</td>
<td>0.349</td>
</tr>
<tr>
<td>nstdKant mL/min/1.73 m²</td>
<td>9.8</td>
<td>1.2</td>
<td>10.5</td>
<td>1.7</td>
<td>0.082</td>
</tr>
<tr>
<td>EKR/V /week</td>
<td>4.64</td>
<td>0.57</td>
<td>4.17</td>
<td>0.62</td>
<td>0.005</td>
</tr>
<tr>
<td>stdK/V /week</td>
<td>3.07</td>
<td>0.36</td>
<td>2.85</td>
<td>0.39</td>
<td>0.036</td>
</tr>
<tr>
<td>Treatment periods n</td>
<td>22</td>
<td></td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ending to death %</td>
<td>13.6</td>
<td>37.1</td>
<td></td>
<td>0.055</td>
<td></td>
</tr>
<tr>
<td>Patient years n</td>
<td>50.6</td>
<td>63.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths n</td>
<td>3</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality /1000 py</td>
<td>59</td>
<td>204</td>
<td></td>
<td>0.040</td>
<td></td>
</tr>
</tbody>
</table>
6 DISCUSSION

6.1 Urea kinetic modeling

The present thesis is based on urea kinetic modeling. A single-pool model was used in Study I, because the Solute-Solver program was not yet available [Daugirdas et al. 2009]. Double-pool UKM used in Studies II-V takes into account all essential factors affecting the urea concentration profile as a function of time. Simulating hemodialysis and creating fairly accurate prescriptions is possible with kinetic modeling, but the patient’s G, V, and Kr may vary between sessions and there are significant error sources in measuring them.

With equal clearance-based dosing the differences in urea concentrations are manifold due to differences in generation rate (Study III). Anorexia is common in uremia. In theory, using a constant urea concentration as the target – as in the NCDS – could lead to a vicious circle as presented by [Gotch et al. 1990] and in the introduction of Study III: the underdialyzed patient loses his or her appetite → dietary protein intake (DPI), PCR, G and concentrations decrease → the dialysis dose will be further diminished. This implies that after decreasing the dialysis dose, DPI, PCR, and G decrease relatively even more than clearance (K) – improbable with current practices (Equation 2c on page 19).

Dialyzer clearance Kd is the most difficult input parameter in UKM. Its errors have only a minimal effect on Kt/V, but a proportional effect on V and G. Kd can be calculated from Qb, Qd and dialyzer K0A with Michaels’ equation (36 on page 93), but manufacturers report K0A inconsistently. Hematocrit, dialyzer structure, clotting or reuse may modify it. In Studies I-III K0A for each dialyzer model was determined by a limited number of own blood-side measurements. K0A reported by the manufacturers was used in Study V. The errors in K0A cause relatively small errors to Kd. The errors of G and V caused by inaccurate Kd cancel each other out in EKR/V and stdK/V.

The main message regarding UKM is that although the ionic dialysance may not be exactly equal to urea clearance, it may well be used as Kd in UKM and in creating prescriptions, because it is derived from circumstances similar to those in
which it will be applied. This method was used in Study IV. IDM does not replace UKM, but makes it more useful.

6.2 Continuous-equivalent urea clearance

Weekly values of dialysis dose are required for comparing different schedules, but as seen in Figures 2 (Study I, page 59), 5 and 6 (Study II, pages 61-62), weekly eKt/V (sum of the eKt/Vs of one week’s sessions) underestimates the therapeutic significance of frequency and ignores RRF.

EKR/V and stdK/V are continuous-equivalent clearances scaled to urea distribution volume. At first sight, EKR/V calculated from the time-averaged urea concentration over the whole week seems to be the correct measure of continuous-equivalent clearance. Currently, however, stdK/V is more popular, perhaps because the numbers are closer to the corresponding values in CAPD. Gotch [Gotch 2001, Gotch 2004] and Casino [Casino 2001] postulate that the relation between Kt/V and EKR is linear and that EKR fails to reflect the effect of dialysis frequency. In Figure 10 of Study III (page 66) the relationship between eKt/V and double-pool EKR/V is not exactly linear and Figures 1 (Study I, page 58) and 12 (Study III, page 68) show that with constant weekly treatment time, increasing frequency lowers TAC and increases double pool EKR/V.

Increasing frequency or RRF lowers concentrations and shortens the weekly treatment time required to achieve the EKR/V and stdK/V targets (Figures 2 in Study I and 6 in Study II, pages 59 and 62). stdK/V is more sensitive to frequency and RRF than EKR/V. With increasing frequency above 3 x/week, using stdK/V as the target results in higher concentrations (PAC and TAC) than using EKR/V (Figures 3 and 4, page 60). With EKR/V as the target, PAC decreases with increasing RRF (Figure 7, page 63). When using stdK/V as the target, TAC increases with increasing RRF (Figure 8, page 63).

Increasing dialyzer clearance (K0A, Kd, Qb, Qd) is an inefficient way to increase stdK/V [Roa and Prado 2004]. With simulated 3 x 4 h/week schedule without RRF in Study III, increasing Kd by 34% from 191 mL/min to 256 mL/min (eKt/V from 1.2 to 1.6) resulted in a 12% fall of average PAC from 24.2 to 21.4 mmol/L and a 13% rise of stdK/V from 2.35 to 2.66/week (Figure 10, page 66).

The stdK/V values in hemodialysis are roughly equal to the fractional clearance K/V in CAPD; EKR/V is higher, but in Study V EKR/V had better predictive
value than stdK/V. HD and CAPD have other differences in addition to the intermittency, e.g. different characteristics of the dialysis membrane and utilization of osmotic instead of pressure gradient in convection. Continuous-equivalent measures of urea clearance may function between different intermittent HD schedules, but not between HD and CAPD. Aiming at equal clearance values in HD and CAPD is artificial [Garred et al. 1994b]. EKR/V and stdK/V are not as commensurable as was desired [Kjellstrand and Twardowski 1999].

In Study III comprising the most representative material the EKR/V and stdK/V values corresponding to eKt/V 1.20 in a conventional 3 x 4 h/week schedule were 3.44 and 2.40/week respectively. The KDOQI guidelines for hemodialysis adequacy have recently been updated to take RRF and UF into consideration and recommend stdK/V 2.3/week as the target for hemodialysis schedules other than thrice weekly [National Kidney Foundation 2015]. Improved versions of the empirical stdK/V equations that include UF and RRF are rather complex and need estimation of V [Daugirdas et al. 2010a]. SRI as a continuous-equivalent dialysis dose measure – recommended by EBPG 2007 – is inconsistently documented and not addressed in the present thesis. The current guidelines give no recommendations on EKR.

In conclusion, continuous-equivalent clearances are the most logical measures to assess the effect of dialysis on urea concentrations. EKR\textsubscript{urea} seemed to be more closely associated with outcome than stdK\textsubscript{urea}.

### 6.3 Scaling

Distribution volume V is an essential parameter in urea kinetic modeling and reflects the patient’s size, but is useless in comparing clearances of substances with different distribution volumes.

The anthropometric TBW is usually higher than the modeled V. There is a certain safety margin in the prescribed Kt/V if anthropometric TBW is used as V (Table 8 in Study IV, page 71). Online monitoring of spKt/V is currently possible in real time. Modeled V should preferably be used instead of anthropometric TBW with IDM to avoid “overdialysis”.

In the HEMO trial, women benefited from higher eKt/V but men did not. This is at least partially associated with scaling by V [Ramirez et al. 2012]. We have either to accept that the dose-and-effect relationship is different in men and
women or to choose a different scaling factor. BSA – used recently also in dialysis [Debowska et al. 2015] – may be better than V [Lowrie et al. 2005, Lowrie et al. 2006] providing more dialysis to women and children, who also will benefit from it.

Women had higher urea concentrations than men with equal V-scaled dialysis doses (Table 5 in Study III, page 67). Dialyzing to an equal concentration would deliver more Kt/V to women. In Study V the anthropometrically normalized ECCs were approximately equal between genders, but the V-scaled significantly higher in women. However, the continuous-equivalent clearances normalized with BSA were not more closely associated with mortality than the V-scaled ones (Table 14 in Study V, page 78), possibly due to the small number of patients.

6.4 Protein catabolic rate and dialysis dose

PCR reflects dietary protein intake (DPI), which correlates with nutritional status and outcome [National Kidney Foundation 2000]. In a recent large registry material mortality decreased with increasing nPCR until 1.3 g/kg/day with constant Kt/V [Ravel et al. 2013]. Often – and also in Study V – a positive correlation between dialysis dose and protein catabolic rate has been observed. This may indicate cause and effect [Buur et al. 1995, Lindsay et al. 1993, Marcus et al. 1999, Spanner et al. 2003] or mathematical coupling [Gotch F 1995a, Harty et al. 1993, Stein and Walls 1994, Uehlinger 1996, Venning et al. 1993] or that dosing of dialysis has been guided by urea concentrations (reverse causality, fear of high urea concentrations). All these factors may have a role in Study V. With low dialysis doses the cause and effect relationship may be valid, but probably not with current dose levels [Di Iorio et al. 1996, Kloppenburg et al. 2004]. In the HEMO trial the effect of dialysis dose on nPCR and the role of mathematical coupling were estimated to be small [Rocco et al. 2004].

Concentrations of several uremic toxins correlate with the protein catabolic rate in dialysis patients [Elloot et al. 2013]. Morton and Singer propose that the dialysis dose should be normalized to the metabolic rate [Morton and Singer 2007, Singer and Morton 2000]. Depner states that more oral protein intake demands more dialysis [Depner 1991a]. Gotch recommends spKt/V 0.9-1.0 for patients with low G and higher for those with high G, about equal numeric value to nPCR in the 3 x/week schedule [Gotch 1990, Gotch and Sargent 1985, Gotch et al. 2000]. Patients with high dietary protein intake, high protein catabolic rate and high G have high urea concentrations when dialyzed with a commonly accepted clearance
(Kt/V, EKR/V or stdK/V; Study III). It may be justified to increase the dialysis dose if urea concentrations are high. Study IV describes how this could be done. Protein catabolic rate is taken into account by cutting high urea concentrations. Continuous-equivalent measures of dialysis dose are needed, because the adjusting procedure may change the frequency. In simulated dialysis sessions the HEMO standard-dose equivalent ECC was insufficient to maintain time-averaged concentration (TAC) and average predialysis concentration (PAC) of urea below the defined upper limits (20 and 30 mmol/L) if nPCR was higher than 1.3 g/kg/day. Concentration limits may help in selecting patients likely to benefit from high frequency, but with the optimization criteria used more than three sessions per week were needed in only 7% of cases (Study IV).

In summary, we do not know the optimal or critical upper limits of TAC and PAC or whether such exist. After seeing a high predialysis urea concentration it is usually fairly simple to intensify the treatment, if we believe that it is justified. High concentration is due either to low clearance or to high generation rate. In both cases the dialysis dose needs to be increased if the hypothesis that patients with high nPCR benefit from higher than normal clearance-based dose actually holds true. This has not been confirmed empirically.

6.5 Treatment duration and frequency

Increasing duration increases Kt/V linearly, but the relationship between duration and concentration is nonlinear (Figure 11 in Study III, page 68). In simple simulations with the double-pool model increasing treatment duration from 240 to 480 min causes concentrations to decrease by 30-50%, those of β2-microglobulin only slightly more than those of urea. Concentrations can be decreased by 7-22%, PAC more than TAC, by increasing the frequency without increasing the weekly treatment time (Figure 12, page 68).

These examples show that urea and β2-microglobulin react similarly to changes in duration and frequency despite their different kinetics. Increasing duration and frequency have also been combined, but the results of the RCTs are not promising [Rocco et al. 2011, Rocco et al. 2015].

In the alternate day schedule the serious complications associated with the long interdialysis interval are avoided [Jun et al. 2013].
The variation of duration and frequency in Study V was rather small and no conclusion can be drawn as to which one is more effective in improving the outcome, but theoretical calculations favor increasing duration for better removal of uremic toxins.

### 6.6 Residual renal function

In hemodialysis patients, RRF may contribute to total urea removal by more than 50% (Figure 9 in Study II, page 64). According to urea kinetics, RRF may replace several hours of weekly dialysis treatment time in a conventional thrice-weekly schedule, if HEMO-equivalent EKR/V and stdK/V values are used as targets in incremental dialysis (Figure 6, page 62). Each mL/min of renal urea clearance corresponds to about 30-60 min of session time. Each weekly dialysis hour replaces about 0.7 mL/min of lacking renal urea clearance. Other uremic solutes behave differently. The positive effect of RRF is probably greater than its contribution to urea clearance.

RRF decreases TAC and especially PAC. Kr is an input parameter in UKM and is needed in the calculation of urea generation rate and PCR. Kr is automatically included in continuous-equivalent clearances if derived from UKM. Urea as a marker makes RRF and dialysis commensurable in a safe way: renal function expressed as urea clearance is “qualitatively better” than equal dialysis urea clearance. In incremental dialysis it is important to check Kr frequently.

The concept of incremental dialysis is compatible with the old concept of [Babb et al. 1972] and the more recent results of [Khan et al. 2002]. A drawback is that patients who have begun with it are reluctant to increase their dialysis time when RRF fades. When to initiate dialysis and how to preserve RRF is not addressed in this thesis.

### 6.7 Solutes with different kinetics

Doubling of td lowers TAC of differently behaving solutes by 30-50% (Figure 11 in Study III, page 68). Increasing frequency (with constant weekly treatment time) from 3 to 7 x/week lowers the TAC of urea and β2-microglobulin by 7-9%, PAC by somewhat more (Figure 12, page 68). Both time and frequency are somewhat unspecific means to control uremic retention solutes with different kinetics.
Decreasing Qd from 500 to 100 mL/min or Qb from 300 to 100 mL/min decreases urea diffusive clearance by 62% and increases TAC\textsubscript{urea} by 114-115%, but decreases β2-microglobulin clearance by only 11-13% and increases TAC\textsubscript{β2M} by 9-10% (Table 6, page 69). Decreasing Qd from 500 to 100 mL/min combined with increasing time from 240 to 480 min changes urea and β2-microglobulin values in opposite directions (Table 7, page 69). Changes in flows cause much greater effects on clearances and concentrations of urea than on those of middle molecules. This decreases the significance of Kt/V\textsubscript{urea} and the value of high Qb. With equal urea clearance (EKR) or concentration (TAC), concentrations of middle molecules are lower with more gentle treatment (lower Qb and/or Qd and longer td; Figure 13, page 70). The calculations are in accordance with the analysis of [Goldfarb-Rumyantzev et al. 2002]. Favoring high-efficiency dialysis and adhering to the single-pool Kt/V may partially explain the poor outcomes in the USA in the 1980's.

The low dialysate flow technique may be suitable for nocturnal home hemodialysis on every other day. In more frequent schedules the complications associated with blood access may outweigh the advantages due to enhanced middle molecule clearance [Jun et al. 2013, Weinhandl et al. 2015].

Uremic toxins, including β2-microglobulin, do not necessarily obey double-pool kinetics. The distribution volumes and intercompartment transfer coefficients cannot be modified. Increasing Kd of middle molecules may be possible by increasing convection. The effect on outcome of a decrease of concentrations of uremic toxins depends of course on the correlation of toxicity with concentration. It is unclear which is the most useful strategy – increasing convection or time or frequency. All of these have been reported to improve outcome. According to the simulations in Study III increasing duration seems to be a more effective means to decrease middle molecule concentrations than increasing frequency. However, short daily and infrequent long nocturnal dialyses are very different treatment modalities with only outcome as the common measure and are not suitable for all. High frequency and long duration with slightly reduced blood and dialysate flows were combined in the (underpowered) FHN nocturnal trial with negative effects [Rocco et al. 2015]. If we knew more about the kinetics of uremic toxins and the concentration-dependence of their toxicity, we might prefer one strategy over the other.

In conclusion, although ECC is probably the best measure of the effect of dialysis on urea concentrations, applying it to other substances detracts from its
value and the significance of urea as a marker solute and shows that the interest should be directed from clearances of urea to concentrations of true uremic toxins.

6.8 Adequacy

In most observational controlled studies, increasing clearance, time, frequency or convection has had a positive effect on both survival and soft endpoints. In RCTs such as HEMO and especially in the FHN trials the patients recruited may not have been a representative sample of the whole hemodialysis population. The dose targeting bias also affected the HEMO results [Greene et al. 2005]. After HEMO the doses have still increased despite its results [Miller et al. 2010].

There are only few reports correlating outcome directly with continuous-equivalent dose measures referred to and discussed in the literature review section 2.6.6 [Barreneche et al. 1999, Manotham et al. 2006, Rocco et al. 2011, The FHN Trial Group 2010]. In a cohort of 191 quotidian home hemodialysis patients survival was independently associated positively with stdK/V up to over 5.00/week without plateauing [Lockridge et al. 2012]. In the short daily arm of the FHN trial stdK/V was higher and outcome better in the high frequency group [The FHN Trial Group 2010], but in the frequent nocturnal arm the differences in stdK/V between the test and control groups were even greater and the long-term outcome worse in the higher dose group [Rocco et al. 2015].

Continuous-equivalent dose measures combine session frequency, the dose of each session and residual kidney function. The best measure of dialysis adequacy is the one which is most closely associated with outcome. In Study V comparing ECCs it was EKR/V. Mortality was also associated significantly with nEKR, but not with stdK/V or nstdK. Associations of EKR and stdK with survival have not been compared earlier.

The effects of concentration fluctuations, frequency, and RRF are reflected differently in EKR/V and stdK/V (Studied I and II). Simulations with substances behaving differently from urea (Tables 6 and 7 in Study III, page 69) impair the value of methods based on urea clearance. EKR/V<sub>urea</sub> and stdK/V<sub>urea</sub> do not accurately reflect middle molecule removal. Probably the outcomes cannot be improved by increasing urea clearance from the current level, but we should concentrate on the more difficult to remove molecules. Other pathways in addition to dialysis may also be involved in their elimination, and it may be possible to
influence the generation rate of some of them. We need more information on the kinetics and effects of real uremic toxins and should compare their concentrations in different treatment modes with equal urea clearance as the common dose measure. Monitoring UV light absorption of the effluent dialysate may offer a new viewpoint if Kt/V<sub>urea</sub> is abandoned as the reference.

In Study V urea clearance and PCR correlate positively with outcome and with each other. nPCR is associated with survival directly and with the dialysis dose through the “fear of high urea concentrations” effect – an example of possible mechanisms behind the dose-targeting bias [Greene et al. 2005]. Patients with high nPCR may benefit from higher dose by this mechanism. nPCR and dialysis dose seem to have a synergistic association with survival.

6.9 Limitations

Inaccuracy of the single-pool model affects the simulations in Study I. K<sub>0A</sub>-values in Studies I-III are based on own blood-side clearance measurements with remarkable dispersion. The K<sub>0A</sub>-values based on IDM used in Study IV also vary within each dialyzer model. In Study V the results were unadjusted for comorbidity (except diabetes), dialysis vintage, vascular access, blood pressure, laboratory values, epoetin use, and many other possible confounding factors. The dialysis dose was not randomly assigned as it is not in most retrospective observational registry studies. The role of convection was ignored; high-flux dialyzers were used only in about 10% of treatments. As expected, there was a correlation between age and mortality, but it was statistically insignificant.

The most serious limitation is the small number of patients in Study V. No robust conclusions can be drawn. The aim was to compare the predictive value of specific risk factors in the same population, not treatments.

6.10 New questions

Do patients with high PCR really benefit from high clearance? The prescription algorithm (Study IV) should be tested on patients. Studies on the association of ionic dialysance, weekly BSA-normalized Kt and dialysate UV light absorption with mortality and other descriptors of treatment outcome are needed. Also, it would be interesting to measure the light absorption of the effluent dialysate with other and
multiple wavelengths reflecting the kinetics of true uremic toxins instead of uric acid and urea (Donadio et al. 2014). The ECC dose measures should be compared in a larger material than that used in Study V. Could the high first half year mortality be decreased by an incremental approach? The peak concentration hypothesis is still unconfirmed. More data is needed on the kinetics and toxicity of uremic retention solutes. The effect of treatment time, frequency, and convection on outcomes should be tested with equal BSA-normalized dose (weekly nKt).
7 CONCLUSIONS

7.1 Is high mortality in hemodialysis due to low dose?

In each study of the thesis mean EKR/V and stdK/V were considerably higher than the corresponding HEMO standard dose equivalent values. Thus, the rather high mortality (140 deaths/1,000 patient years) – although lower than in the USA – was probably not mainly due to universal underdialysis. An association between dose and mortality was also detected in this population. The mortality might have been lower if the lowest doses had been higher – assuming that the association reflects causality. However, dose is not the only descriptor of treatment quality.

7.2 How should the dialysis dose be measured?

Residual renal function contributes significantly to urea removal and even more to the removal of true uremic toxins. Taking it into consideration by incremental dialysis relieves the burden of the treatment. ECC is a rational way to note treatment frequency and RRF. EKR seems to be more closely associated with mortality than stdK.

The treatment dose has to be scaled to patient size. BSA may be a better scaling factor than urea distribution volume. Normalizing with BSA gives more dialysis to women and children and they also benefit from it.

No single absolutely correct dialysis dose measure exists. Urea does not universally represent the behavior of uremic toxins. Small dialyzable molecules like potassium are important in the short term. If the patient dies rapidly due to retention of small molecules, large molecules with slow harmful effects are not significant. EKR and stdK handle treatment frequency and RRF appropriately, but are not ideal predictors of treatment effectiveness when based solely on urea kinetics. Hemodialysis adequacy cannot be described with only one number.

Dialyzer urea clearance is a good descriptor of the method. The delivered dialysis dose (efficiency of toxin removal) can be defined technically as weekly
dialyzer urea clearance, normalized with BSA (nKt\textsubscript{urea}), e. g. 180 L./week/1.73m\textsuperscript{2} corresponding to about 14 mL./min of EKR, 3.6/week of EKR/V and 2.4/week of stdK/V in a 3 x 4 h/week schedule, which guarantees sufficient removal of small molecules. In fact, this is like weekly spKt/V, but with BSA as the scaling factor instead of V. It is less than 180 L./week/1.73m\textsuperscript{2} of continuous clearance. The target can be safely reduced by nKr\textsubscript{urea} (L./week/1.73 m\textsuperscript{2}). Kt is easily monitored with an online device based on ionic dialysance. Dialyzer clearance and weekly treatment time determine the delivered dose externally, reflecting consumption of resources. Blood samples, UKM and computers are not needed. A distinction must be made between dose and effect. ECC, Kt/V and URR reflect patient-dependent effects of treatment, modified by treatment schedule and individual intercompartment transfer coefficients and compartment volumes.

### 7.3 How could dosing be improved?

Improving hemodialysis outcomes may be possible by increasing clearance, duration, frequency, and convection. Increasing treatment duration with constant weekly Kt\textsubscript{urea} lowers concentrations of middle molecules. Increasing frequency without increasing weekly treatment time decreases concentrations of all solutes, PAC more than TAC, but may increase inconvenience, complications, and costs. The possible beneficial effect of higher frequency is not based solely on the efficiency of solute removal. Fluctuation of concentrations and volumes and the compartment effects (disequilibrium) are associated with frequency and may affect outcome. However, stdK may overestimate the benefits of increased frequency and result in higher concentrations when used as the dosing target in frequent dialysis. An alternate day schedule may be a useful compromise between daily and conventional schedules.

Urea concentration depends heavily on its generation rate, which is also an independent prognostic factor. Instead of urea clearances we should concentrate on the concentrations of true uremic toxins.

The outcomes probably cannot be improved by increasing urea removal from the current level. Future investigations with constant delivered dose (weekly nKt) will hopefully reveal the best strategies (duration, frequency or convection) to control the long-term effects of uremic toxins. The relative clearances of small and large molecules can be adjusted by blood and dialysate flow but not by time or frequency.
Classic single-pool variable volume urea kinetic model equations [Gotch FA 1995b]. V0 and Vt are the distribution volumes at the beginning and end of treatment; Qf is the rate of volume contraction during dialysis (= ultrafiltration rate), td is treatment duration; G is the interdialytic urea generation rate; Kd and Kr are the dialyzer and kidney urea clearances; C0 and Ct are the urea concentrations at the beginning and end of treatment.
beginning and end of treatment, $\alpha$ is the rate of interdialytic volume expansion calculated by the total interdialytic weight gain divided by the length of the interdialytic interval, $\theta$.

\[
Kd = Qb \left[ e^{\left( \frac{KdA}{Qb} \times \frac{Qd-Qb}{Qd} \right)} - 1 \right] - \frac{Qb}{Qd}
\]

(36)

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Savonlinna, March 2016


REFERENCES


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Effect of treatment frequency on haemodialysis dose: comparison of EKR and stdKt/V

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Abstract

Background. Haemodialysis outcome cannot be improved by increasing the dialysis session dose above the current standard in conventional schedules. Promising results have been reported from daily dialysis, but the optimal dose has not been established.

Methods. Weekly eKt/V, equivalent renal clearance (EKR) and stdKt/V were compared retrospectively in 588 complete urea kinetic modelling sessions of 35 haemodialysis patients. Equivalent values of EKR and stdKt/V corresponding to the standard and high doses of the HEMO study were defined by computer simulation. The effect of frequency on the dose measures was demonstrated by simulating different schedules.

Results. EKR and stdKt/V take into consideration both frequency and RRF, but appreciate them differently. The values of EKRc (EKR in millilitres per minute, normalized to distribution volume 40 l), stdEKR (EKR in litres per week divided by urea distribution volume in litres) and stdKt/V corresponding to eKt/V 1.20—close to the standard dose in the HEMO study were defined by computer simulation. The effect of frequency on the dose measures was demonstrated by simulating different schedules.

Conclusions. Haemodialysis efficiency can be increased by increasing frequency. EKR and stdKt/V are more appropriate than weekly eKt/V as measures of dialysis dose in different schedules. With increasing frequency, stdKt/V as the dosing target results in shorter treatment times and higher concentrations than EKR.

Keywords: computer simulation; dialysis dosing; EKR; eKt/V; stdKt/V

Introduction

According to the HEMO study [1], the outcome of haemodialysis (HD) cannot be improved by increasing the session dose (Kt/V) above the current standard of a three times per week schedule.

Kt/V is a measure of a single dialysis session. Weekly Kt/V (wKt/V) is the sum of the Kt/Vs of 1-week sessions. It is—in theory—the same whether the patient is dialysed 6 h two times per week or 2 h six times with the same dialyser clearance (Kd). According to numerous reports, the latter schedule yields better outcomes.

In CAPD (continuous ambulatory peritoneal dialysis) patients with total ‘weekly Kt/V’ 2.0 do equally well as patients on HD with wKt/V 3.6. What we call ‘weekly Kt/V’ in CAPD is the fractional clearance (K/V): continuous clearance K divided by distribution volume V relating it to body size. The unit is ‘/wk’. The only problem is estimation of V, which in intermittent HD comes from the urea kinetic model (UKM). Fractional clearance can be used as a measure of renal function, too.

Equilibrated Kt/V (eKt/V) takes the compartment disequilibrium into account and helps in avoiding underdialysis in short-high efficiency treatments and in small patients, but weekly eKt/V (weKt/V)—like wKt/V—ignores the significance of frequency.

Weekly Kt/V and weKt/V have been reported to be higher in short daily HD with equal weekly treatment time and other dialysis parameters [2–4]. The dialyser clearance may decrease during the session due to clotting and accumulation of material on the membrane, so, on average, it may be higher in shorter sessions with equal blood and dialysate flow. On the other hand, wKt/V [5] and weKt/V [6] have also been reported to remain unchanged on switching from three to six times per week treatment with the same weekly treatment time.

In addition to wKt/V and weKt/V, several methods have been proposed for evaluation of the equivalency of renal function and different intermittent and continuous dialysis techniques:

Chen et al. [7] observed that weekly Kt/V values of CAPD patients and weekly URRs of HD patients were similar to each other. Cheng et al. [10] reported higher weekly URR values for CAPD than for HD patients despite markedly higher wKt/V in HD. Maduell et al. [5] and Williams et al. [6] observed higher weekly URR in short daily than in conventional treatment with the same weekly treatment time and wKt/V or weKt/V.

The optimal dose measure for schedules other than three times weekly has not been established [15]. The European guidelines [16] recommend stdKt/V, EKR and SRI. Unfortunately, SRI has conflicting definitions.

The objective of the current retrospective observational analysis is

1. to determine the EKR and stdKt/V values corresponding to the standard and high doses of the HEMO study and
2. to compare EKR and stdKt/V as measures of dialysis dose in symmetric schedules with different frequencies.

**Subjects and methods**

Detailed description of the abbreviations, symbols, definitions and equations is presented in the Appendix.

Data have been gathered by a dialysis information system in the routine care of HD patients. No randomization, control group or study protocol has been used.

Urea kinetic modelling with three blood samples and interdialysis urine collection was done once per month (modelling session). Postdialysis blood samples were taken at the termination of the session with a modified KDOQI slow-blood-flow technique [17]. Postdialysis urea concentrations were converted to equilibrated ones by the Tattersall method [18]. Then all calculations were done using the classic single-pool variable-volume urea kinetic model (spvvUKM) [19,20] with the equilibrated postdialysis values. The urea generation rate (G) and distribution volume (V) are required in computing the protein equivalent of total nitrogen appearance (nPNA), EKR and stdKt/V.

**Dialysis sessions**

The analysis is based on 588 data sets collected between 1 January 2004 and 31 December 2006 from 35 prevalent HD patients having at least one complete urea kinetic modelling session after the first 4 weeks of dialysis. All patients were white Europeans. The modelling sessions are described in Table 1.

**Residual renal function (RRF)**

RRF is expressed as renal urea clearance Kr (ml/min) and renal fractional urea clearance rFC (/wk). The entire interdialysis urine was collected. The calculation of Kr is described in the Appendix. If Kr was below 1 ml/min in three consecutive measurements, Kr and diuresis were stated as zero and urine was not collected in subsequent modelling sessions.

**Dialysis dose**

All variables, including G, Vt, Kr, rFC, nPNA, EKR and std/V, are based on equilibrated postdialysis concentrations although explicitly noted only on eKt/V.

Dialysis dosing is expressed in four ways:

1. EKRc: EKR normalized to distribution volume of 40 l, expressed in ml/min units (Casino and Lopez)
2. stdEKR: EKR divided by distribution volume, expressed in /wk units to facilitate comparison to stdKt/V
3. stdKt/V (Gotch) in /wk units

**Table 1. Modelling sessions**

<table>
<thead>
<tr>
<th>Data</th>
<th>Value/</th>
<th>Unit</th>
<th>average</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
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<tbody>
<tr>
<td>Number of sessions</td>
<td>588</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sessions with RRF</td>
<td>%</td>
<td></td>
<td>32.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>%</td>
<td></td>
<td>37.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Years</td>
<td></td>
<td>65.1</td>
<td>16.0</td>
<td>16.0</td>
<td>91.6</td>
</tr>
<tr>
<td>Height</td>
<td>cm</td>
<td></td>
<td>169</td>
<td>10</td>
<td>150</td>
<td>187</td>
</tr>
<tr>
<td>Postdialysis weight</td>
<td>kg</td>
<td></td>
<td>78.7</td>
<td>18.7</td>
<td>43.3</td>
<td>134.5</td>
</tr>
<tr>
<td>Total body water (Watson)</td>
<td>l</td>
<td></td>
<td>39.5</td>
<td>8.1</td>
<td>24.6</td>
<td>61.0</td>
</tr>
<tr>
<td>Kinetic urea distribution volume</td>
<td>l</td>
<td></td>
<td>40.0</td>
<td>7.4</td>
<td>20.2</td>
<td>65.2</td>
</tr>
<tr>
<td>Urea generation rate</td>
<td>µmol/min</td>
<td></td>
<td>218</td>
<td>73</td>
<td>76</td>
<td>547</td>
</tr>
<tr>
<td>nPNA</td>
<td>g/kg/day</td>
<td></td>
<td>1.01</td>
<td>0.24</td>
<td>0.45</td>
<td>2.13</td>
</tr>
<tr>
<td>Diuresis</td>
<td>l/day</td>
<td></td>
<td>0.19</td>
<td>0.35</td>
<td>0.00</td>
<td>1.69</td>
</tr>
<tr>
<td>Renal urea clearance</td>
<td>ml/min</td>
<td></td>
<td>0.65</td>
<td>1.29</td>
<td>0.00</td>
<td>5.10</td>
</tr>
<tr>
<td>Renal fractional urea clearance</td>
<td>/wk</td>
<td></td>
<td>0.16</td>
<td>0.27</td>
<td>0.00</td>
<td>0.98</td>
</tr>
</tbody>
</table>

(4) weekly eKt/V: the sum of the eKt/Vs of 1-week treatment sessions, in /wk units.

Time-averaged concentration (TAC) and average predialysis concentration (PAC), needed in calculating EKR and stdKt/V, cannot be derived from a single modelling session. Treatment parameters were averaged over 4 weeks preceding and including the modelling session. The actual dialyser urea clearance (Kd) of each treatment was calculated from actual blood and dialysate flow (Qb, Qd) and the mass transfer area coefficient (KoA) of the dialyser [21]. KoA is based on several blood side blood water clearance measurements of each dialyser model. Dialysers were used only once.

Treatments were equalized by iterating the spvvUKM concentration equation [19] sequentially over average treatment time and average interval time until plateauing of the predialysis concentration (see the Appendix). This procedure modifies an asymmetric schedule to an evenly distributed one, but has no influence on the patient-specific values.

**Simulations**

The effect of treatment frequency on the measures of dialysis dose was studied by computer simulations. They are based on the classic spvvUKM with the patient-dependent values G, Vt and Kr from the modelling session and varying treatment values, keeping weekly ultrafiltration unchanged and assuming that dialysis has no effect on urea generation and renal function.

**Statistical methods**

Microsoft Excel 2002 software was used in calculating minimum and maximum values and standard deviations and in creating the graphs.

**Results**

**Equivalent doses**

Equivalent values corresponding to the standard and high dialysis doses of the HEMO study were determined by simulating a conventional dialysis with a symmetric 3 × 4 h/wk schedule and eKt/V 1.20 and 1.60 in the study material (Table 2), respectively. Dialysis intensity was adjusted by dialyser clearance. Numbers in the table are averages of the 588 sessions. The most important parameters are in bold.

The simulated values of EKRc, stdEKR and stdKt/V corresponding to eKt/V 1.20—close to the standard dose in the HEMO study (1.16)—are 13.2 ml/min/40 l, 3.34/wk and
Table 2. Average equivalent measures of HEMO standard and high doses

<table>
<thead>
<tr>
<th>Data</th>
<th>Unit</th>
<th>Actual equalized</th>
<th>HEMO standard</th>
<th>HEMO high</th>
<th>HEMO high</th>
<th>HEMO high</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 × 4 h</td>
<td>3 × 4 h</td>
<td>3 × 5 h</td>
<td>6 × 2.5 h</td>
</tr>
<tr>
<td>Dialysis frequency</td>
<td>/wk</td>
<td>3.12</td>
<td>3.00</td>
<td>3.00</td>
<td>3.00</td>
<td>6.00</td>
</tr>
<tr>
<td>Dialysis time</td>
<td>min</td>
<td>292</td>
<td>240</td>
<td>240</td>
<td>300</td>
<td>150</td>
</tr>
<tr>
<td>Weekly dialysis time</td>
<td>h</td>
<td>15.2</td>
<td>12.0</td>
<td>12.0</td>
<td>15.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Predialysis concentration</td>
<td>mmol/l</td>
<td>19.8</td>
<td>23.3</td>
<td>20.3</td>
<td>20.1</td>
<td>15.4</td>
</tr>
<tr>
<td>Equilibrated postdialysis</td>
<td>mmol/l</td>
<td>5.5</td>
<td>8.6</td>
<td>5.3</td>
<td>5.4</td>
<td>7.8</td>
</tr>
<tr>
<td>Time-averaged concentration</td>
<td>mmol/l</td>
<td>12.7</td>
<td>16.1</td>
<td>12.9</td>
<td>12.8</td>
<td>11.6</td>
</tr>
<tr>
<td>Dialyser clearance</td>
<td>ml/min</td>
<td>213</td>
<td>284</td>
<td>266</td>
<td>213</td>
<td>213</td>
</tr>
<tr>
<td>Ultrafiltration volume</td>
<td>l</td>
<td>2.73</td>
<td>2.84</td>
<td>2.84</td>
<td>2.84</td>
<td>1.42</td>
</tr>
<tr>
<td>Equilibrated Kt/V</td>
<td>ml/min/40 l</td>
<td>1.59</td>
<td><strong>1.20</strong></td>
<td><strong>1.60</strong></td>
<td>1.60</td>
<td>0.80</td>
</tr>
<tr>
<td>Weekly equilibrated Kt/V</td>
<td>/wk</td>
<td>4.93</td>
<td>3.60</td>
<td>4.80</td>
<td>4.80</td>
<td>4.80</td>
</tr>
<tr>
<td>EKRc (Casino and Lopez)</td>
<td>ml/min/40 l</td>
<td>16.9</td>
<td><strong>13.2</strong></td>
<td><strong>16.4</strong></td>
<td>16.5</td>
<td>18.6</td>
</tr>
<tr>
<td>stdEKR</td>
<td>/wk</td>
<td>4.26</td>
<td><strong>3.34</strong></td>
<td><strong>4.14</strong></td>
<td>4.16</td>
<td>4.68</td>
</tr>
<tr>
<td>stdKt/V (Gotch)</td>
<td>/wk</td>
<td>2.63</td>
<td><strong>2.23</strong></td>
<td><strong>2.54</strong></td>
<td>2.57</td>
<td>3.48</td>
</tr>
</tbody>
</table>

2.23/wk, respectively. Weekly eKt/V and stdEKR are remarkably higher than stdKt/V, far above the range achieved in CAPD. The values of EKRc, stdEKR and stdKt/V corresponding to eKt/V 1.60—close to the high dose in the HEMO study (1.53)—are 16.4 ml/min/40 l, 4.14/wk and 2.54/wk, respectively.

It may be difficult to achieve eKt/V 1.60 in 4 h. The last two columns of Table 2 represent the HEMO high dose equivalent values in symmetric 3 × 5 h/wk and 6 × 2.5 h/wk schedules, respectively. Uraemic toxicity is probably related to concentrations. Predialysis and TACs are lower with higher frequency, although generation and elimination rates, treatment time and dialysis fluid consumption are equal. This may be interpreted as better efficiency and is reflected in higher EKR and stdKt/V, but not in weKt/V.

Effect of frequency

The simulations are based on weekly eKt/V, stdEKR and stdKt/V as measures of dialysis dose.

Figure 1 describes the effect of frequency on different measures of dialysis dose in a patient with average characteristics of the study material (Table 1). Frequency affects stdKt/V more than stdEKR. Weekly eKt/V is not dependent on frequency.

Figures 2–4 represent the patient dialysed with the standard-equivalent doses defined in Table 2.

Figure 2 describes the effect of frequency on the weekly treatment time required to achieve the standard-equivalent doses with constant Kd. Much more time is needed to achieve the stdKt/V target in a two times per week schedule than in three times per week. The effect of frequency is less steep with stdEKR as the target dose measure.

With higher frequency, using stdKt/V as the target results in higher concentrations (C0 and TAC) than stdEKR (Figures 3 and 4).

The curves in Figures 1–4 are based on a simulated patient with G = 218 µmol/min, V = 40.0 l, Kr = 0.65 ml/min (Table 1) and UF = 8.5 l/wk (Table 2). With the spreadsheet DoseOpt.xls in http://www.verkkomunuainen.net/optimize.html, the dialysis prescription can be planned individually.

Discussion

The current analysis is based on the UKM. One of the parameters in this model is renal urea clearance, which is lower than the glomerular filtration rate.

HD urea kinetics can be described rather accurately by a two-pool model that requires several blood samples or a dialysate urea monitor. Using single-pool UKM with dialyser clearance and equilibrated postdialysis concentration as input parameters is a practical shortcut, although incorrect in theory. It involves mixing of single- and double-pool models and overestimates Vt to compensate the difference between dialyser clearance and whole body patient clearance to give a ‘correct’ eKt/V. This concept was used as the...
Fig. 2. Effect of treatment frequency on weekly treatment time required to achieve different HEMO standard dose equivalent targets. Kd 200 ml/min.

Fig. 3. Effect of treatment frequency on predialysis concentration (C0) with different HEMO standard dose equivalent targets. Kd 200 ml/min, dose adjusted by treatment time.

Fig. 4. Effect of treatment frequency on time-averaged concentration (TAC) with different HEMO standard dose equivalent targets. Kd 200 ml/min, dose adjusted by treatment time.

In CAPD, stdKt/V and stdEKR are equal to the fractional clearance (‘weekly Kt/V’). In standard HEMO-equivalent dialysis (Table 2), the average stdKt/V (2.23 /wk) is comparable to the stdKt/V of CAPD patients. Possibly the greater unphysiology (fluctuation of volume and concentrations, compartment disequilibrium) and different sieving profiles of the membrane have to be compensated by a slightly greater dose in HD to achieve equal outcome.

According to the European guidelines [16], in anuric patients, treated by three times per week dialysis, the prescribed target eKt/V should be at least 1.2, and for patients with renal function or those with dialysis schedules other than three times per week, weekly dialysis dose should be at least equivalent to an SRI of 2. In a symmetric schedule, SRI—as defined in the guidelines—is equal to stdKt/V. In the current material, the SRI or stdKt/V value corresponding to a delivered eKt/V of 1.2 is considerably higher. The difference corresponds to 42 min of session time (198 versus 240 min) in a symmetric three times per week schedule with a Kd of 200 ml/min. SRI 2.00/wk corresponds to eKt/V 0.99. With significant RRF, a lower value of SRI or stdKt/V may be acceptable, because it, based on the UKM, underestimates renal function.

Future investigation is needed to elucidate whether increasing the dialysis dose above the equivalents of the HEMO standard dose by increasing the frequency is of any prognostic benefit and whether increased dose or decreased unphysiology [23] is more important in frequent dialysis.

stdKt/V appreciates frequency more than EKR. If diminished unphysiology is the most essential advantage of frequent dialysis, then dosing is best guided by stdKt/V resulting in shorter weekly treatment time with increasing frequency, but if dose is important, then EKR is more suitable resulting in lower concentrations.

Conflict of interest statement. None declared.
Appendix

Abbreviations and symbols

UKM = urea kinetic model
spvvUKM = single-pool variable volume UKM
RRF = residual renal function
HD = haemodialysis
CAPD = continuous ambulatory peritoneal dialysis
Qb = blood flow
Qd = dialysate flow
t = observation period duration
td = dialysis session duration
ti = dialysis interval duration
fr = dialysis session frequency
G = generation rate
E = removal rate
K = clearance
Kd = diffusive blood water dialyser clearance
KoA = mass transfer area coefficient of the dialyser
Kr = renal clearance
rFC = renal fractional clearance
C = concentration
C1 = concentration at the beginning of the observation period
C2 = concentration at the end of the observation period
C0 = concentration at the beginning of a dialysis session
Ct = equilibrated postdialysis concentration
C02 = concentration at the beginning of the next dialysis session
TAC = time-averaged concentration, computed using equilibrated postdialysis concentration
PAC = average predialysis concentration, average C0
Cu = urine concentration
V = distribution volume
V1 = distribution volume at the beginning of the observation period
V0 = distribution volume at the beginning of a dialysis session
V02 = distribution volume at the end of a dialysis session
Va = average distribution volume
Vu = interdialysis urine volume
VG = fluid accumulation during the observation period
VGD = fluid accumulation during a dialysis session, usually negative
VGi = fluid accumulation between dialysis sessions
WGI = weight gain between dialysis sessions
UF = ultrafiltration volume (positive, if fluid is removed)
URR = urea reduction ratio
SRI = solute removal index
FSR = fractional solute removal
tFSR = average total fractional solute removal rate (renal + dialysis)
wFSR = weekly total fractional solute removal (renal + dialysis)
RUR = renal urea removal, amount of urea in interdialysis urine
DUR = amount of urea removed in a dialysis session
Kt/V = dialysis session dose, single pool
eKt/V = equilibrated dialysis session dose
wKt/V = weekly Kt/V
weKt/V = weekly eKt/V
EKR = equivalent renal urea clearance, a measure of dialysis dosing defined by Casino and Lopez [12]
EKRc = EKR normalized to a urea distribution volume of 40 l
stdKt/V = a measure of dialysis dosing defined by Gotch [13]
stdEKR = EKR divided by V; comparable to stdKt/V
NBW = normal body weight
PNA = protein equivalent of total nitrogen appearance
nPNA = normalized PNA

Definitions and calculations

VGi = WGi (in conjunction with the actual modelling session)  \hspace{1cm} (A.1)

VGi = UF (in the equalized schedule) \hspace{1cm} (A.2)

V0 = Vt + UF \hspace{1cm} (A.3)

V02 = Vt + VGi \hspace{1cm} (A.4)

Va = (V0 + Vt)/2 \hspace{1cm} (A.5)

RUR = Vu*Cu \hspace{1cm} (A.6)

DUR = V0^*C0 − Vt^*Ct + td^*G \hspace{1cm} (A.7)

G = (V0^*C02 − Vt^*Ct + RUR)/ti \hspace{1cm} (A.8)

rFC = Kr/Vt \hspace{1cm} (A.9)

Kt/V = Kd*td/Vt \hspace{1cm} (A.10)

wKt/V = fr*Kt/V \hspace{1cm} (A.11)

weKt/V = fr*eKt/V \hspace{1cm} (A.12)

nKt/V = 0.92*fr*(1 − exp(−1.1*Kt/V)) \hspace{1cm} (A.13)

NBW = Vt/0.58 (assuming 1 litre weighs 1 kg) \hspace{1cm} (A.14)

nPNA = PNA/NBW \hspace{1cm} (A.15)

The Sargent modification [24] of the original Borah equation [25] was used in calculating PNA.

EKR (equivalent renal urea clearance) and stdKt/V are based on the definition of clearance:

K = E/C. \hspace{1cm} (A.16)

In steady state E = G, so

K = G/C. \hspace{1cm} (A.17)

In EKR, the term C of equation (A.18) is the time-averaged concentration (TAC), in stdKt/V, the average predialysis concentration (PAC). According to the definition, stdKt/V
is normalized by dividing the value of equation (A.18) by the distribution volume \( V \). Dividing EKR by \( V \) yields a variable called here as stdEKR (eqKRt/V in [26]):

\[
\text{stdEKR} = \frac{G}{TAC/Va} \quad \text{(A.19)}
\]

\[
\text{stdKt/V} = \frac{G}{PAC/V0} \quad \text{(A.20)}
\]

The unit of stdEKR and stdKt/V is \( \text{ml/min/40l} \). To ensure conformity with wtFSR, predialysis volume \( (V0) \) is used in stdKt/V, average volume \( (V_a) \) in stdEKR.

EKRc is stdEKR multiplied by a ‘normal’ distribution volume 40 l and divided by the number of minutes in a week (10 080) [12]:

\[
\text{EKRc} = 3.97^*\text{stdEKR}. \quad \text{(A.21)}
\]

The unit of EKRc is \( \text{ml/min/40l} \).

Weekly total fractional solute removal (wtFSR) is the amount of urea removed by dialysis and the kidneys during 1 week divided by the average predialysis amount of urea in the body. More generally

\[
\text{tFSRR} = \frac{E}{PAC^*V0}. \quad \text{(A.22)}
\]

As seen from equations (A.20) and (A.22), tFSRR = stdKt/V, if \( E = G \), wtFSR is \( \text{tFSRR} \) with week as the time unit like in stdKt/V. Only stdKt/V is used in the Results section.

Kr is computed by searching for the value that yields \( C_02 \) from Ct. Calculations of G, V and Kr are included in the same iteration loop:

\[ V_t = \text{ASV} \quad \text{‘arbitrary starting value} \]

Repeat

\[ V_p = V_t \quad \text{‘previous Vt} \]

\[ G = ((V_t + VG_i)^*C_02 - V_t^*C_t + RUR)/t_i \quad \text{‘different from classic UKM} \]

\[ Kr = fK(C_t, C_02, V_t, VG_i, t_i, G) \quad \text{‘binary search (declared below)} \]

\[ V_t = fV_t(C_0, C_t, -UF, \text{td, Kd, Kr, G}) \quad \text{‘spvvUKM Vt equation} \]

Until Abs\((V_t - V_p)/V_t\) < 0.00001

The parameters of function \( fV_t() \) are \( C_1, C_2, V_G, t, K_d, \) and \( G \). It returns \( V_t \).

function \( fK(C_1, C_2, V_1, V_G, t, G) \)

\[ K_1 = 0 \quad \text{‘lowest possible value of clearance K} \]

\[ K_2 = \text{MAX} \quad \text{‘highest possible value of clearance K} \]

Repeat

\[ K = (K_1 + K_2)/2 \]

\[ C_c = fC_t(C_1, V_1, V_G, t, K, G) \quad \text{‘spvvUKM concentration equation} \]

If \( C_c > C_2 \) Then

\[ K_1 = K \]

Else

\[ K_2 = K \]

End If

Until Abs\((C_c - C_2)/C_2\) < 0.00001

\( fK = K \).

### Equalizing the schedule to a symmetric one

In column ‘Actual equalized’ of Table 2, dialysis frequency, dialysis time, weekly dialysis time, dialyser clearance, ultrafiltration volume, equilibrated \( K_t/V \) and weekly equilibrated \( K_t/V \) are averages of the 4-week averages associated with each modelling session.

Treatments are equalized by iterating the classic spvvUKM concentration equation sequentially over the average treatment time and average interval time until plateauing of \( C_0 \), using \( K_r, G \) and \( V_t \) from the modelling session and average \( K_d \) and average UF:

\[ C_0 = \text{ASV} \quad \text{‘arbitrary starting value} \]

Repeat

\[ C_p = C_0 \quad \text{‘previous C0} \]

\[ C_t = fC_t(C_0, V_t + \text{AvgUF}, -\text{AvgUF}, \text{Avgtd}, \text{AvgKd}, K_r, G) \quad \text{‘spvvUKM concentration equation, dialysis} \]

\[ C_0 = fC_t(C_t, V_t, \text{AvgUF}, \text{Avgti}, 0, K_r, G) \quad \text{‘spvvUKM concentration equation, interval} \]

Until Abs\((C_0 - C_p)/C_0\) < 0.00001

The equalization procedure modifies \( C_0 \) and \( C_t \) and facilitates calculations of TAC, PAC, EKR, stdKt/V and wtFSR. PAC is \( C_0 \) computed by equalizing. TAC is the cycle area_under_the_time/concentration_curve divided by the cycle duration, calculated from the equalized values according to Casino and Lopez [12]. RUR is calculated by multiplying the equalized interdialysis area_under_the_time/concentration_curve (used in TAC calculation) by \( K_r \). In a symmetric schedule, wtFSR is \( \text{fr}^*(\text{RUR} + \text{DUR})/(C_0^*V_0) \). (A.23)

The FSR concept enables assessment of the renal and dialysis components of urea elimination separately without dialysate collection.

### References


The impact of dialysis modality on skin hyperpigmentation in haemodialysis patients

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Abstract

Background. Skin hyperpigmentation in end-stage renal disease (ESRD) patients has been attributed to the accumulation of middle-molecular-weight (MMW) substances. Although an MMW mechanism suggests that hyperpigmentation may be improved by high-flux haemodialysis (HF-HD) and haemodiafiltration (HDF), this possibility has not been explored. In the present study, we investigated the impact of different dialysis modalities on skin colour in HD patients.

Methods. Eighty-two ESRD patients on HD were divided into low-flux HD (LF-HD), HF-HD and HDF groups. The melanin index (MI) and erythema index (EI) of the abdomen and the flexor side of the forearm (non-sun-exposed areas) and the forehead (sun-exposed area) were determined by using a narrow-band reflectance spectrophotometer at baseline and after 12 months.

Results. Even though absolute values of baseline and follow-up MI and EI of the three sites were comparable among the three groups, forehead MI and EI were significantly decreased after 12 months in the HDF group (P < 0.05). In addition, the change in forehead MI was significantly greater in the HDF than in the LF-HD group (−1.0 ± 2.4% versus 0.3 ± 1.6%, P < 0.05). Moreover, β2-microglobulin reduction rates were negatively correlated with both changes in forehead MI (P < 0.01) and EI (P < 0.05).

Conclusions. Skin colour of sun-exposed areas was significantly decreased in ESRD patients receiving HDF therapy, suggesting that enhanced removal of MMW substances by convection may prevent or reduce hyperpigmentation in HD patients.

Keywords: β2-microglobulin; haemodiafiltration; hyperpigmentation; low-flux haemodialysis; spectrophotometer
Equivalent continuous clearances EKR and stdK in incremental haemodialysis

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Abstract

Background. Many haemodialysis patients have residual renal function (RRF), which as such is insufficient to maintain satisfactory quality of life but reduces the demands of treatment and improves outcomes. In incremental dialysis, the dose is adjusted according to RRF, but how should it be done?

Methods. Urea generation rate (G) and distribution volume (V) were determined by the double-pool urea kinetic model in 225 haemodialysis sessions of 30 patients. The effect of different degrees of RRF on equivalent renal urea clearance (EKR), standard urea clearance (stdK) and urea concentrations and required treatment times to achieve the HEMO study standard dose equivalent EKR and stdK targets were studied by computer simulations.

Results. Ignoring RRF leads to underestimation of EKR, stdK, urea generation rate and protein equivalent of nitrogen appearance. Both EKR and stdK increase linearly with renal urea clearance (Kr). The HEMO standard dose equivalent EKRc is 13.8 mL/min/40 L and stdK/V 2.29 (9.1 mL/min/40 L). The required treatment time to achieve the HEMO study standard dose equivalent EKR and stdK targets were studied by computer simulations.

Conclusions. RRF is included in the original EKR and stdK concepts. EKR and stdK—determined by kinetic modelling—are promising measures of adequacy in incremental dialysis.

Keywords: computer simulation; EKR; incremental dialysis; residual renal function; stdK/V

Introduction

Patients having residual renal function (RRF) are not a marginal group in the haemodialysis population. In a Dutch study, only 25.5% were anuric at 12 months from beginning of dialysis and 58.1% at 36 months [1].

The renal excretion profile of uraemic solutes is different from that in dialysis. Diuresis helps in managing fluid overload with all of its consequences. RRF lowers predialysis concentrations and reduces the required dialysis dose, diminishing the concentration and volume fluctuations and inconvenience of the treatment.

In the CANUSA study [2], the differences in CAPD outcome were due to differences in RRF [3]. In haemodialysis, RRF correlates positively to outcome [1, 4–10], but early initiation of dialysis [11–23] and extreme attempts to preserve RRF [24–26] are not unequivocally beneficial.

Incremental dialysis [9, 27–32] is a concept of adjusting dialysis dose according to RRF. It was used in 16.5% of patients in the IDEAL study [20]. The most straightforward application of incremental dialysis is a treatment frequency < 3/wk used for example by Casino and Lopez [28].

RRF is in effect 168 h per week and may contribute significantly to the total solute removal but only minimally to session Kt/V. Renal function is the reference to which dialysis should be compared. Kt/V, where ‘K’ is defined as dialysate urea clearance, is a measure of a single session and does not permit comparison of different intermittent and continuous treatments and renal function.

Equivalent renal urea clearance (EKR, Casino and Lopez [28]) and standard urea clearance (stdK, Gotch [33, 34]) take the treatment frequency and RRF into account and were intended to be used in comparing dialysis doses in different schedules and to continuous dialysis and renal function. EKR and stdK are based on the definition of clearance (K):

\[ K = E/C. \]  

In steady state, the excretion rate equals the generation rate: \( E = G \), so

\[ K = G/C. \]

In EKR, C is the time-averaged concentration (TAC) and in stdK, the average pre-dialysis concentration (PAC). stdK
is normalized by dividing the value of equation (2) by the distribution volume \( V \) and expressed usually as weekly stdKt/\( V \). Dividing EKR by \( V \) yields a variable denoted here as stdEKR. \( G, V, TAC \) and PAC can be determined by kinetic modelling.

\[
EKR = \frac{G}{TAC},
\]

(3)

\[
\text{stdEKR} = \frac{\text{EKR}}{V}
\]

(4)

\[
\text{weekly stdEKR} = \frac{\text{EKR} \times t}{V}
\]

(5)

\[
\text{stdK} = \frac{G}{\text{PAC}},
\]

(6)

\[
\frac{\text{stdK}}{V} = \frac{\text{stdK}}{V} = \frac{G}{\text{PAC}/V},
\]

(7)

\[
\text{weekly stdKt}/V = \text{stdK} \times t/V.
\]

(8)

In the above equations, \( t \) is the length of a week. The most practical unit of stdEKR and stdK/\( V \) is /wk; weekly stdEKR and weekly stdKt/\( V \) are dimensionless. stdEKR is always higher than stdK/\( V \) because PAC > TAC. PAC has also been called peak average concentration, too [35]. In a symmetric schedule, the peak concentration is equal to the average pre-dialysis concentration. In continuous treatment, TAC, PAC and peak concentrations are equal.

Corrected EKR (EKRc) is stdEKR multiplied by a ‘normal’ distribution volume of 40 L with appropriate unit conversions [28]. The proposed unit of EKRc is mL/min/40 L. It is comparable to a clearance expressed in mL/min/1.73m\(^2\), but with a different scaling factor.

\[
\text{EKRc} (\text{mL/min}/40 \text{L}) = 3.97 \times \text{stdEKR} (/\text{wk}).
\]

(9)

The total fractional solute removal rate (tFURR) of urea is defined here as the amount removed by dialysis and the kidneys during a time unit divided by the average predialysis amount in the body:

\[
\text{tFURR} = \frac{E}{(\text{PAC} \times V)}.
\]

(10)

As seen from equations (7) and (10), in a symmetric schedule \( \text{tFURR} = \text{stdKt}/V \) if \( E = G \). The most practical unit is /wk. tFURR can be divided into renal fractional solute removal rate (rFURR) and dialysis fractional solute removal rate (dFURR) components without dialysate collection. The sum of the urea reduction ratios (URR) of 1 week’s sessions is a rough approximate of dFURR.

In the double-pool model, it is not obvious, which concentration should be used as TAC and PAC: whole body water, external pool water or plasma concentration. It is a convention, which has not yet been done. In fractional solute removal rate, the whole body water concentration without converting to plasma concentration must be used and tFURR \( \neq \text{stdKt}/V \).

The European Best Practice Guidelines recommend EKR [36] or Solute Removal Index [37] for measuring the dialysis dose in incremental dialysis. Casino and Lopez [28] have created a rough linear regression equation between EKRc and spKt/\( V \), used for example in ref. [38].

The Leypoldt’s weekly stdKt/\( V \) formula [39, 40], as expressed and recommended in the 2006 DOQI guidelines [41], ignores RRF leading to underestimation of weekly stdKt/\( V \) if the patient has remarkable RRF. Recently, an improved weekly stdKt/\( V \) equation taking ultrafiltration (UF) and RRF into account has been published [42] and used in the Frequent Hemodialysis Network (FHN) Trial [43].

The a priori assumption is that renal function is not worse than dialysis with equal urea clearance, but the problem is how to measure urea clearances in intermittent dialysis. This study compares EKR and stdK as dialysis dose measures when RRF is present.

### Materials and methods

A detailed description of the abbreviations, symbols, definitions and equations is presented in ref. [44].

The data have been gathered by a dialysis information system in the routine care of haemodialysis patients and analysed retrospectively. No randomization, control group or study protocol has been used.

#### Dialysis sessions

The analysis is based on 225 urea kinetic modelling sessions with measurable interdialysis urine volume (Table 1). All the patients were white Europeans.

#### Dialyser clearances

Dialyser clearances are based on 964 in vivo blood side clearance measurements. From these, the average blood water KoA is calculated for each dialyser model. The actual clearance of each session in this study is calculated from the actual blood and dialysate flow and the dialyser KoA. In the tables and figures, the ‘dialyser blood water clearance’ means the total (diffusive + convective) clearance used in calculations.

#### Double-pool UKM

Urea kinetic modelling with three blood samples and interdialysis urine collection was done routinely once per month as suggested in the European [37] and American [45] guidelines. Post-dialysis blood samples were taken at the termination of the session with the KDOQI slow-blood-flow

| Table 1. The current material |

<table>
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<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
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\( ^a \text{Renal fractional urea clearance (rFC) is renal urea clearance (Kr) divided by urea distribution volume (F) with appropriate unit conversions, sometimes called as ‘weekly renal Kt/V’. nPNA, normalized Protein equivalent of Nitrogen Appearance.} \)}
technique. Originally, classic single-pool variable volume urea kinetic model [46–48] was used, but the data permitted three blood sample double-pool calculations for this retrospective analysis. Plasma concentrations were converted to plasma water concentrations before calculations and back to plasma concentrations in the tables and figures, but renal and dialyser clearances are expressed as blood water clearances. Plasma clearances, used commonly in renal function measurements, are 7.5% and whole blood clearances, used as dialyser efficiency measures, 16.3% higher.

Runge-Kutta numeric integration procedure—modified from the Solute-Solver programme code (version 1.97; [49])—was used in the double-pool model. The constants were the same as in Solute-Solver: blood water clearance, 0.86 × blood volume; plasma water, 0.93 × plasma volume; internal compartment volume = 2/3 of total post-dialysis volume does not change during dialysis cycle; external compartment post-dialysis volume = 1/3 of total post-dialysis volume; intercompartment clearance (Kc, L/min) = 0.016 (L/min) × total postdialysis volume (L).

Renal blood water urea clearance (Kr) was determined by an extra iteration and double-pool eKt/V calculated as in Solute-Solver programme code.

For best comparability to earlier studies, external pool water concentrations converted to plasma concentrations were used in calculating stdEKR and stdK/V. The difference between whole body and external pool pre-dialysis concentrations is small. Fortunately, all TACs (external and internal pool and whole body water) are equal.

Time-averaged concentration (TAC) and average pre-dialysis concentration (PAC), needed in calculating EKR and stdK, were determined after equalizing the schedule to a symmetric one as described in ref. [44], using the double-pool model. Then, the analysis could be concerned with only one dialysis cycle. Time-averaged deviation (TAD) was calculated according to Lopot and Válek [50].

**HEMO-equivalent stdEKR and stdK/V**

In the HEMO study [51], standard dose group average eKt/V was 1.16. To get a safety margin for anuric patients, and due to the bias of the HEMO modification of the Daugirdas rate equation [52], stdEKR and stdK/V values corresponding to eKt/V 1.20 in a conventional 4-h dialysis given three times per week (3 × 4 h/wk) schedule were calculated from 619 modelling sessions (including the 225 of the proper study) as follows:

Single-pool urea distribution volume V1p was calculated for each session with the classic single-pool variable volume urea kinetic model, using Kr determined by the double-pool method. Kd was solved from the Daugirdas eKt/V rate equation:

\[
Kd = \frac{(eKt/V - a) \times V1p}{(td - b)},
\]

and 1.20 assigned to eKt/V, 240 min to td and Kd calculated. Dialysis treatment 3 × 4 h/wk was simulated with the double-pool model for each session with this Kd and Kr = 0. stdEKR and stdK/V were calculated. In the HEMO study and in this analysis, a = 0 and b = 24 min. No distinction is made between A – V and V – F blood access.

**Simulations**

The effect of RRF on measures of dialysis dose was studied by simulations based on the double-pool model with the patient-dependent values G and F from the modelling session and varying Kr and treatment parameters, assuming that dialysis has no effect on urea generation and renal urea clearance. The simulations give C0, Ct, TAC, eKt/V, EKR and stdK. With simple computing techniques, one may search for appropriate values of dialysis parameters to achieve a specific stdEKR or stdK/V target.

**Statistical methods**

Microsoft Excel 2002 software was used in calculating minimum and maximum values and standard deviations and in creating the graphs.

**Results**

The HEMO-equivalent values of stdEKR and stdK/V were 3.48 /wk and 2.29 /wk, respectively. The stdEKR value corresponds to EKRc 13.8 mL/min/40 L and stdK/V to 9.1 mL/min/40 L.

In the subsequent analysis, only the 225 sessions with measurable RRF were included. The mean renal urea clearance was 1.98 mL/min (0.03–6.32).

The data in Figures 1–6 and in Tables 2–3 are derived from simulations as described in the Materials and methods section. In all figures, the treatment frequency is 3 × /wk and dialyser blood water clearance 187 mL/min to achieve HEMO eKt/V 1.20 in 4 h. In the figures G, V and weekly UF are the average values of the study material (211 µmol/min, 32.6 L and 6.72 L/wk, Tables 1 and 2).

**Effect of Kr on measures of RRF and dialysis dose**

stdEKR increases in parallel with renal fractional clearance (rFC = Kr/V), stdK/V in parallel with rFURR (Figure 1).

![Fig. 1. Effect of Kr on measures of RRF and dialysis dose. Standard dialysis (3 × 4 h/wk, Kd 187 mL/min, HEMO eKt/V 1.20, UF 2.24 L).](http://ndt.oxfordjournals.org/)

![Fig. 2. Dependence of required weekly treatment time on RRF. Frequency 3 × /wk, Kd 187 mL/min.](http://ndt.oxfordjournals.org/)
Effect of RRF on the required treatment time

In Tables 2 and 3, the results are calculated individually from \( t_d \), \( K_d \), \( G \), \( V \) and \( U_F \) of each session and the means of these calculations are presented. The true double-pool \( eKt/V \) is shown. It is \(-0.05\) less than that calculated by the modified Daugirdas rate equation used in the HEMO study. Weekly \( eKt/V \) is \( eKt/V \) multiplied by treatment frequency individually for each session.

Ignoring RRF does not affect \( V \) or \( eKt/V \) but lowers considerably \( G \), normalized Protein equivalent of Nitrogen Appearance, stdEKR and stdK/V. RRF lowers concentrations and increases stdEKR and stdK/V (Columns 5 and 3 in Table 2). The treatment time had to be increased by 56 or 123 min per dialysis session to achieve the actual stdEKR or stdK/V, respectively, without RRF.

Because the actual stdEKR and stdK/V values (Table 2) were substantially greater than the HEMO-equivalent standard dose, simulations with lower dialysis intensity were done to confirm the effect of RRF on the required dialysis time. To achieve the HEMO standard dose equivalent targets, 64 or 123 min more treatment time per session were needed if the patients had had no RRF (Table 3). Of course, in most instances, it had been possible to increase \( K_d \) to achieve the target in a shorter time. In this material, the average renal urea clearance 1.98 mL/min corresponds to 0.25–0.36 units of \( eKt/V \).

The average renal urea removal rate is lower with higher dialysis intensity (Column 3 in Table 2 and Columns 3 and 5 in Table 3). Total urea removal rate equals generation rate.

In Figures 2–6, the dialysis dose is varied in an incremental fashion by adjusting the treatment time to achieve the HEMO standard dose equivalent stdEKR and stdK/V targets.

**Fig. 3.** Dependence of pre-dialysis urea concentration \( C_0 \) on RRF. Frequency 3 × /wk, \( K_d \) 187 mL/min, dose adjusted by treatment time.

**Fig. 4.** Dependence of TAC on RRF. Frequency 3 × /wk, \( K_d \) 187 mL/min, dose adjusted by treatment time.

**Fig. 5.** Dependence of TAD on RRF. Frequency 3 × /wk, \( K_d \) 187 mL/min, dose adjusted by treatment time.

**Fig. 6.** Renal fraction of total urea excretion. Frequency 3 × /wk, \( K_d \) 187 mL/min, dose adjusted by treatment time.
Table 2. Required treatment time to achieve the actual stdEKR and stdK/V without RRF

<table>
<thead>
<tr>
<th>Unit</th>
<th>3 Actual</th>
<th>4 Ignored</th>
<th>5 Without</th>
<th>6 stdEKR</th>
<th>7 stdK/V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-dialysis urea distribution volume L</td>
<td>32.6</td>
<td>32.8</td>
<td>32.6</td>
<td>32.6</td>
<td>32.6</td>
</tr>
<tr>
<td>Urea generation rate μmol/min</td>
<td>211</td>
<td>211</td>
<td>211</td>
<td>211</td>
<td>211</td>
</tr>
<tr>
<td>nPNA g/kg/day</td>
<td>1.15</td>
<td>1.15</td>
<td>1.15</td>
<td>1.15</td>
<td>1.15</td>
</tr>
<tr>
<td>Renal blood water urea clearance mL/min</td>
<td>1.98</td>
<td>0.0</td>
<td>1.98</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Dialysate blood water urea clearance mL/min</td>
<td>199</td>
<td>199</td>
<td>199</td>
<td>199</td>
<td>199</td>
</tr>
<tr>
<td>Dialysis frequency /wk</td>
<td>2.97</td>
<td>2.97</td>
<td>2.97</td>
<td>2.97</td>
<td>2.97</td>
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<tr>
<td>Dialysis time min</td>
<td>285</td>
<td>285</td>
<td>285</td>
<td>341</td>
<td>408</td>
</tr>
<tr>
<td>Weekly dialysis time h</td>
<td>14.1</td>
<td>14.1</td>
<td>14.1</td>
<td>16.8</td>
<td>19.9</td>
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<tr>
<td>Ultrafiltration volume L</td>
<td>2.26</td>
<td>2.26</td>
<td>2.26</td>
<td>2.26</td>
<td>2.26</td>
</tr>
<tr>
<td>Weekly ultrafiltration volume L</td>
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<td>6.72</td>
<td>6.72</td>
<td>6.72</td>
<td>6.72</td>
</tr>
<tr>
<td>Pre-dialysis plasma concentration mmol/L</td>
<td>20.8</td>
<td>20.9</td>
<td>24.4</td>
<td>22.2</td>
<td>20.8</td>
</tr>
<tr>
<td>Post-dialysis plasma concentration mmol/L</td>
<td>5.2</td>
<td>5.2</td>
<td>6.1</td>
<td>4.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Time-averaged plasma concentration mmol/L</td>
<td>13.5</td>
<td>13.4</td>
<td>15.6</td>
<td>13.5</td>
<td>12.1</td>
</tr>
<tr>
<td>Time-averaged deviation mmol/L</td>
<td>3.9</td>
<td>3.9</td>
<td>4.6</td>
<td>4.4</td>
<td>4.3</td>
</tr>
<tr>
<td>URR /session</td>
<td>0.75</td>
<td>0.75</td>
<td>0.75</td>
<td>0.80</td>
<td>0.83</td>
</tr>
<tr>
<td>Double-pool eKt/V /wk</td>
<td>4.50</td>
<td>4.48</td>
<td>4.50</td>
<td>5.41</td>
<td>6.46</td>
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<tr>
<td>Weekly double-pool eKt/V /session</td>
<td>1.51</td>
<td>1.51</td>
<td>1.52</td>
<td>1.83</td>
<td>2.19</td>
</tr>
<tr>
<td>stdEKR /wk</td>
<td>4.73</td>
<td>4.14</td>
<td>4.16</td>
<td>4.73</td>
<td>5.27</td>
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<tr>
<td>stdK/V /wk</td>
<td>2.95</td>
<td>2.54</td>
<td>2.55</td>
<td>2.76</td>
<td>2.95</td>
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<tr>
<td>Total fractional urea removal rate /wk</td>
<td>2.76</td>
<td>2.38</td>
<td>2.38</td>
<td>2.59</td>
<td>2.76</td>
</tr>
<tr>
<td>Renal urea removal rate μmol/min</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dialysate urea removal rate μmol/min</td>
<td>181</td>
<td>181</td>
<td>211</td>
<td>211</td>
<td>211</td>
</tr>
<tr>
<td>Total urea removal rate μmol/min</td>
<td>211</td>
<td>211</td>
<td>211</td>
<td>211</td>
<td>211</td>
</tr>
<tr>
<td>Renal fraction of urea removal %</td>
<td>13.6</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*The mean actual values of the material are shown in Column 3. Column 4 shows the values calculated by ignoring RRF. Column 5 shows the values if the patients really had had no RRF and they had been dialysed as they actually were. Columns 6 and 7 show the treatment times required to achieve the actual stdEKR and stdK/V with equal dialyser clearances but without RRF. The most important values are in bold. nPNA, normalized Protein equivalent of Nitrogen Appearance.

Table 3. Required treatment time to achieve the HEMO-equivalent stdEKR and stdK/V without RRF

<table>
<thead>
<tr>
<th>Unit</th>
<th>3 HEMO stdEKR</th>
<th>4 HEMO stdK/V</th>
<th>5 HEMO stdEKR</th>
<th>6 HEMO stdK/V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal blood water urea clearance mL/min</td>
<td>1.98</td>
<td>0.0</td>
<td>1.98</td>
<td>0.0</td>
</tr>
<tr>
<td>Dialysate blood water urea clearance mL/min</td>
<td>146</td>
<td>146</td>
<td>124</td>
<td>124</td>
</tr>
<tr>
<td>Dialysis frequency /wk</td>
<td>3.00</td>
<td>3.00</td>
<td>3.00</td>
<td>3.00</td>
</tr>
<tr>
<td>Dialysis time min</td>
<td>240</td>
<td>304</td>
<td>240</td>
<td>363</td>
</tr>
<tr>
<td>Weekly dialysis time h</td>
<td>12.0</td>
<td>15.2</td>
<td>12.0</td>
<td>18.2</td>
</tr>
<tr>
<td>Ultrafiltration volume L</td>
<td>2.24</td>
<td>2.24</td>
<td>2.24</td>
<td>2.24</td>
</tr>
<tr>
<td>Weekly ultrafiltration volume L</td>
<td>24.7</td>
<td>26.5</td>
<td>26.7</td>
<td>26.7</td>
</tr>
<tr>
<td>Pre-dialysis plasma concentration mmol/L</td>
<td>10.1</td>
<td>8.9</td>
<td>12.7</td>
<td>9.6</td>
</tr>
<tr>
<td>Post-dialysis plasma concentration mmol/L</td>
<td>18.1</td>
<td>18.1</td>
<td>20.4</td>
<td>18.5</td>
</tr>
<tr>
<td>Time-averaged plasma concentration mmol/L</td>
<td>3.7</td>
<td>4.4</td>
<td>3.5</td>
<td>4.3</td>
</tr>
<tr>
<td>Time-averaged deviation mmol/L</td>
<td>0.59</td>
<td>0.66</td>
<td>0.53</td>
<td>0.64</td>
</tr>
<tr>
<td>Urea reduction ratio /session</td>
<td>0.90</td>
<td>1.14</td>
<td>0.75</td>
<td>1.11</td>
</tr>
<tr>
<td>Double-pool eKt/V /wk</td>
<td>2.69</td>
<td>3.42</td>
<td>2.26</td>
<td>3.33</td>
</tr>
<tr>
<td>Weekly double-pool eKt/V /session</td>
<td>3.48</td>
<td>3.48</td>
<td>3.11</td>
<td>3.42</td>
</tr>
<tr>
<td>stdEKR /wk</td>
<td>2.47</td>
<td>2.30</td>
<td>2.29</td>
<td>2.29</td>
</tr>
<tr>
<td>stdK/V /wk</td>
<td>2.30</td>
<td>2.15</td>
<td>2.14</td>
<td>2.14</td>
</tr>
<tr>
<td>Total fractional urea removal rate /wk</td>
<td>40</td>
<td>0</td>
<td>47</td>
<td>0</td>
</tr>
<tr>
<td>Renal urea removal rate μmol/min</td>
<td>171</td>
<td>211</td>
<td>164</td>
<td>211</td>
</tr>
<tr>
<td>Dialysate urea removal rate μmol/min</td>
<td>211</td>
<td>211</td>
<td>211</td>
<td>211</td>
</tr>
<tr>
<td>Renal fraction of urea removal %</td>
<td>18.1</td>
<td>0.0</td>
<td>21.1</td>
<td>0.0</td>
</tr>
</tbody>
</table>
In incremental dialysis, with $Kr = 4$ mL/min, the target stdEK/$V$ is achieved in one half of the time required without RRF. Somewhat longer treatment time is required to achieve the stdEK target. In both cases, the required treatment time has an almost linear inverse relationship to $Kr$ (Figure 2).

**Effect of RRF on urea concentrations**

With increasing $Kr$, dialysing to a constant stdEK results in decreasing pre-dialysis concentration $C0$ (Figure 3). Dialysing to a constant stdEK/$V$ results in increasing TAC with increasing $Kr$ (Figure 4). TAD reflects the fluctuation of concentrations. It decreases when $Kr$ increases with constant stdEK or stdEK/$V$ (Figure 5).

**Contribution of RRF to urea excretion**

Figure 6 presents the fraction (%) of total urea elimination excreted by the kidneys. With $Kr = 4$ mL/min, using the HEMO-equivalent stdEK/$V$ as target, almost one half of the total urea excretion takes place through the kidneys. Dialysis and the kidneys interfere with each other and compete for solutes.

**Discussion**

The current analysis is based on the urea kinetic model. One of the parameters in the model is the renal urea clearance ($Kr$), which is lower than the glomerular filtration rate. European guidelines [36, 37] suggest glomerular filtration rate. The average kinetic urea distribution volume $32.6$ L is $17.5\%$ lower than the anthropometric total body water estimate, only $40\%$ of body mass, but the patients were on the average overweight [body mass index (BMI) $28.8$ kg/m$^2$]. Daugirdas et al. [53] have observed volume differences of equal magnitude in the HEMO material, where BMI was lower ($25.7$ kg/m$^2$) and kinetically determined volume was $43–44\%$ of body weight.

The HEMO standard dose equivalent stdEK and stdEK/$V$ values calculated by the double-pool model ($3.48$ /wk and $2.29$ /wk, respectively) are higher than those reported earlier using the single-pool model with equilibrated post-dialysis concentrations ($3.34$ /wk and $2.23$ /wk) [44].

According to urea kinetics, RRF may replace several hours of weekly dialysis treatment time in a conventional three times per week schedule, if HEMO-equivalent stdEK and stdEK/$V$ values are used as targets. Each mL/min of renal urea clearance corresponds to about $30–60$ min of session time in a standard $3 \times /wk$ schedule with HEMO-equivalent intensity. Each weekly dialysis hour replaces $0.7$ mL/min of missing renal urea clearance. Other uraemic solutes may behave differently.

Originally Casino and Lopez [28] held EKRc $11$ mL/min/40 L (stdEK 2.77 /wk) and Gotch [29, 33] stdEK/$V$ 2.0 /wk (7.8 mL/min/40 L) as an adequate dose. Later higher targets were proposed. The HEMO standard dose equivalent stdEK/$V$ 2.29 /wk is equal to $9.1$ mL/min/40 L corresponding to an acceptable urea clearance without dialysis. Patients with renal urea clearance of $13.8$ mL/min/40 L (stdEK 3.48 /wk) may have months or even years of satisfactory life left before they begin to benefit from dialysis. Empirically, the optimal stdEK and stdEK/$V$ values are in conventional haemodialysis considerably higher than in CAPD (HEMO [51], ADEMEX [54]). This discrepancy may have several explanations:

1. the lower TAC in intermittent treatment compensates the drawbacks of concentration and volume fluctuations;
2. the relationship between toxicity and concentration is not linear (the peak concentration hypothesis [55]) and
3. the excretion profile of uraemic solutes is different in renal function and CAPD and haemodialysis, i.e. urea is not a good marker solute.

These and other possible factors have been managed in stdK by using a different denominator in the clearance equation (2), making stdK therapeutically ‘more equivalent’ than EKR, which is a ‘mathematically correct’ average clearance.

RRF is inherently included in stdEK and stdEK/$V$ calculated by the urea kinetic model. RRF lowers especially the pre-dialysis concentrations (denominator in equation (6)) and is included in the UKM formula of $G$ (numerator in equations (3) and (6); Table 2). Using stdEK/$V$ as the dosing guide in incremental dialysis results in shorter treatment times, lower $Kt/V$, lower TAD and higher urea concentrations than using EKR (Figures 2–4 and Table 3).

When the dialysis intensity increases, the renal excretion of urea decreases (Table 3, Columns 5 and 3) and when RRF increases, elimination by dialysis decreases (Figure 6). In intermittent dialysis, the average $RFU$ is lower than the renal fractional urea clearance ($rFC = Kr/V$, /wk) (Figure 1, [42]). $dFU$ and $RFU$ depend on each other because both RRF and dialysis affect pre-dialysis concentrations (the denominator) and compete for excretion (the numerator). Total stdK/$V$ cannot be calculated by adding $rFC$ to stdK/$V$ calculated with the Leypoldt formula [41] (Figure 1).

Residual renal urea clearance $4$ mL/min/40 L may be the threshold above which concrete short-term benefits may be obtained from incremental dialysis, in the form of a twice per week treatment schedule. It is not far below the threshold above which dialysis is usually not useful. In only $5.5\%$ of all UKM sessions in one centre during 3 years, $Kr$ was $>4$ mL/min (Vartia A, unpublished). The HEMO standard dose equivalent EKR was not achieved in a $2 \times /wk$ schedule with an average session $Kt/V$ 1.86 [56]. But many patients appreciate shortening of the session time, too.

In conclusion, if we use systematically stdEK and stdEK/$V$ as adequacy measures, RRF and treatment frequency may be automatically be taken into account. Urea kinetic modelling and a computer are needed in creating the prescriptions. There is in the literature very scanty information about the correlation of stdEK or stdEK/$V$ to outcome [38, 43] and no studies comparing outcomes in incremental and full-dose approaches. In the FHN trial [43], the average stdK/$V$ was considerably higher in the frequent haemodialysis group than in the conventional treatment group (3.60 versus 2.57 /wk), but it is difficult to estimate whether the

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better outcome was due to the lower concentrations (higher ‘dose’), smaller fluctuation of concentrations and volume, longer weekly treatment time or other factors. Has there been any difference in outcomes, if stdK/V had been equal in both groups? There is no empiric proof showing that equal stdEEK or stdK/V results in equal outcomes in different schedules and with different degrees of RRF, i.e. that they are really universal measures of adequacy.

There is also no data showing which is better as the dosing guide (with different target values), stdEEK or stdK/V, i.e. which correlates more tightly to outcome. stdK/V is more sensitive to RRF and treatment frequency [44, 57] than stdEEK. It is based on the hypothesis that pre-dialysis and peak urea concentrations are important. Using stdK/V as target may lead to high time-averaged urea concentrations and short treatment times, which may hamper water, middle molecule and protein-bound toxin removal. If we apply incremental dialysis, it is important to measure RRF frequently because it may deteriorate unexpectedly.

Conflict of interest statement. None declared.

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Cinacalcet treatment and serum FGF23 levels in haemodialysis patients with secondary hyperparathyroidism

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Abstract
Background. Elevated fibroblast growth factor 23 (FGF23) is associated with adverse clinical outcomes and development of secondary hyperparathyroidism (SHPT) refractory to active vitamin D. Cinacalcet hydrochloride is effective in treating SHPT, but little is known as to whether treatment with cinacalcet alters these levels and whether pretreatment FGF23 levels predict response to this therapy.

Methods. We measured serum full-length FGF23 levels in 55 haemodialysis patients, who participated and completed the 52-week, multicentre, open-label single-arm trial that examined the effectiveness of cinacalcet for treating SHPT.

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Clinical Study

Urea Concentration and Haemodialysis Dose

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Background. Dialysis dose is commonly defined as a clearance scaled to some measure of body size, but the toxicity of uremic solutes is probably associated more to their concentrations than to their clearance. Methods. 619 dialysis sessions of 35 patients were modified by computer simulations targeting a constant urea clearance or a constant urea concentration. Results. Urea generation rate G varied widely in dialysis patients, rather independently of body size. Dialysing to eKt/V 1.2 in an unselected patient population resulted in great variations in time-averaged concentration (TAC) and average predialysis concentration (PAC) of urea (5.9–40.2 and 8.6–55.8 mmol/L, resp.). Dialysing to equal clearance targets scaled to urea distribution volume resulted in higher concentrations in women. Dialysing to the mean HEMO-equivalent TAC or PAC (17.7 and 25.4 mmol/L) required extremely short or long treatment times in about half of the sessions. Conclusions. The relation between G and V varies greatly and seems to be different in women and men. Dialysing to a constant urea concentration may result in unexpected concentrations of other uremic toxins and is not recommended, but high concentrations may justify increasing the dose despite adequate eKt/V, std EKR, or std K/V.

1. Introduction

The morbidity caused by uremic toxins is probably associated more to their concentrations than to their clearances. Urea is a marker of dialysable uremic toxins, which, however, are not produced and eliminated in a stoichiometric proportion to urea [1].

Big patients are supposed to need more dialysis than small: higher clearance (K) and/or more time (t). Equation

\[ \frac{K \cdot t}{V} = \ln \left( \frac{C_0}{C_t} \right), \]

where V is urea distribution volume, ln natural logarithm, \( C_0 \) predialysis, and \( C_t \) postdialysis concentration, describes the simplest urea kinetic model. It seems just what we want: a measure of dialysis dose automatically scaled to body size (represented by V) and calculated from only two simple variables. It is the basis of the popular second generation Daugirdas equation, which includes empiric correction factors for ultrafiltration and urea generation individually. It requires iterative calculation and correct value of actual dialyser clearance (\( K_d \)) to give correct urea generation rate G and distribution volume V. The double-pool model is even more accurate.

V is a kinetic parameter required in modelling and simulating dialysis. But is V-scaled clearance the best variable to correlate dialysis dose to outcome? Small patients have worse outcome in haemodialysis than big if \( Kt/V \) is used as the dosing guideline [6–8]. An observational study based on a large material [9] and the prospective randomized HEMO trial [10] suggested that women—but not men—may benefit from higher urea reduction ratio (URR) or equilibrated \( Kt/V \) (e\( Kt/V \)).

It has been stated that dialysis intensity should be dimensioned to the metabolic needs instead of the size of the body [11]. Protein catabolic rate (PCR) or protein equivalent of nitrogen appearance (PNA) is a measure of protein metabolism [12]. Urea is a product of protein catabolism like probably many uremic toxins. Urea generation rate G is used in the present report as the descriptor of protein metabolism.

In the NCDS study [13, 14], higher time-averaged concentration (TAC) of urea was associated with worse outcome. Using a constant urea concentration as the target—like in
the NCDS—may lead to a vicious cycle: the underdialysed patient loses his or her appetite → dietary protein intake (DPI), PCR, G and concentrations decrease → the dialysis dose will be diminished further. This can be avoided by using clearance instead of concentration as the dosing guide as presented by Gotch and Sargent [15] after the NCDS. Since then almost all studies and guidelines correlating outcome to dialysis dose have been based on V-scaled clearance (Kt/V) or fractional removal (URR). Only few defend concentration-based dosing [16–18].

Equivalent renal urea clearance (EKR, Casino and Lopez [19]) and std K (Gotch [20]) take the treatment frequency and residual renal function (RRF) into account and were intended to be used in comparing dialysis doses in different schedules and to continuous dialysis and renal function. EKR and std K are based on the definition of clearance (K):

\[ K = \frac{E}{C}. \] (2)

In steady state, the excretion rate equals the generation rate: \( E = G \), so

\[ K = \frac{G}{C}. \] (3)

In EKR, \( C \) is the time-averaged concentration (TAC), in std K, the average predialysis concentration (peak average concentration, PAC). std K is scaled to body size by dividing by V and expressed as std K/V. Dividing EKR by V yields a variable called here as std EKR. G, V, TAC, and PAC can be determined by kinetic modelling.

\[ \text{EKR} = \frac{G}{\text{TAC}}, \] (4)

\[ \text{std EKR} = \frac{\text{EKR}}{V} = \frac{G}{\text{TAC} \times V}, \] (5)

\[ \text{std K} = \frac{G}{\text{PAC}}, \] (6)

\[ \text{std K/V} = \frac{\text{std K}}{V} = \frac{G}{\text{PAC} \times V}. \] (7)

The most practical unit of std EKR and std K/V is /wk. In std EKR, the term “std” means dividing EKR by V in (5); in std K/V it means dividing G by PAC in (6).

With a constant clearance, \( C \) is linearly proportional to \( G \). With a constant std EKR or std K/V, TAC and PAC are linearly proportional to \( G/V \), a patient-specific variable not dependent on dialysis.

Using a clearance scaled to \( G \) as the target means dialysing to a constant urea concentration:

\[ \text{generation-scaled clearance} \quad \frac{K}{G} = \frac{1}{C}. \] (8)

The required clearance \( K \) is determined by \( G \) and the desired concentration (3); \( V \) is needed as a kinetic parameter—not as a scaling factor—for creating the prescription \( (K_d \text{ and } t_d) \) in an intermittent schedule.

The purpose of this study is to pay attention to the wide variation of concentrations when dialysing to a constant \( eKt/V \), std EKR, or std K/V and to show with computer simulations what happens if we try to dialyse to a constant concentration.

2. Subjects and Methods

2.1. Patients and Dialysis Sessions. 619 consecutive urea kinetic modelling sessions of 35 unslected haemodialysis patients were included (Table 1).

The dialysis dose prescription was not unambiguously defined. The patient’s clinical condition, fluid removal requirement, and both \( eKt/V \) and single-pool std K/V, and predialysis urea concentration from the previous kinetic modelling sessions were taken into account. There were some long nightly, but not daily sessions. Dialysis time varied between 240 and 494 min, frequency between 1.75 and 4.45/wk, and \( K_d \) between 137 and 263 mL/min. The patients were encouraged by a dietician to use a diet containing protein 1.2 g/day/kg of normal weight (V/0.58). Protein intake was not actually measured.

2.2. Urea Kinetic Modelling. In the routine care of haemodialysis patients, a single-pool variable volume urea kinetic modelling with three blood samples and interdialysis urine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unit</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
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<tr>
<td>Females</td>
<td>%</td>
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<td>Age</td>
<td>years</td>
<td>64.7</td>
<td>16.2</td>
<td>16.0</td>
<td>91.6</td>
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<tr>
<td>Height</td>
<td>cm</td>
<td>169</td>
<td>10</td>
<td>150</td>
<td>187</td>
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<tr>
<td>Postdialysis weight</td>
<td>kg</td>
<td>78.9</td>
<td>18.7</td>
<td>43.3</td>
<td>134.5</td>
</tr>
<tr>
<td>Body mass index</td>
<td>kg/m²</td>
<td>27.5</td>
<td>5.6</td>
<td>16.0</td>
<td>44.7</td>
</tr>
<tr>
<td>Total body water (Watson)</td>
<td>L</td>
<td>39.5</td>
<td>8.1</td>
<td>24.6</td>
<td>61.0</td>
</tr>
<tr>
<td>Postdialysis urea distribution volume</td>
<td>L</td>
<td>33.0</td>
<td>7.1</td>
<td>14.4</td>
<td>57.5</td>
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<tr>
<td>Urea generation rate</td>
<td>μmol/min</td>
<td>198</td>
<td>71</td>
<td>66</td>
<td>494</td>
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<tr>
<td>Normalised protein catabolic rate</td>
<td>g/kg/day</td>
<td>1.09</td>
<td>0.27</td>
<td>0.48</td>
<td>2.34</td>
</tr>
<tr>
<td>Diuresis</td>
<td>L/day</td>
<td>0.25</td>
<td>0.43</td>
<td>0.00</td>
<td>2.30</td>
</tr>
<tr>
<td>Renal urea clearance</td>
<td>mL/min</td>
<td>0.77</td>
<td>1.31</td>
<td>0.00</td>
<td>6.79</td>
</tr>
</tbody>
</table>

Note: the most important values are in bold.
collection was done once per month. Afterwards double-pool calculations were done by methods modified from the Solute-Solver programme [21] as described earlier [22]. Plasma concentrations were converted to plasma water concentrations before calculations and back to plasma concentrations in the results. Time-averaged concentration (TAC) and average predialysis concentration (PAC), needed in calculating EKR and std K, were determined after equalizing the schedule to a symmetric one as described earlier [23], using the double-pool model. TAC and PAC are expressed as external pool water concentrations converted to plasma concentrations. All clearances are expressed as plasma values. V is the sum of the external (V e) and internal (V i) pools at the end of the dialysis session.

2.3. Simulations. The dialysis sessions were modified by computer simulations with the double-pool UKM. After the patient-specific parameters V, G, renal urea clearance (K r), and fluid removal requirement have been determined by UKM, K d and t d can be varied in dialysis simulations and concentrations, eKt/V, std EKR and std K/V calculated. It is also possible to compute the required K d or t d to achieve a desired concentration or std EKR or std K/V.

3. Results

3.1. Urea Generation Rate G and Distribution Volume V. G and V are true—not simulated—patient-specific variables independent of dialysis. The range of G in this material is 66–494 μmol/min (variation 7.5-fold, Table 1) and G/V (G scaled to V) 2.0–14.3 μmol/min/L (7.1-fold). The correlation between G and V is weak (Figure 1).

3.2. Determining HEMO-Equivalent std EKR, std K/V, TAC, and PAC with K r 0 mL/min. In the HEMO study [24], the mean eKt/V in the standard dose group was 1.16 ± 0.08/session. In the present study, the material was "dialysed" (simulated) 3 × 4 h/wk without residual renal function (RRF) to eKt/V 1.2 by adjusting K d as described in detail earlier [22]. The mean K d was 189 mL/min. The mean HEMO standard dose equivalent std EKR was 3.44/wk and std K/V 2.40/wk with little variation. Instead, TAC and PAC varied 6.8–6.5-fold (Table 2). The mean HEMO-equivalent TAC was 17.7 mmol/L (equal to the lower target in the NCDS) and PAC 25.4 mmol/L.

<table>
<thead>
<tr>
<th>Label</th>
<th>Variable</th>
<th>Unit</th>
<th>Mean</th>
<th>SD</th>
<th>Min</th>
<th>Max</th>
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</thead>
<tbody>
<tr>
<td>K d</td>
<td>Dialyser urea clearance</td>
<td>mL/min</td>
<td>189</td>
<td>37</td>
<td>93</td>
<td>315</td>
</tr>
<tr>
<td>f_d</td>
<td>Dialysis frequency</td>
<td>/wk</td>
<td>3.00</td>
<td>0.00</td>
<td>3.00</td>
<td>3.00</td>
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<tr>
<td>t_d</td>
<td>Dialysis time</td>
<td>min</td>
<td>240</td>
<td>0</td>
<td>240</td>
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<td>t_dw</td>
<td>Weekly dialysis time</td>
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<td>12.0</td>
<td>0.0</td>
<td>12.0</td>
<td>12.0</td>
</tr>
<tr>
<td>wUF</td>
<td>Weekly ultrafiltration volume</td>
<td>L</td>
<td>8.33</td>
<td>2.97</td>
<td>0.55</td>
<td>18.66</td>
</tr>
<tr>
<td>TAC</td>
<td>Time-averaged urea concentration</td>
<td>mmol/L</td>
<td>17.7</td>
<td>5.2</td>
<td>5.9</td>
<td>40.2</td>
</tr>
<tr>
<td>PAC</td>
<td>Average predialysis urea concentration</td>
<td>mmol/L</td>
<td>25.4</td>
<td>7.3</td>
<td>8.6</td>
<td>55.8</td>
</tr>
<tr>
<td>std EKR</td>
<td>std EKR</td>
<td>/wk</td>
<td>3.44</td>
<td>0.08</td>
<td>3.23</td>
<td>3.92</td>
</tr>
<tr>
<td>std K/V</td>
<td>std K/V</td>
<td>/wk</td>
<td>2.40</td>
<td>0.07</td>
<td>2.21</td>
<td>2.83</td>
</tr>
</tbody>
</table>

Note: the most important values are in bold.

Figure 1: G versus V.

3.3. Dialysing to HEMO-Equivalent std EKR and std K/V with Actual K r. The material was dialysed (simulated) 3 × 4 h/wk with actual K r to the mean HEMO-equivalent std EKR and std K/V targets 3.44/wk and 2.40/wk by adjusting K d. With std EKR target, TAC had a trend to be higher in women with lower V. With all levels of G, TAC was higher in women. The correlation between TAC and V is weak, between TAC and G quite strong (Figure 2). With std K/V target, the relations of PAC to V and G are similar (not shown). The mean TAC and PAC were higher in women than in men when dialysed to a constant eKt/V, std EKR, or std K/V (Table 3).

3.4. Dialysing to HEMO-Equivalent TAC and PAC with Actual K r. The material was dialysed (simulated) three times per week with actual K r and dialysis clearance K d 189 mL/min to the mean HEMO-equivalent TAC and PAC by adjusting t_d.
The required $t_d$ varied widely and had only a weak correlation to $V$, stronger to $G$ (Figure 3); $t_d$ is determined mainly by $G$.

To avoid the vicious cycle of underdialysis in patients with low $G$, 164 sessions (26%, TAC target) and 205 sessions (33%, PAC target), where the simulation produced std EKR or std $K/V$ below that corresponding to $eKt/V$ 0.9, were dialysed to $eKt/V$ 0.9 with $K_d$ 189 mL/min (Group 1 in Tables 4 and 5). This resulted in TAC and PAC lower than the mean HEMO-equivalent values. The shortest treatment time was 48 min with std EKR 2.74/wk and 25 min with
Table 3: Mean TAC and PAC of urea in females and males dialysed to HEMO-equivalent V-scaled targets.

<table>
<thead>
<tr>
<th>Dialysed to</th>
<th>Sex</th>
<th>TAC mmol/L</th>
<th>PAC mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>eKt/V 1.2 (without RRF)</td>
<td>Females</td>
<td>18.7</td>
<td>26.8</td>
</tr>
<tr>
<td></td>
<td>Males</td>
<td>17.2</td>
<td>24.6</td>
</tr>
<tr>
<td>Std EKR 3.44/wk</td>
<td>Females</td>
<td>18.9</td>
<td>26.3</td>
</tr>
<tr>
<td></td>
<td>Males</td>
<td>17.0</td>
<td>23.8</td>
</tr>
<tr>
<td>Std K/V 2.40/wk</td>
<td>Females</td>
<td>19.8</td>
<td>27.1</td>
</tr>
<tr>
<td></td>
<td>Males</td>
<td>17.8</td>
<td>24.4</td>
</tr>
</tbody>
</table>

std K/V 2.05/wk. For sufficient fluid and toxin removal, longer treatment times may be required.

To avoid extremely long treatment times, 109 (18%) and 142 (23%) (TAC and PAC targets) sessions with simulated $t_d > 5$ h were changed to a symmetric 5 */wk schedule (Group 3 in Tables 4 and 5). In these groups the mean $G$ was over two times that of groups 1. Of course, in many cases it had been possible to increase $K_d$ instead of frequency.

With TAC target, 346 sessions (56%), and with PAC target, only 272 sessions (44%) achieved the target in the 3 */wk schedule with reasonable session time (Group 2 in Tables 4 and 5). Figure 4 and the last column (All) of Tables 4 and 5 describe the whole material dialysed with the dual targets and schedule modifications.

4. Discussion

The present analysis is based on the double-pool variable volume urea kinetic model. The mean kinetic urea distribution volume 33.0 L is 16.5% lower than the mean anthropometric total body water estimate, only 42% of mean body weight (females 40.3, males 43.9), but the patients were overweight (mean body mass index 27.5 kg/m$^2$; females 27.0, males 27.9). Daugirdas et al. [25] have observed volume differences of equal magnitude in the HEMO material, where BMI was lower (25.7 kg/m$^2$) and kinetically determined volume was 43-44% of body weight.

The correlation between $G$ and $V$ is weak although they are derived by UKM from the same input variables, permitting mathematical coupling [26, 27]. $G$ is quite independent of body size. The relation between $G$ and $V$ in women is different from that in men. Dialysing to the same eKt/V, std EKR, or std K/V results in higher concentrations in women (Table 3).

nPCR and $G$ depend on dietary protein intake (DPI). Low-protein diet may have beneficial effects in uraemia, but rather high protein intake is recommended for dialysis patients. On the average, in this study females seemed to follow the recommendations better than males: nPCR 1.15 versus 1.05 g/day/kg of normal weight, but the variation in nPCR was great (Table 1). This material is too small to conclude whether the difference in nDPI and nPCR between women and men is a universal phenomenon.

Patient-specific variables $G$ and $G/V$ vary over 7-fold in this unselected material (66–494 μmol/min and 2.0–14.3 μmol/min/L, resp.). Dialysing 3 * 4 h/wk to eKt/V 1.2 by adjusting dialyser clearance results in a 6.8-fold variation in TAC and 6.5-fold variation in PAC. Dialysing to a constant TAC (17.7 mmol/L, equal to the NCDS lower target and mean HEMO standard dose equivalent TAC) means a 7-fold variation in std EKR (1.15–8.12/wk).
It is difficult to believe that the huge differences in urea concentrations resulting from \( V \)-scaled dosing (Table 2) are without significance. The means are probably not the whole truth. The variation is not mere simulation: the mean of the actual predialysis urea concentrations after the longest interval was 23.8, SD 6.5, minimum 7.1, maximum 43.5 mmol/L, and range 6.1-fold.

Urea concentrations reflect the balance between \( G \) and \( K \). In contrast to the NCDS, in some studies—where DPI, PCR, and \( Kt/V \) were not fully controlled—higher PAC is associated to better outcome [28]. In registry studies the correlation of predialysis urea concentration to mortality is J- or U-shaped [29, 30]. High mortality associated to low urea concentration [31] may be due to malnutrition and wasting caused by comorbidity. High mortality associated to high concentration is due to underdialysis. In cachectic moribund patients, it is easy to achieve low concentrations.

How should we dialyse patients with unusually low or high dietary protein intake and urea generation rate? Patients with high \( G/V \) have high concentrations when dialysed to a constant \( eKt/V \), std EKR, or std \( K/V \). Would they benefit from more intensive treatment? Gotch and Sargent recommend [15, 32] sp \( Kt/V \) 0.9 for patients with low \( G \) and higher for patients with high \( G \), about equal numeric value to nPCR in the 3 */wk schedule. This strategy has seldom been used in outcome studies. In the present study, \( eKt/V \) 0.9 was used as the target in sessions with low \( G \) (Group 1 in Tables 4 and 5; 26–33% of all sessions). Actually, the simulated dialysis prescription was determined by setting a lower limit for \( eKt/V \), std EKR, or std \( K/V \) and an upper

<table>
<thead>
<tr>
<th>Label</th>
<th>Variable</th>
<th>Unit</th>
<th>Group 1 Mean</th>
<th>Group 1 SD</th>
<th>Group 2 Mean</th>
<th>Group 2 SD</th>
<th>Group 3 Mean</th>
<th>Group 3 SD</th>
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<th>All SD</th>
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<tr>
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<td>272</td>
<td>142</td>
<td>619</td>
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<td></td>
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</tr>
<tr>
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<td>L</td>
<td>34.7</td>
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<td>30.1</td>
<td>6.1</td>
<td>36.1</td>
<td>7.9</td>
<td>33.0</td>
<td>7.1</td>
</tr>
<tr>
<td>( G )</td>
<td>Urea generation rate</td>
<td>( \mu )mol/min</td>
<td>143</td>
<td>34</td>
<td>191</td>
<td>40</td>
<td>290</td>
<td>66</td>
<td>198</td>
<td>71</td>
</tr>
<tr>
<td>nPCR</td>
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<td>g/kg/day</td>
<td>0.80</td>
<td>0.10</td>
<td>1.14</td>
<td>0.13</td>
<td>1.41</td>
<td>0.21</td>
<td>1.09</td>
<td>0.27</td>
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<td>1.06</td>
<td>1.01</td>
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<td>0.66</td>
<td>1.33</td>
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<td>1.31</td>
</tr>
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<td>mL/min</td>
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<td>0</td>
<td>189</td>
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<td>Dialysis frequency</td>
<td>/wk</td>
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<td>0.00</td>
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<td>0.00</td>
<td>3.46</td>
<td>0.84</td>
</tr>
<tr>
<td>( t_d )</td>
<td>Dialysis time</td>
<td>min</td>
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<td>177</td>
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<td>192</td>
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<tr>
<td>( t_{del} )</td>
<td>Weekly dialysis time</td>
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<td>9.0</td>
<td>2.2</td>
<td>10.4</td>
<td>2.5</td>
<td>14.7</td>
<td>3.5</td>
<td>11.0</td>
<td>3.4</td>
</tr>
<tr>
<td>wUF</td>
<td>Weekly ultrafiltration volume</td>
<td>L</td>
<td>7.99</td>
<td>2.87</td>
<td>7.82</td>
<td>2.86</td>
<td>9.80</td>
<td>2.83</td>
<td>8.33</td>
<td>2.97</td>
</tr>
<tr>
<td>TAC</td>
<td>Time-averaged concentration</td>
<td>mmol/L</td>
<td>15.5</td>
<td>2.8</td>
<td>18.2</td>
<td>1.2</td>
<td>19.3</td>
<td>0.9</td>
<td>17.6</td>
<td>2.4</td>
</tr>
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<td>PAC</td>
<td>Average predialysis concentration</td>
<td>mmol/L</td>
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<td>3.4</td>
<td>25.4</td>
<td>0.1</td>
<td>25.4</td>
<td>0.0</td>
<td>23.7</td>
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<td>std EKR</td>
<td>/wk</td>
<td>2.70</td>
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<td>3.58</td>
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<td>4.28</td>
<td>0.95</td>
<td>3.45</td>
<td>0.86</td>
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<tr>
<td>std ( K/V )</td>
<td>std ( K/V )</td>
<td>/wk</td>
<td>2.05</td>
<td>0.00</td>
<td>2.54</td>
<td>0.34</td>
<td>3.23</td>
<td>0.54</td>
<td>2.54</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Note: the predefined treatment parameters and target values are in bold.
limit for concentration (Figure 4). The average HEMO-
equivalent TAC and PAC (17.7 and 25.4 mmol/L) used here as
concentration limits are too low, because they include the low
values of sessions with low G. Excluding Group 1 gives 19.9
and 28.6 mmol/L, respectively, as averages of TAC and PAC
of the remaining 455 sessions. Group 1 is dialysed to eKt/V
0.9, not to any concentration limit.

TAC is more stable and results in smaller variation in Kt
than PAC (SD 17.5 versus 25.3 L). When using PAC as target,
high G may result in lower TAC than low G, but when using
TAC as target, high G results always in higher PAC than low
G [33]. TAC had tighter association to outcome than PAC in
the NCDS [14].

This study reveals great interindividual differences in urea
concentrations resulting from using eKt/V, std EKR, and
std K/V as dialysis dose targets in an unselected population.
Perhaps some patients will be underdialysed and some
overdialysed with V-scaled dosing. If higher normalised
dPI, nPCR, G/V, and urea concentrations in women are
a common phenomenon in the dialysis population, it may
explain why women did benefit from bigger V-scaled dialysis
dose in the HEMO study. Using only urea concentration
as the target (G-scaled dosing) means great modifications
to conventional treatment times and schedules, results in
unexpected deviations in the elimination of other solutes
[34], and endangers the outcomes. The dialysis dose could
be determined by setting a lower limit for V-scaled clearance
(eKt/V 0.9 × 3/wk, std EKR 2.7, or std K/V 2.1), an upper limit
for urea concentration (TAC 20 mmol/L or PAC 30 mmol/L),
and a lower limit for time (4 h).

In the present study, the dialysis treatments were modi-
fied afterwards by simulation. This is not possible in real life.
Creating a quite accurate prescription is possible by kinetic
modelling if we know the patient's G, V, and Kₜ, but they can
vary between sessions, and there are significant error sources
in measuring them.

So long we do not know enough about the metabolism
and toxicity of dialysable uraemic solutes, we must search the
optimal treatment by trial and error as until now.

Conflict of Interests

The author declares no conflict of interests.

References


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Adjusting Hemodialysis Dose for Protein Catabolic Rate

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Abstract

Background: Patients dialyzed with equal eKt/V may have huge variations in their urea concentrations. Methods: Urea generation rate, distribution volume and renal clearance were determined in 205 hemodialysis sessions of 33 patients with double pool urea kinetic modeling using dialyzer clearance from online monitoring. From these data, optimized prescriptions were computed. Results: In simulated dialysis sessions, the HEMO standard-dose equivalent clearance was not sufficient to keep time-averaged concentration (TAC) and average predialysis concentration (PAC) of urea below the defined upper limits (20 and 30 mmol/l), if normalized protein catabolic rate (nPCR) was greater than 1.3 g/kg/day. Protein catabolic rate was taken into account in the optimized prescription by cutting high urea concentrations. Conclusions: If patients having high urea concentrations with conventional clearance will benefit from higher dialysis dose – an unconfirmed hypothesis – this approach helps in identifying those who need more than three sessions per week.

Glossary: E = Excretion rate; EKR = equivalent renal clearance G/TAC; eKt/V = equilibrated Kt/V; fr = dialysis frequency; G = generation rate; K = clearance; Kr = renal clearance; Kt/V = dialyzer clearance × session time, scaled to distribution volume; LBM = lean body mass; nPCR = PCR scaled to LBM; PAC = average predialysis concentration, peak average concentration; PCR = protein catabolic rate; Qb = dialyzer blood flow; Qd = dialysate flow; RRF = residual renal function; spKt/V = single pool Kt/V; stdEKR = EKR scaled to V; stdK = standard clearance G/PAC; stdK/V = stdK scaled to V; stdKt/V = weekly stdK/V; TAC = time-averaged concentration; td = dialysis time; UF = ultrafiltration volume; V = total distribution volume (external + internal pool); V1 = single-pool V; Ve = external pool V; Vi = internal pool V.
centation. Since then the doses have increased. The HEMO study [4] showed that increasing Kt/V above current levels in conventional three times per week schedule had an insignificant effect on outcome.

Patients with high protein catabolic rate (PCR) have high urea concentrations when dialyzed with a commonly accepted clearance (Kt/V, stdEK or stdK/V). In an unselected hemodialysis population, the variation of predialysis urea concentrations was 6.1-fold [5].

Morton and Singer [6] propose that the dialysis dose should be normalized to the metabolic rate. Concentrations of several uremic toxins correlate to the protein catabolic rate in hemodialysis patients [7]. Gotch and Sargent [3, 8] recommend spKt/V 0.9–1.0 for patients with a low urea generation rate (G) and higher for those with a high G, roughly equal to the numeric value of nPCR in the 3×/week schedule. This strategy has not been tested in outcome trials.

In this study, I describe a hemodialysis prescription model, which resembles the Gotch’s and Sargent’s old concept, but includes residual renal function (RRF) and utilizes double pool urea kinetics, variable schedules and online clearance monitoring (OCM). The dialysis dose will be increased for patients with a high nPCR. The optimized prescriptions generated with this model are compared to the conventional and HEMO-equivalent ones. Patient outcomes are not reported.

### Materials and Methods

#### Patients and Dialysis Sessions

Data of 205 dialysis sessions of 33 chronic hemodialysis patients with online clearance monitoring and complete double pool urea kinetic modeling (UKM) were derived retrospectively from the information system of a hospital dialysis unit with permission of the hospital (table 1). The author has been part of the care of all patients.

The patient’s clinical condition, fluid removal requirement and eKt/V, stdK/V and laboratory values from the previous sessions were taken into account in defining the prescription. The patients were encouraged by a dietician to use a diet containing protein 1.2 g/kg/day, but the actual dietary protein intake was not controlled.

**EKR and stdK as Measures of Dialysis Dose**

Equivalent renal urea clearance (EKR, Casino and Lopez) [9] and stdK (Gotch) [8, 10] take the treatment frequency and residual renal function (RRF) into account and were intended to be used in comparing dialysis doses in different schedules and to continuous dialysis and renal function [11, 12].

EKR and stdK are based on the definition of clearance (K):

$$K = \frac{E}{C}$$

### Adjusting Hemodialysis Dose

| Table 1. Characteristics of 205 dialysis sessions of 33 patients |
|-------------------|-----------------|-----------------|-----------------|
| Avg               | stDev           | Min             | Max             |
| Age, years        | 66.3            | 14.6            | 16.3            | 91.4            |
| Height, cm        | 170             | 10              | 150             | 187             |
| Weight, kg        | 80.6            | 19.1            | 43.4            | 134.5           |
| BSA, m²           | 1.91            | 0.24            | 1.35            | 2.43            |
| BMI, kg/m²        | 28.0            | 5.8             | 16.0            | 44.7            |
| V, l              | 32.6            | 6.5             | 21.8            | 48.7            |
| Kr, ml/min        | 0.9             | 1.3             | 0.0             | 6.3             |
| nPCR, g/kg/day    | 1.09            | 0.26            | 0.53            | 1.86            |

**In steady state, the excretion rate equals the generation rate:**

$$E = G$$

$$K = \frac{G}{C}$$

**In EKR, C is the time-averaged concentration (TAC), in stdK, the average predialysis concentration (peak average concentration, PAC). stdK is scaled to body size by dividing by the urea distribution volume (V) and expressed as stdK/V (originally as stdKt/V = weekly stdK/V, a dimensionless variable, where ‘t’ is fixed to 7 days). Dividing EKR by V yields a variable called here as stdEKR. The most practical unit of stdEKR and stdK/V is /week. G, V, TAC and PAC can be determined by kinetic modeling.**

$$\text{stdEKR} = \left(\frac{G}{TAC}\right) / V$$

$$\text{stdK/V} = \left(\frac{G}{PAC}\right) / V$$

**In this article, postdialysis urea distribution volume is used as V in equations (3) and (4).**

In the NCDS study, TAC had tighter association to outcome than PAC [2]. stdEK is less sensitive to treatment frequency [11] and RRF [12] but more sensitive to a poorly spaced schedule than stdK/V [13].

### Urea Kinetic Modeling

Double pool urea kinetic modeling with three blood samples and interdialysis urine collection was done by calculation methods modified from the Solute-Solver application [14] and G, V and Kr determined in each session. The model assumes that the patient is in stable metabolic steady state, which was not confirmed. The Borah equation [15] with Sargent’s modification [16] was used in the nPCR calculation.

The average of several OCM measurements during the session was used as the dialyzer clearance (Kd) in the UKM equations. Plasma concentrations were converted to plasma water concentrations before calculations and back to plasma concentrations in the results.

TAC and PAC were determined after equalizing the schedule to a symmetric (equally spaced) one by simulation [11], using the double pool model.
**HEMO-Equivalent stdEKR and stdK/V**

In the standard-dose group of the HEMO study [4], the average eKt/V was 1.16. One-third of the patients had RRF. To get a safety margin for anuric patients, stdEKR and stdK/V values corresponding to eKt/V 1.20 in a conventional four-hour dialysis given three times per week (3 × 4 h/week) schedule without residual renal function (RRF) were calculated for each session as follows:

Single pool urea distribution volume (V1) was calculated with the classic single pool variable volume urea kinetic model (spvv UKM), using online Kd and Kr determined by the double pool method. Then Kd was solved from the Daugirdas eKt/V rate equation [17, 18]:

\[ eKt/V = (Kd \ast td / V1) - b \ast (Kd \ast td / V1) / td + a \]  
\[ Kd = (eKt/V - a) \ast V1 / (td - b). \]

1.20 was assigned to eKt/V and 240 min to td. In sessions with arteriovenous blood access, \( a \) was 0.03 and \( b \) 36 min, with venovenous access 0.02 and 28 min. Dialysis treatment 3 × 4 h/week was then simulated with the double pool model for each session with this Kd and Kr = 0. stdEKR and stdK/V were calculated and used as the minimum (HEMO-equivalent) limits in the optimization algorithm individually for each session.

**Simulations**

The dialysis sessions were modified by computer simulations with the double pool UKM, assuming that variations in dialysis do not affect urea generation rate. Kd, td and fr were varied and concentrations, stdEKR and stdK/V, were calculated. By numeric solution of the UKM equations it was also possible to compute the required Kd or td to achieve the desired concentrations or stdEKR or stdK/V.

Dialyzer mass area coefficient (KoA) was calculated in each session from dialysate flow (Qd), blood flow (Qb) and online Kd [19]. This KoA was then used in simulations to compute the Qb and Qd to achieve the required Kd.

**Optimization Algorithm**

V, G, Kr and weekly fluid removal requirement are the patient data needed in creating the dialysis prescription. They are derived from the real actual dialysis sessions. The goal of the optimization procedure is to generate from each dataset a prescription fulfilling twelve criteria (table 2).

Qb and td are continuous variables. The frequency values are 2, 3, 3.5 (alternate day), 4, 5, 6 and 7/week and dialysate flow 300, 500 and 800 ml/min.

Prescription generation starts with simulations with minimum fr, Qb, Qd and td. If more dialysis is needed, Qb is increased first, then Qd to 500 ml/min, then td, then Qd to the maximum value and the treatment frequency only as the last means. Weekly UF volume and the dialyzer (KoA) are held constant within each simulation. RRF (Kr) is taken into account.

A detailed description of the optimization procedure and some examples can be found in the online supplementary APPENDIX Online Material (www.karger.com/doi/10.1159/000365347). A simplified version of the program used in generating the optimized prescriptions can be downloaded from http://www.verkkomunuainen.net/optimize.html. It is intended to be used only in demonstrating and testing of the optimization method, not in treating patients.

### Results

HEMO-equivalent and optimized prescriptions are computed from V and G determined by double-pool UKM from the actual data. Table 3 shows the actual and simulated sessions.

In 80 (39%) of the simulated HEMO-equivalent sessions, the required blood flow is greater than the actual maximum, which means that eKt/V 1.2 cannot be achieved with the conventional schedule. The stdEKR and stdK/V targets can still be computed despite this virtual Qb.

In 38 optimized sessions (19%), stdEKR or stdK/V is over 10% higher than the HEMO-equivalent target due to TAC and PAC limits. Average and minimum eKt/V are in the optimized sessions lower than 1.2/session due to RRF and/or higher frequency.

The simulated optimized treatments differ considerably from the conventionally prescribed actual ones. Actual average values of TAC and PAC are lower and average values of stdEKR and stdK/V are higher than the optimized ones (table 3), but possible underdialysis is still detected in six actual sessions (3%) by at least one clearance or concentration value differing more than 10% from the optimized one. In 165 sessions (80%), both actual stdEKR and actual stdK/V are over 10% higher than the optimized values. Low concentrations with normal clearance are not interpreted as overdialysis. Overdialysis means at least wasting of resources. In this material, optimization decreases the weekly treatment time and dialysate consumption (table 3).

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**Table 2. Optimization criteria**

<table>
<thead>
<tr>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment frequency, week</td>
<td>2</td>
</tr>
<tr>
<td>Treatment time, min</td>
<td>240</td>
</tr>
<tr>
<td>Dialysate flow, ml/min</td>
<td>300</td>
</tr>
</tbody>
</table>
| Blood flow, ml/min | 50 | 287
| stdEKR, week | 3.44
| stdK/V, week | 2.35 |
| TAC, mmol/l | 20.0 |
| PAC, mmol/l | 30.0 |

1 Average value. The blood flow upper limit used in each optimized session was 90% of the patient’s maximum blood flow during the previous four weeks. 2 Average value. The minimum stdEKR and stdK/V were defined individually for each session to correspond to eKt/V 1.2 in a 3 × 4 h/week schedule without RRF.

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Vartia
By optimization, 173 (84%) of the actual sessions fall into the 3×/week schedule, 15 (7%) need more; in 17 (8%) 2×/week is sufficient (table 4). These proportions are of course dependent on the targets (table 2).

Table 4 may be interpreted as follows: with normal nPCR, two sessions per week is sufficient only if the patient has moderate RRF, but with high nPCR, a high frequency is required to achieve the TAC and PAC targets despite RRF, and this is reflected in high clearances.

In 43 sessions (21%), the optimized dialysis dose is determined by the concentration limits. The HEMO-equivalent clearance is not enough to keep TAC and PAC below the defined upper limits (20 and 30 mmol/l), if nPCR is greater than 1.3 g/kg/day. Figure 1 summarizes the results.

Discussion

In this model, the hemodialysis dose is scaled not only to body size but also to the protein catabolic rate by cutting high urea concentrations. The optimized prescription fulfills the conventional clearance-based adequacy criteria (stdEKR and stdK/V), but if this is not enough to guarantee moderate concentrations, the dose is increased. This means more individualized dosing. The nPCR value above which the clearance-based prescription is modified by the protein catabolic rate (about 1.3 g/kg/day; fig. 1) depends of course on the concentration limits.

The optimized prescription shows how the patient should have been dialyzed according to this model. The patient-specific variables V and G are derived by UKM from real dialysis sessions. Online clearance is used as Kd in the UKM. The optimization procedure calculates a new Kd and determines the required Qb and Qd from it and KoA, which is calculated from the actual Qb, Qd and online Kd. The new Qb and Qd can be applied to next treatments, if the patient-specific parameters and other circumstances remain constant. Kd from the OCM device can be compared to the prescribed one. The measured and prescribed Kd, Qb and Qd are commensurable and have same error sources.

Creating an accurate prescription is possible by kinetic modeling, but the patient’s G, V and Kr can vary between sessions and there are significant error sources in measur-
ing them. In this study, the session-specific KoA values, based on online clearance, Qb and Qd, had considerable variation within each dialyzer model (not shown), which refers to some uncontrolled factors. Using a symmetric schedule in demonstrating the optimization principle is a shortcut, which simplifies the procedure and shortens the computer time, but it is an extra source of inaccuracy.

In a recent study, women had higher urea concentrations than men when simulating dialysis with equal eKt/V, stdEKR or stdK/V [5]. Dialyzing to an equal concentration would deliver more Kt/V to women. In the HEMO study, women but not men benefitted from the higher eKt/V. This is at least partially associated to scaling by V. Adjusting dialysis dose for protein catabolic rate by concentration limits modifies the scaling.

There are no investigations confirming the hypothesis that patients having high urea concentrations with conventional clearance would benefit from more intensive dialysis. The optimization procedure described here is based on 205 hemodialysis sessions of 33 individual patients. It is absolutely impossible to confirm the hypothesis in this scale. Perhaps it could be confirmed or discarded by reanalyzing the HEMO material. Kt/V and nPCR were monitored monthly and there was considerable variation in nPCR at baseline [20]. Did patients with high nPCR benefit from the higher dose? The role of nPCR is more difficult to assess than that of gender because it may change during the study, the dialysis dose may have an effect on it and there may be a mathematical coupling between Kt/V and nPCR. However, the HEMO investigators could probably overcome these difficulties.

Urea concentrations can be efficiently decreased by increasing treatment frequency. Increasing dialyzer clearance (KoA, Qb, Qd, Kt/V) is an inefficient way to decrease PAC and increase stdK/V. In this material with simulated 3 × 4 h/week schedule without RRF, increasing Kd by 34% from the average 191 ml/min to 256 ml/min (eKt/V from 1.2 to 1.6) resulted in 12% fall of average PAC from 24.2 to 21.4 mmol/l and 13% rise of stdK/V from 2.35 to 2.66/week.

Increasing frequency in a whole dialysis population had some favorable effects on outcome in the FHN trials, but ‘the net effects of frequent hemodialysis will need to be balanced against the added burden for the patient and societal cost’ [21]. Concentration limits may help in selecting patients who might benefit from high frequency.

We don’t know the optimal or critical upper limits of TAC and PAC or whether they exist. A computer is needed in creating a multi-target prescription, but after seeing a high predialysis urea concentration it is usually rather simple to intensify the treatment, if we accept that it is justified. High concentration is either due to a low clearance or due to a high generation rate. In both cases, the dialysis dose needs to be increased – if the hypothesis that patients with a high nPCR value benefit from higher dose is true.

Is it reasonable to be satisfied with an adequate Kt/V if concentrations are high? This study does not answer this question, but presents a solution, if the answer is ‘no’.

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