An Exploratory Study in Three Parts to Determine Sex-Specific Differences in Chronic Kidney Disease Recognition, Progression and Treatment

(Explorative Studie in Drei Teilen zur Erhebung Geschlechtsspezifischer Unterschiede in der Identifizierung von Patienten mit präterminaler Niereninsuffizienz sowie bei Progression der Erkrankung und Beginn mit der Nierenersatztherapie)

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ZUSAMMENFASSUNG DES PROJEKTES

Frauen stellen trotz größerem Anteil an der Gesamtpopulation den geringeren Patientenanteil an der Dialyse. Signifikante regionale und altersgruppenbezogene Unterschiede an der Ratio zwischen Frauen und Männern an der Dialyse und die Tatsache, dass die Prävalenz der chronischen Niereninsuffizienz zB. bei weiblichen US-Amerikanern höher ist als bei männlichen, lässt vermuten, dass eher psychosoziale bzw. sozioökonomische Ursachen als biologische Unterschiede dieser ungleichen Geschlechterverteilung zu Grunde liegen. Präliminäre internationale Daten der Chronic Kidney Disease Outcomes and Pratice Patterns Study (CKDOPPS) zeigen, dass in verschiedenen Ländern weibliche Patienten in den nephrologischen Ambulanzen (Chronische Niereninsuffizienz /CNI - Ambulanzen), relativ zum Frauenanteil in der Gesamtpopulation und angesichts der höheren Prävalenz der CNI, unterrepräsentiert sind. KDIGO empfiehlt offiziell die MDRD oder Cockroft-Gault Gleichung zur Bestimmung der Nierenfunktion. Zwar inkludieren diese Formeln das Geschlecht als Korrekturvariable jedoch wird vermutet, dass die Korrekturvariablen vor allem für Frauen <65 Jahren inkorrekt sein könnten. Es wäre anzunehmen, dass für Frauen mit ihrem niedrigeren Muskelanteil im Vergleich zu Männern die GFR (basierend auf dem Goldstandard der Kreatininclearence) niedriger geschätzt und somit eine Indikation zur Dialyse rascher gestellt würde. Im Vergleich zu Männer hatten Frauen in den USA jedoch ein 1,7-fach höheres Risiko eins späten (etwa bei GFR< 5 ml/min) Dialysebeginns. Eine geringere Awareness gegenüber ihrer Nierenerkrankung bei Frauen, wie in einer NHANES Studie gezeigt werden konnte, könnte zu diesen Phänomenen beitragen. Doch auch die Entscheidung des behandelnden Arztes und die Meinung der Familienangehörigen könnte einen größeren Einfluss zur Entscheidung für oder gegen eine Dialysetherapie darstellen als die persönliche Meinung der Patienten. Aus der kontrovers geführten Diskussion ob Männer eine schnellere CNI Progression zeigen als Frauen und aufgrund vorliegender Studien zur Mortalität bei CNI ergibt sich die Frage ob weibliche CNI Patienten möglicherweise ein höheres prä-dialyse Mortalitätsrisiko aufweisen als männliche.

Basierend auf den Daten der Dialysis Outcomes and Practice Patterns Studie (DOPPS, o.a. Referenz) erscheint die Hypothese der CNI Missklassifikation und verzögerten CNI Progression bei Frauen unwahrscheinlich. So vermuten wir eher psychosoziale bzw. sozioökonomische Hintergründe als Ursache für die Unterrepräsentanz der Frauen an nephrologischen Ambulanzen und bei Nierenersatztherapien.

Die Ziele der vorliegenden Studie sind die Darstellung geschlechtsspezifischer Unterschiede in der Population mit Nierenersatztherapie in Österreich, die Analyse geschlechtsspezifischer Unterschiede bei Therapie und Outcomes von hospitalisierten Patienten mit CNI und die Darstellung der Entscheidungsfindung betreffend der Einleitung eines Nierenersatzverfahrens.

Die Studie wurde in 3 Substudien unterteilt, bestehend aus einer nationalen und einer lokalen retrospektiven Datenanalyse sowie einer Fragenbogenstudie:

1) Darstellung und Analyse geschlechtsspezifischer Unterschiede von Hämodialysepatienten und Hämodialyse assoziierter Mortalität in Österreich

Methode: Abfrage epidemiologischer, klinischer und Hämodialyse-spezifischer Daten aller Patienten aus dem österreichischen Dialyseregister (1965-2015).

2) Erfassung geschlechtsspezifischer Unterschiede in Behandlung und Outcome von hospitalisierten Patienten im Krankenanstaltsverbund mit eingeschränkter Nierenfunktion.

Methode: Geschlechtsspezifische Erfassung aller Patienten, welche mit einer GFR < 60 mL/min/1.73m2 im Jahr 2015 auf einer internistischen Abteilung des Krankenanstaltsverbundes hospitalisiert wurden und deren Outcomes (Hospitalisierungsdauer, Mortalität während der Hospitalisierung, Dialyseinitiierung).

3) Darstellung geschlechterspezifischer Unterschiede in der Entscheidungsfindung der Patienten mit terminaler Niereninsuffizienz und der betreuenden Ärzte bezüglich der Einleitung einer Nierenersatztherapie.

Methode: Anonymisierter Patientenfragenbogen für Patienten und Ärzteteam an nephrologischen Ambulanzen. Adressiert werden alle nephrologischen Ambulanzen Österreichs.

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1. INTRODUCTION

1.1 Women are under-represented in the dialysis population

A recent report from the international Dialysis Outcomes and Practice Patterns Study (DOPPS) followed the call of *Nature*[1, 2] and *Lancet*[3] to "put gender on the agenda" and analyzed sex-specific differences in hemodialysis patients.[4] As an addition to previous studies,[5, 6] the principal goal was to identify aspects of dialysis care that could be improved for females and males on hemodialysis, by studying the interaction between sex and modifiable treatment practices on mortality. The most important result of this analysis was the suggestion that a large number of females are currently not being dialyzed at all. Specifically, among 206,374 patients from 12 countries who participated in the DOPPS from 1996 through 2011, 59% were male and 41% female. The regional differences by age group and country were so large (Table 1) that they seemed unlikely explainable by biology.[4]

	18-44			45-54			55-64			65-74			75+		
Country	**GP**	**HD_p**	**HD_i**	**GP**	**HD_p**	**HD_i**	**GP**	**HD_p**	**HD_i**	**GP**	**HD_p**	**HD_i**	**GP**	**HD_p**	**HD_i**
Aus-NZ	49.8	49.1	25.3	50.6	42.3	27.7	50.3	43.8	41.6	51.2	42.4	30.6	58.4	31.9	24.6
Belgium	49.6	42.5	41.0	49.7	34.0	39.8	50.4	42.1	37.6	53.4	43.8	38.1	62.6	42.1	39.7
Canada	49.4	43.9	38.0	50.0	40.8	33.5	50.8	42.9	38.9	52.2	39.3	38.4	60.0	48.9	40.1
France	50.2	35.6	33.7	51.1	40.1	37.2	51.3	36.2	38.4	53.9	39.3	33.1	63.3	45.9	37.5
Germany	49.1	39.4	32.4	49.4	34.9	47.1	50.6	39.8	32.7	52.9	35.0	31.3	64.4	45.9	41.5
Italy	49.5	35.6	37.3	50.6	36.3	37.1	51.4	38.5	36.3	53.7	38.8	32.9	62.6	45.5	37.4
Japan	49.1	29.4	32.4	49.9	32.1	27.5	50.8	35.8	28.6	52.9	37.7	30.0	62.3	43.6	38.8
Spain	48.6	34.4	37.2	50.2	37.4	32.8	51.5	36.3	31.0	53.8	40.0	27.4	61.2	42.9	37.8
Sweden	48.9	44.4	27.0	49.3	42.6	35.6	49.9	34.9	26.0	51.4	32.9	32.5	60.4	40.0	35.1
UK	50.1	40.9	41.7	50.5	40.1	26.9	50.8	39.2	42.2	52.3	45.0	37.7	60.7	40.2	36.1
US	49.7	41.5	41.6	50.8	39.1	42.5	51.8	44.9	43.3	53.6	49.2	39.3	61.1	46.3	40.8

Table 1: Percentage of women in the general population (GP) versus in the hemodialysis population (DOPPS) in the year 2009, by country and age group.
Categories 18-44, 45-54, 55-64, 65-74, 75+ are age categories [in years]. General population (GP) data are from the Human Mortality Database, 2009. Hemodialysis prevalent population (HDp) data are from the initial census of patients in facilities at the start of DOPPS Phase 4 (2009), cross-sectional, regardless of duration of end-stage renal disease. Hemodialysis incident population (HDi) restricted to patients on dialysis <90 days, when added to the facility census of patients in the DOPPS (includes patients in DOPPS facilities at the start of DOPPS Phase 4 data collection as well as patients who started dialyzing at DOPPS facilities during 2009–2012). Abbreviations: GP, general population; HDp, hemodialysis prevalent population; HDi, hemodialysis incident population; Aus-NZ=Australia and New Zealand; UK=United Kingdom; US=United States.

The percentage of women in the general population, derived from the „Human Mortality Database", was 50% and above and increased throughout older age-groups. By contrast, in the dialysis population, the percentage of women was consistently below 50% for both prevalent and incident patients, indicating that gender-specific differences in early dialysis mortality -if any such differences might exist- had not influenced the results.

Regional differences between men and women on dialysis were perhaps the most interesting finding: For example, only 31.9% of >75 year-old dialysis patients in Australia and New Zealand were females, while 48.9% in the same age group in Canada. These regional differences suggest that psycho-socio-economic factors, rather than biological ones are responsible for the under-representation of women on dialysis.

1.2 The under-representation of women in the dialysis population runs counter to their possibly higher prevalence of chronic kidney disease prevalence

Women could be under-represented in the hemodialysis population, because chronic kidney disease might affect more males than females. However, in the National Health and Nutrition Examination Survey (NHANES), chronic kidney disease among US individuals without end-stage renal disease has been found to be more frequent among women (Table 2).

	All CKD		**eGFR <60 ml/min/1.73m^2**		**ACR ≥30 mg/g**	
	1988-1994	**2005-2010**	**1988-1994**	**2005-2010**	**1988-1994**	**2005-2010**
Male	10.2	12.1	4.1	5.6	7.4	8.6
Female	14.2	15.8	5.6	7.7	10.2	10.2

Table 2: Prevalence [%] of chronic kidney disease in the NHANES population within gender category.
Data published in the USRDS Annual Data Report 2013, page 44.[7]
Abbreviations: CKD=chronic kidney disease, eGFR=estimated glomerular filtration rate, ACR=albumin creatinine ratio.

Specifically, NHANES data showed for 2005-2010 that the percentage of individuals those with an albumin creatinine ratio ≥30 mg/g was substantially higher among all women analyzed (10.2%) than among all men analyzed (8.6%), and that the percentage of those with an eGFR <60 mL/min/1.73m^2 was substantially higher among all women analyzed (7.7%) than among all men analyzed (5.6%, Table 2).

Consistent with NHANES and still in the United States, data from a large, integrated system of health care delivery (Kaiser Permanente of Northern California) indicated that chronic kidney disease is more frequent among women.[8] As compared to the general population in the United States where the percentage of women among all those who were aged 65-74 years in 2009 was 53.6% (Table 1), the percentage of women among all those who held their insurance with Kaiser Permanente and had an eGFR <60 mL/min/1.73m^2 and ≥15 mL/min/1.73m^2 was between 57.7% and 60.7% (Table 3).

eGFR [mL/min/1.73m2]	**≥60**	**45-59**	**30-44**	**15-29**	**<15 without dialysis**
Age [years]	49.1 ±1 5.1	65.4 ± 13.5	71.2 ± 12.9	70.1 ± 14.5	63.0 ± 16.1
Female Sex [%]	53.4%	60.7%	61.6%	57.7%	50.6%

Table 3: Percentage of women among individuals with chronic kidney disease.
Data are derived from the analysis of a large, integrated system of health care delivery (Kaiser Permanente of Northern California).[8]

Abbreviation: eGFR=estimated glomerular filtration rate.

Importantly, while the Kaiser Permanente data showed that the majority (57.7%) of all those with eGFR 15-29 mL/min/1.73m^2 were women, the majority (50.6%) of those who had a dialysis indication (eGFR <15 mL/min/1.73m^2) but still were without dialysis also were women.

Data from NHANES and Kaiser Permanente are consistent with the majority of population-based studies.[9] Specifically, most of the included studies presented a gender-specific prevalence of chronic kidney disease. In general, the prevalence of chronic kidney disease was greater in women than in men, regardless of age.[10-12] Also consistent with NHANES, proteinuria, as defined by dipstick result of trace or greater was more prevalent in women in a study of 107,192 Japanese volunteers, although fewer women than men ended up receiving renal replacement therapy during 10 years of follow-up.[13] Finally, a most recent systematic analysis of worldwide population-based data showed consistently that the prevalence of chronic kidney disease stages 3-5 in 2010 was higher for women than for men in all countries, except for the age group of 20-29.[14]

1.3 Women could be under-represented in chronic kidney disease clinics

The Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDOPPS) collects data on advanced chronic kidney disease and the transition of patients to end-stage renal disease, aiming to identify practices associated with the best outcomes.[15] Data on chronic kidney disease patients are currently starting to become available from Germany[16], France[17], Brazil[18] and the United States. Preliminary results from CKDOPPS indicate that 40%-52% of patients in chronic kidney disease clinics of France, Brazil, the United States and Germany are women (Figure 1).

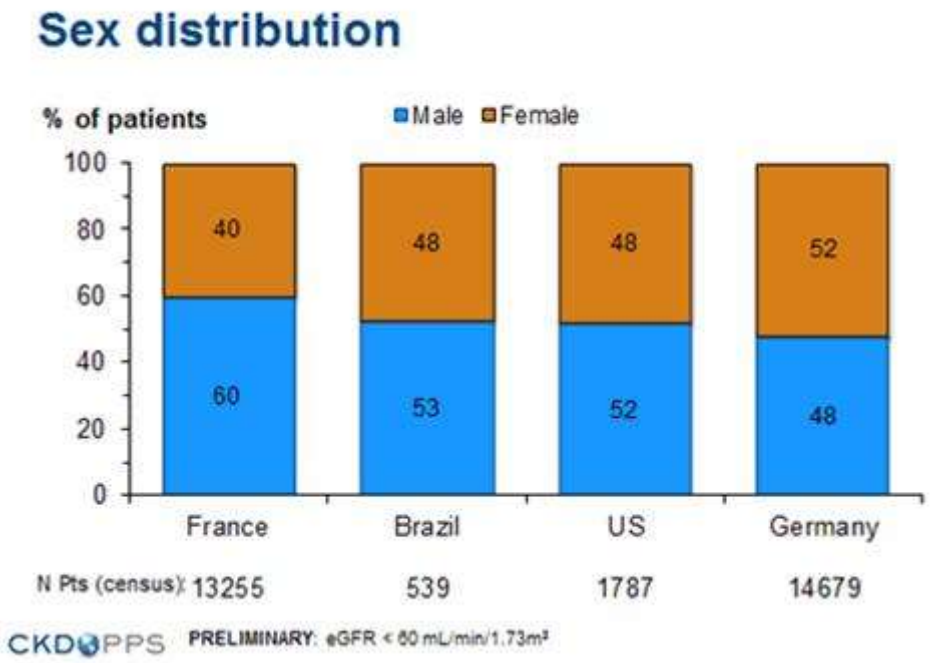

Figure 1: Sex distribution of patients in chronic kidney disease clinics.

Preliminary data from the Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDOPPS).

Respective to the percentage of women in the general population (Table 1) and respective to the percentage of women among patients with chronic kidney disease (Table 3), the finding that only 40%-52% of patients in chronic kidney disease clinics are women might suggest their under-representation.

1.4 A potential sex-bias in estimated glomerular filtration does not explain the under-representation of women in the dialysis population

Most of the formulae used to assess renal function are based on serum creatinine.[19] Serum creatinine values are influenced among other things by protein intake and muscle mass. It is obvious that for the standard general population muscle mass is higher in men than in women, and therefore, creatinine-based formulas to estimate kidney function rightly include sex as a variable (MDRD equation without ethnicity factor: 175 x Serum Creatinine$^{-1.154}$ x age$^{-0.203}$ x 0.742 [if female][20]). The correction factors for female sex in both MDRD and Cockroft-Gault formulae might be incorrect,[10] although European validation studies support only some, but not large errors in correction factors between men and women.[21] Specifically, for women aged <65 years, the bias of the MDRD formula (compared to Cr-EDTA clearance) was -3.1±17.2 mL/min/1.73m^2.[21] These findings, however, did not discourage KDIGO from advising measurement of the kidney function by MDRD or Cockroft-Gould equation as a level A recommendation in both men and women, while measurement of creatinine clearance is advised in extraordinary health conditions (vegetarian diet, malnutrition or obesity). Importantly, misclassification of women with a presumably lower GFR than might be expected from performing the gold standard renal clearance would result in *more* women dialyzing, if GFR was used as the primary trigger for dialysis initiation. The opposite is the case, as shown by the aforementioned DOPPS study.[4] US data analyzed at Arbor Research Collaborative for Health showed in accordance with the DOPPS,[4] that the adjusted estimated glomerular filtration rate was 1.07 ml/min/1.73m^2 lower in women than in men at dialysis initiation (95% CI 1.03–1.10 ml/min/1.73m^2).[22]

1.5 Late dialysis initiation and poor kidney disease awareness among women

Kausz et al. have shown as early as 2000 that among those 23% of patients who began dialysis late in the United States between 1995 and 1997 (i.e. glomerular flitration rate <5 ml/min/1.73m^2), women had an odds ratio of 1.70 compared with men, surpassing that of Hispanics and Asians (compared with Caucasians), uninsured patients (compared with private insurance), and employed patients (compared with unemployed).[23] These data are consistent with more recent results.[24, 25]

Coresh et al. analyzed chronic kidney disease awareness among US adults using NHANES surveys conducted in 1999 to 2000 and found that less than one fifth (18.6±6.3%) of adults with chronic kidney disease stage 3 and albuminuria (>30 mg/g creatinine) reported previous knowledge/diagnosis of weak or failing kidneys. Among

those in chronic kidney disease stage 3 but without proteinuria, less than one tenth (8.2±2.3%) of adults were aware of their chronic kidney disease. In the latter group, awareness levels were significantly lower among women (2.9±1.6% awareness in women versus 17.9±5.9% awareness in men).[26] This observation might explain the potential under-representation of women in chronic kidney disease clinics (Figure 1).

1.6 The decision to initiate dialysis is doctor-driven

Davison et al. conducted a survey, asking the following question (Table 4) among 584 patients with chronic kidney disease stages 4 and 5 as they presented to dialysis, transplantation or predialysis clinics in a Canadian, university-based renal program:[27]

"If you are currently receiving dialysis, why did you choose dialysis over conservative care (no dialysis)?"	
Your doctor's wish:	51.9%
Your own personal wish:	34.2%
Your family's wish:	13.9%

Table 4: Excerpt from a survey on and-of-life care preferences and needs in patients with chronic kidney disease.[27]

The response to the question asked by Davison et al. suggests that the decision to be treated with dialysis reflects physicians' and family members' preferences rather than personal choice.[27] This opens room for the possibility that women are under-represented in the dialysis population, because doctors might be more reluctant to initiate renal replacement therapy in women than in men.

1.7 Sex-specific differences in chronic kidney disease progression and death risk before the start of dialysis

The effect of sex on the progression of renal disease has been a matter of debate, until Neugarten et al., in a meta-analysis of 68 published studies, were able to show that men have a more rapid decline of renal function than women.[28] However, of the eight studies that were selected for meta-analysis[29-36], the association between sex and the rate of fall in glomerular filtration rate was attenuated in one study and became non-significant after adjusting for differences in blood pressure, proteinuria and high density lipoprotein cholesterol.[29] Moreover, two studies[33, 34] not only used decline in glomerular filtration rate, but also end stage renal failure as an outcome in order to define "progression to end stage renal disease". This analytical strategy has been shared by a recent study conducted on 185,431 individuals in Austria, which found an increased risk of end stage renal disease, as defined by initiation of renal replacement therapy, for men.[37] Clearly, if women were to initiate dialysis later, or not at all, in comparison to men, the bias that might be introduced by a sex-dependent decision to initiate renal replacement therapy would be carried over into the aforementioned analyses. Thus the progression in women might be underestimated due to the inclusion of dialysis initiation in the calculations.

If more women than men have chronic kidney disease don't they progress? An alternative explanation is that they either die more often or die before they reach dialysis: A meta-analysis on two million participants (54% women) from general population and high-risk cohorts conducted by the Chronic Kidney Disease Prognosis Consortium analyzed the mortality risk for women and men, by eGFR.[38] As shown in Figure 2, the slopes of the risk relationship for all-cause mortality and for cardiovascular mortality were steeper in women as compared to men. Specifically, compared with an estimated glomerular filtration rate of 95 ml/min/1.73m^2, the adjusted hazard ratio for all-cause mortality at estimated glomerular filtration rate 45 ml/min/1.73m^2 was 1.32 (95% CI 1.08 to 1.61) in women and 1.22 (1.00 to 1.48) in men ($P_{interaction}$ <0.01).

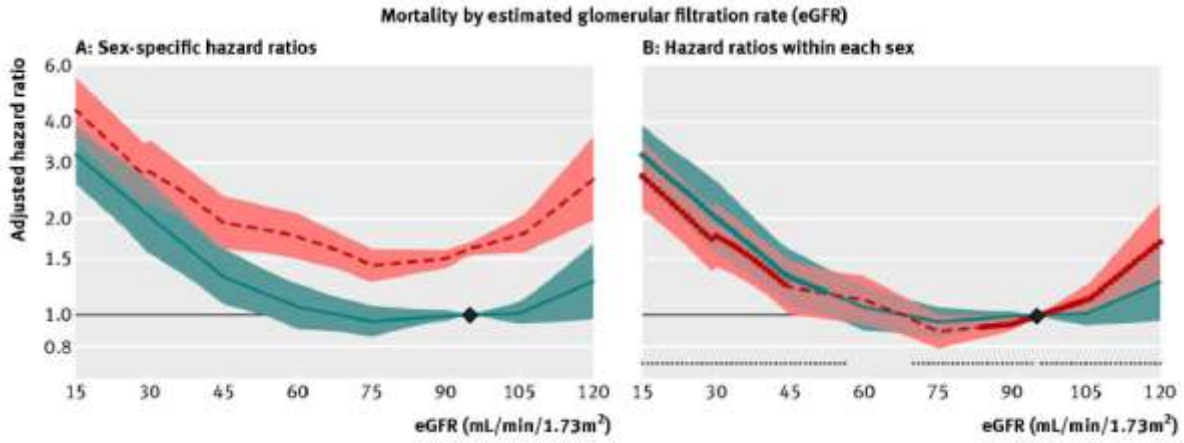

Figure 2: Hazard ratios of all-cause mortality according to estimated glomerular filtration rate in men (red) versus women (green).
Data are derived from general population cohorts and high cardiovascular risk cohorts.[38] Panel A shows sex-specific hazard ratios including a main effect for male sex at the reference point. Panel B shows hazard ratios within each sex, thus visually removing the baseline difference between men and women.[38]

The slope being steeper for women led to the authors' conclusion that "kidney disease is not less important in women than in men".[38] However, our interpretation is that women are likely to die before reaching delayed dialysis. The abridged life table method was applied in the Alberta Network Healthcare extraction (Canada) to calculate the life expectancies of men and women from age 30 to 85 years by levels of kidney function:[39] In agreement with the notion that women live longer, women aged 30-60 years with chronic kidney disease stage 3 had a life expectancy of 3-5 years more than men. However, women aged 30-60 years lived 1-2 more years than men if having chronic kidney disease stage 4 and actually lived 1-2 years less than men if having chronic kidney disease stage 5.

No analysis has, to our knowledge tested the hypothesis that death competes with the possibility to reach dialysis and that this may explain the controversy among studies analyzing progression rates by sex.[39]

The large regional differences in dialysis prevalence observed in the DOPPS-study [4] (Table 2) render the previous hypotheses of chronic kidney disease misclassification among women and delayed chronic kidney disease progression unlikely. Psycho-socio-economic factors, rather than biological ones could be responsible for the fact that fewer women than men are dialyzing, consistent with the findings that dialysis initiation is later among women than among men, and that women are more likely to die in the late, pre-dialysis chronic kidney disease stages (Figure 2).[38]

The present study aims at further investigating sex-specific differences in recognition, progression and treatment of chronic kidney disease in Austria.

2. STUDY OBJECTIVES AND INVESTIGATIONAL PLAN /METHODOLOGY

Objectives
This study aims to describe sex specific differences of the hemodialysis population in Austria, to quantify sex specific differences in treatment and outcomes in hospitalized patients with chronic kidney disease and to examine decision making by doctors and patients with regards to hemodialysis initiation.

To adequately serve the needs of these research questions, the study is divided into 3 parts (sub-studies).

1. Description and analysis of sex-specific differences in hemodialysis patients and the associated male-to-female mortality in Austria.

2. Description and analysis of sex-specific differences in treatment and outcomes in hospitalized patients with chronic kidney disease.

3. Descriptive analysis of decision-making by doctors and patients with regard to hemodialysis initiation.

2.1 Description and analysis of sex-specific differences in hemodialysis patients and the associated male-to-female mortality in Austria

Hypothesis:

There are sex-specific differences in hemodialysis incidence/prevalence and mortality among hemodialysis patients in Austria.
There are differences in male-to-female mortality among hemodialysis patients as compared to the general population in Austria.

Methodology:

Data extraction will be performed from the Austrian Dialysis registry which holds complete longitudinal entries of all Austrian hemodialysis patients since 1970[40] and contains data of all patients undergoing hemodialysis in Austria since the year 1965.
Demographic data, laboratory values, clinical characteristics and hemodialysis specific data will be collected for every patient registered in the Austrian Dialysis registry between 1865 and 2015.
Male and female population structure and mortality data of the Austrian general population will be retrieved from the ´Statistik Austria´ registry

Statistics:

Standard descriptive statistics will be used for tabulations of patient characteristics by sex and decade, of the Austrian hemodialysis population versus general population by sex and age group over time. The unadjusted male-to-female mortality rate ratio in

the hemodialysis population will be compared with that of the Austrian general population. Adjusted hazard ratios for the male-to-female mortality risk in hemodialysis patients, by region will be performed using Cox regression analysis. Statistical modeling will closely follow a previously published study of hemodialysis data, analyzed by sex and country/region.[4] All obtained p-values will be considered exploratory in nature.

2.2 Description and analysis of sex-specific differences in treatment and outcomes in patients with chronic kidney disease.

Hypothesis:

There are sex-specific differences in treatment, length of hospitalization, mortality and dialysis initiation in patients with chronic kidney disease admitted to internal medicine wards.

Methodology:

Patients hospitalized at internal medicine wards of the Krankenanstaltsverbund (KAV) between Jan 1st 2015 and Dec 31st 2015 with eGFR <60 mL/min/1.73m will be included.
Primary study endpoints are length of hospital stay, death within hospitalization and dialysis initiation. Secondary endpoints are renal function parameters (eGFR, serum creatinine, blood urea nitrogen) and proteinuria during hospital stay. Laboratory data will be extracted from the KAV laboratory database and patient characteristics will be derived from the KAV patient management database.

Statistics:
Descriptive statistics will be used for presentation of demographic and clinical patient characteristics and prevalence of chronic kidney disease in women as compared to men.
Further statistical methods will be chosen according to data availability and quality: The present plans include logistic regression to calculate the male-to-female odds of reaching one of the endpoints, conditional logistic regression for pair-matched data or logistic regression with propensity scoring.

2.3 Descriptive analysis of decision-making by doctors and patients with regards to renal replacement therapy initiation

Hypothesis

There are sex-specific differences in decision-making of doctors and patients with end-stage renal disease with regards to renal replacement therapy initiation.

Methodology

Questionnaires will be sent to every Austrian chronic kidney disease outpatient clinic willing to participate. Doctors and patients will complete the questionnaire anonymously and questionnaires will be sent back after a 3 months-time period of data collection /questionnaire completion.

The following questions will be included in the questionnaire:

Doctor level:

In your chronic kidney disease clinic

1. How many men (a) and how many women (b) were registered in the year 2016?
2. According to the first lab result that was taken in 2016, how many men (a) and how many women (b) were in chronic kidney disease stage 4, 3a, 3b, and 2?
3. How many times did the registered men (a) and the registered women (b) have their labs checked and saw the doctor during the year 2016? Please subdivide also by chronic kidney disease stage.
4. How many men (a) and how many women (b) have you informed they will likely need renal replacement therapy (RRT) in the next 12 months?
5. How many men (a) and how many women (b) already have a fistula, and how many have a graft for vascular access?
6. How many men (a) and how many women (b) have you informed about pre-emptive transplantation as an option for RRT?
7. How many men (a) and how many women (b) have you informed about peritoneal dialysis as an option for RRT?
8. How many men (a) and how many women (b) have you informed about hemodialysis as an option for RRT?
9. How many men (a) and how many women (b) ended up on RRT (HD, PD or preemptive transplantation) during the year 2016?
10. How many men (a) and how many women (b) did you consider end stage and thus in need of undergoing RRT in 2016?
11. How many men (a) and how many women (b) refused RRT in 2016 despite your advice?
12. Among those whom you considered end stage in the year 2016, in how many men (a) and how many women (b) was the decision to withhold or not do RRT mutual (taken by doctor and patient together)?
13. How many men (a) and how many women (b) started RRT in 2016 against your advice?
14. How would you judge your own decision making regarding RRT initiation
    a) Influenced by patient sex, with men more likely to start RRT
    b) Influenced by patient sex, with women more likely to start RRT
    c) Not influenced by patient sex

To obtain adequate data, a reimbursement based on the number of patients seen by the center will be offered to the medical director of the outpatient clinic in December 2016. A specific plan on how to arrive at answering the questions correctly must be submitted; in principle, this plan should encompass several meetings with the outpatient clinic doctors in early 2017, in order to obtain an answer from all of them together (only question 14 must be individually answered).

Patient level:

1. I am a man (a), a woman (b).
2. My age is … years.
3. My nationality is Austrian (a), Non-Austrian (b).
4. My native language is German (a), not German (b).
5. I am married (a), living with my partner (b), separated or divorced (c), single (d), widowed (e).
6. My highest level of education is less than high school.
7. I know the reason (a), don't know the reason (b) why my kidneys are weak or failing.
8. The most important reason why my kidneys are weak or failing, to the best of my knowledge is hypertension (a), diabetes (b), glomerulonephritis (c), polycystic kidney disease (d); another reason not mentioned here (e).
9. I come to the clinic seldom [once a year at the most] (a), frequently [at least 3 times a year] (b) in order to check my labs and/or discuss treatment and progression of my disease.
10. A doctor at this clinic has told me (a) has not told me (b) that I will likely need renal replacement therapy (RRT) within the next 12 months.
11. I already have (a) / don't yet have (b) a fistula or graft for vascular hemodialysis access.
12. A doctor at this clinic has informed me (a) has not informed me (b) about the possibility to undergo pre-emptive transplantation as an option for RRT.
13. A doctor at this clinic has informed me (a) has not informed me (b) about peritoneal dialysis as an option for RRT.
14. A doctor at this clinic has informed me (a) has not informed me (b) about the possibility to undergo hemodialysis as an option for RRT.
    1. I consider myself end stage and thus in need of undergoing RRT within the next 12 months.
15. RRT is not an option for me. I would rather die than go on dialysis.
16. I suffer from nausea/vomiting (a), fatigue/tiredness (b), edema (c), dyspnea (d).
17. I can take care (a), cannot take care (b) of my household.

Methodological Note: The questionnaire will be handed out to all patients coming to the outpatient clinic in the year 2017 by non-medical (administrative) personnel. The number of returned questionnaires will be counted and compared to the number of questionnaires that was handed out. Only the sex of the patient receiving the questionnaire will be recorded. The return of the questionnaire will be anonymous, by placing a box in the patient waiting area.

Statistics:

Data will be entered into an IBM SPSS statistics database. Descriptive analysis and graphical illustrations will be performed.

3. TIME TABLE

	Task	Year 1				Year 2				Year 3			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
1	Objective 1 (data collection, data analysis, manuscript [MS])												
2	Study objective 2 (data source identification & approval of data collection, analysis, MS)												
3	Objective 5 (questionnaire development & testing, distribution, retrieval, data analysis, MS)												

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