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INFECTIVE ENDOCARDITIS AND STAPHYLOCOCCUS AUREUS BACTEREMIA IN PATIENTS WITH END-STAGE KIDNEY DISEASE

THE IMPACT OF RENAL REPLACEMENT THERAPY MODALITIES

BY
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Infective endocarditis and *Staphylococcus aureus* bacteremia in patients with end-stage kidney disease

The impact of renal replacement therapy modalities

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“If your experiment needs statistics, you ought to have done a better experiment.”

- Ernest Rutherford.

Preface

This thesis was undertaken at the Department of Cardiology, Herlev-Gentofte Hospital. Countless individuals have contributed to the completion of this journey, and I owe my deepest gratitude to all.

Niels Eske Bruun convinced me to conduct my research in epidemiology in the field of endocarditis. He introduced me to the research department, PA Forskning, at Herlev-Gentofte Hospital and assembled a project group. I would like to thank Niels for his thoughtful considerations, for establishing the fundament of this thesis and for sharing his unlimited passion for microbes.

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Last but not least, I am deeply indebted and thankful to my family for the endless support, understanding and encouragement all the way through.

Mavish Safdar Chaudry, 2018

Abbreviations

ATC	Anatomical Therapeutic Classification
CVC	Central venous catheter
ESKD	End-stage kidney disease
HD	Hemodialysis
ICD	International Classification of Diseases
IE	Infective endocarditis
KT	Kidney transplanted
NCSP	Nordic-Medical Statistical Committee's Classification of Surgical Procedures
PD	Peritoneal dialysis
SAB	*Staphylococcus aureus* bacteremia
S. aureus	*Staphylococcus aureus*
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography
RCT	Randomized clinical trial
RRT	Renal replacement therapy

Papers

This thesis is based on the following original papers:

Paper I

Risk of Infective Endocarditis in Patients with End Stage Renal Disease

Clin J Am Soc Nephrol 2017 Oct 3.

Mavish Safdar Chaudry, Nicholas Carlson, Gunnar Hilmar Gislason, Anne-Lise Kamper, Marianne Rix, Vance Garrison Fowler Junior, Christian Torp-Pedersen, Niels Eske Bruun

(Enclosed in Appendix I)

Paper II

The Impact of Hemodialysis on Mortality Risk and Cause of Death in *Staphylococcus aureus* Endocarditis

Submitted to BMC Nephrology

Mavish Safdar Chaudry, Gunnar Hilmar Gislason, Anne-Lise Kamper, Marianne Rix, Anders Dahl, Lauge Østergaard, Emil Loldrup Fosbøl, Trine Kiilerich Lauridsen, Louise Bruun Oestergaard, Christian Hassager, Christian Torp-Pedersen, Niels Eske Bruun

(Enclosed in Appendix II)

Paper III

Increased risk of *Staphylococcus aureus* bacteremia in hemodialysis – a nationwide study

Submitted to BMC Nephrology

Mavish Safdar Chaudry, Gunnar Hilmar Gislason, Anne-Lise Kamper, Marianne Rix, Anders Rhod Larsen, Andreas Petersen, Paal Skytt Andersen, Robert Leo Skov, Emil Loldrup Fosbøl, Henrik Westh, Henrik Carl Schønheyder, Thomas Lars Benfield, Vance Garrison Fowler Junior, Christian Torp-Pedersen, Niels Eske Bruun

(Enclosed in Appendix III)

Summary

Patients with end-stage kidney disease (ESKD) have a high risk of infective diseases in part as a consequence of renal replacement therapy (RRT) modalities.

This dissertation aimed to investigate incidence and risk factors of infective endocarditis (IE) and *Staphylococcus aureus* bacteremia (SAB) in Danish ESKD patients by using nationwide Danish administrative registries.

Paper I investigated the incidence and risk factors of IE in different modalities of RRT during 1996-2012 in 10,612 ESKD patients. The main finding was an increased risk of IE in patients receiving hemodialysis compared with peritoneal dialysis patients. Central venous catheters (CVC) carried the highest risk in patients receiving hemodialysis. The risk of IE in patients with CVC (cuffed and uncuffed) was comparable. The initial 6 months of RRT carried a high risk of IE.

Paper II evaluated the mortality rate and cause of death in hemodialysis- and non-ESKD patients with *Staphylococcus* (S.) *aureus* endocarditis. The major finding was a similar in-hospital mortality rate in hemodialysis- compared with non-ESKD patients, whereas the mortality rate at one-year follow-up was higher in hemodialysis- compared with non-ESKD patients. The risk of all-cause- and cardiovascular mortality in patients receiving hemodialysis exceeded the risk in non-ESKD patients at more than 70 days and 81 days after admission with *S. aureus* endocarditis, respectively.

Paper III investigated the risk and incidence of SAB by hemodialysis vascular access types from 1996-2011 in 9997 ESKD patients. The primary finding was an increased risk of SAB in patients receiving hemodialysis compared with those receiving peritoneal dialysis. The risk of SAB was markedly increased in patients receiving hemodialysis with CVC. The SAB risk did not differ in cuffed- and uncuffed CVC. The initial 90 days of RRT with CVC carried the highest risk of SAB followed by arteriovenous fistula.

The main results of this thesis outline the high risk of IE and SAB in patients with ESKD. The findings emphasize the importance of increased awareness among health professionals of IE and SAB especially in the initial period of RRT.

Introduction

End-stage kidney disease and renal replacement therapy

End-stage kidney disease (ESKD) is the final stage of chronic kidney disease and is defined as a GFR below 15 ml/min per 1.73 m^2. At this stage, the renal capacity is insufficient to maintain the functions of the kidney. The main renal functions include the regulation of water-, acid- and electrolyte balance, blood pressure and bone mineral homeostasis. Additionally, the kidney contributes to the maintenance of the hematopoietic homeostasis by producing erythropoietin. The imbalance in these regulative mechanisms emerges at GFR below 60 ml/min per 1.73 m^2 and continues to deteriorate parallel to the decline in kidney function (1). At the last stage of chronic kidney disease, the disorders are severe and require renal replacement therapy (RRT) to continue life.

Diabetes is the predominant known reason to ESKD in Denmark followed by vascular and hypertensive causes. The proportion of patients progressing towards ESKD with diabetes as the underlying cause was 26% in 2016. Hypertensive and vascular causes accounted for 16%. Patients with an unknown etiology of ESKD attribute as well to a major part of emerging ESKD cases. The proportion has been stable over the last decade and represented 17% in 2016 (2).

In Denmark, patients with ESKD are provided government-supported RRT, which includes hemodialysis (HD), peritoneal dialysis (PD), pre-emptive kidney transplantation and kidney transplantation (KT) after initiation of dialysis. The decision to initiate RRT relies on the physician and is based on individual evaluation of the ESKD patient. The Danish ESKD population of RRT recipients consisted of 5363 patients in 2016. Of these, 2566 (48%) were in maintenance dialysis and 2797 (52%) had a functioning KT. The annual number of chronic kidney disease patients progressing towards ESKD requiring RRT was 703 in 2016. This proportion has been stable over the last decade (2). The majority of these patients received HD as the initial RRT modality, followed by PD and pre-emptive kidney transplantation. In most cases, the establishment of a vascular access is easier to facilitate and apply than a peritoneal catheter. The availability of kidney donors, pre-emptive, is sparse and consequently only a limited number of patients are transplanted pre-emptively.

ESKD patients receiving RRT are subject to change of RRT modality during the treatment course. These changes are either based on continuously individual evaluation by physicians, a consequence of complications second to the respective RRT modality or a sudden opportunity of receiving a KT. HD is initiated either by a cuffed central venous catheter (CVC), an uncuffed CVC, an arteriovenous fistula or an arteriovenous graft. The uncuffed CVC is a temporary vascular access and serves primarily as a bridge therapy to cuffed CVC at immediate initiation of HD. The insertion of an uncuffed CVC is easier to facilitate than a cuffed CVC, which requires expertise. The cuffed CVC is a bridge device to maturation of arteriovenous fistula or a final option in patients with no possibilities of establishing an arteriovenous fistula. The CVCs are associated with certain complications, which result in replacement of the CVC or switch in treatment modality primarily from cuffed CVC to uncuffed CVC in order to maintain the vascular access. The complications related to CVC use include the development of infection, thrombosis and vascular stenosis (3;4).

The arteriovenous fistula is the vascular access of choice for HD. It requires a surgical procedure and consists of an end-to-end arteriovenous anastomosis. The maturation time of an arteriovenous fistula is two to four months and necessitates in meanwhile bridging with CVC if immediate HD is needed. The arteriovenous fistula may be subject to maturation failure, which prolongs the period with CVC use. Infection, thrombosis and steal syndrome are few of the related complications to arteriovenous fistula, which result in temporary use of CVC (5).The arteriovenous graft is a prosthetic vascular access applied in patients with fragile vessels. This vascular access type is complicated with a high frequency of infection, thrombosis and stenosis compared with arteriovenous fistula (6).

PD treatment is facilitated by a catheter inserted into the peritoneal cavity. The catheter is ideally applicable for dialysis two to four weeks after insertion and HD may be a temporary necessity. CVC is easy to facilitate and is commonly applied as the temporary vascular access. A major cause of technique failure that can occur during PD treatment is peritonitis, which can lead to temporary switch to HD with CVC as vascular access (7;8). Pleuroperitoneal communication and encapsulating peritoneal sclerosis are few of the rare issues associated to PD treatment, which result in temporary and permanent switch to HD, respectively (9;10).

KT patients are at risk of graft failure. The most common cause of graft loss is patient death followed by chronic allograft nephropathy in KT patients. Few less frequent causes are graft rejection, glomerulonephritis and BK nephropathy (11). Graft loss necessitates institution of RRT with either HD or PD.

Hence, shifts in modality of RRT is common within the ESKD population, and many of these shifts are acute or subacute leaving HD with CVC, as the rescue treatment.

Infection and immune dysfunction

Infective diseases are the second leading cause of death in patients with ESKD receiving RRT (12;13). The proportion of death caused by infective diseases was 11% in a large European population of ESKD patients treated with RRT (13). Access-related infection, pneumonia and urinary tract infection remain the most common infections in patients on dialysis (14). The predominant infections in KT recipients are urinary tract infection followed by pneumonia (15). As the renal disease progresses and the renal function declines, various solutes accumulate in the body. These retained solutes are called uremic toxins and are considered to contribute to immune dysfunction (16). Patients with ESKD receiving RRT are disposed to infections and the impared immune system second to uremic toxins is a contributing factor.

Cardiovascular disease

Cardiovascular disease remains the leading cause of death in patients with ESKD and responsible for 24% of deaths in a recent European study with ESKD patients (13). The frequency of vascular calcification in patients with ESKD is high and is presumed to contribute to cardiovascular disease (17;18). Risk factors of vascular calcification include dialysis vintage, diabetes, aging and mineral disorders (19). In addition to cardiovascular disease, chronic kidney disease patients are at increased risk of contracting stroke and developing peripheral artery diseases as the renal disease progresses (20;21). Moreover, heart valve diseases are common in dialysis patients with thickening and calcification of the valves (22;23). The most severely affected heart valves include

the aortic- and mitral valves (22;23). The valvular degenerations evolve at younger age in dialysis patients than in those without chronic kidney disease (24;25). Duration of dialysis treatment, age and calcium-phosphate disorders may in part explain the deformation of the heart valves (23;24). The gradual calcification of the aortic- and mitral valves may render these susceptible to the development of infective endocarditis (IE) (22;24).

Infective endocarditis

IE is an infection with serious morbidity and mortality with an incidence rate of 8-10/100,000 person-years in the general Danish population (26-29). In Denmark, the most common microbiological causes of IE are streptococci- and staphylococci species followed by enterococci species (26). Stroke, heart failure and metastatic infections are serious and common complications of IE (29). The IE diagnosis is confirmed with imaging techniques as echocardiography. Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) are both techniques applied in the diagnosis of IE. However, TEE is superior to TTE in detecting IE. The sensitivity of identifying vegetations on native valves is 96% for TEE and 70% for TTE. Moreover, TEE is superior to TTE to rule out small vegetations on the valves and paravalvular pathology (30).

The incidence rate of IE is high in dialysis patients. The incidence rate of IE in a US ESKD population was 483/100,000 person-years in HD and 248/100,000 person-years in PD (31). The most frequent cause of IE in HD is *S. aureus* followed by coagulase-negative staphylococci-, enterococci- and streptococci species (32-36). The risk of IE in KT compared with PD is unexplored.

Existing data on the occurrence of IE, classified by HD vascular access, are limited to the vascular access types with IE cases of 17-150 patients (32-40). Thus, incidence rates and risk factors of IE related to each vascular access of HD with time-updated RRT modalities in patients with ESKD remain to be resolved.

IE remains a contributor to mortality in HD patients (31-38;41-43). Depending on the study population, the in-hospital mortality rates subsequent to IE ranged from 14%-52% in HD patients (32;36;37;43). The one-year mortality rate was 56% in a single center study in 32 cases of IE among 2239 HD patients (33). Septic embolism and mitral valve disease are recognized as

mortality risk factors (35). Neither of these aforementioned studies determined cause of death and mortality risk factors of *S. aureus* endocarditis in a nationwide population of HD patients compared with a non-ESKD population.

Staphylococcus aureus **bacteremia**

The incidence rate of *Staphylococcus aureus* bacteremia (SAB) in the Danish general population was 0.035/100 person-years in 2015 (44). The incidence rate of SAB has been increasing steadily during the past several decades. The recent rise in SAB cases has been attributed to the elderly population. SAB contributes to severe secondary infective complications. In Denmark, the most frequent infections second to SAB include IE followed by spondylitis and prosthetic infections (44).

Bacteremia is a complication in patients with ESKD receiving RRT. The most prevalent isolated microorganisms in Danish PD patients were Escherichia coli and *S. aureus*. Peritonitis followed by urinary tract- and respiratory tract infections were the most common infections in these PD patients (45). The distribution of bacteria in relation to bacteremia in patients with KT differs from dialysis patients and correlate with the most prominent location of infection. The urinary tract system is the most frequent location of infection in patients with KT and as a result of this; Escherichia coli and Klebsiella pneumonia are the most common isolated microorganisms (15;46;47).

In patients with HD, bacteremia is a consequence of repeated access to the vascular system along with uremia related suppression of the immune system and the acquired local granulocyt defect at the access site (16;48). SAB is frequent in HD patients and leads to infections with severe morbidity and mortality (49-63). Although, the CVCs (cuffed and uncuffed) are well-established causes of bacteremia (61;64), the incidence rate and risk factors of SAB, classified according to each HD vascular access has not been investigated with time-updated HD vascular access.

Objectives

The present thesis focused on the analyses of IE, SAB and outcomes in ESKD patients with established RRT with the following objectives:

Paper 1

To examine the incidence rate and risk factors of IE in a nationwide ESKD population treated with RRT.

Hypothesis: The risk of IE is increased in HD compared with either PD or KT.

Paper 2

To examine the mortality risk and cause of death subsequent to *S. aureus* endocarditis in a nationwide population of HD patients compared with a non-ESKD population.

Hypothesis: The long-term mortality rate is higher in the HD population with *S. aureus* endocarditis compared with the non-ESKD population with *S. aureus* endocarditis.

Paper 3

To examine the incidence rate and risk factors of SAB in ESKD patients receiving RRT with focus on the type of HD vascular access.

Hypothesis: The incidence rate of SAB is higher in patients with CVC as HD vascular access than other RRT modalities.

Materials and methods

Denmark possesses nationwide administrative registries that provide a variety of variables pertaining health care status at an individual level. The Danish Civil Registration System assigns each residence at birth or immigration a unique personal identification number that is used in all nationwide registries and allows linkage between these registries at an individual level (65). The studies in this thesis used a number of these registries.

Data sources

1) The Danish National Patient Registry was established in 1978 and holds information on diagnoses and surgical procedural codes. Each inpatient admission and outpatient consultation is at discharge or end of appointment registered with one primary and one or more secondary diagnoses according to the International Classification of Diseases revision 8th (ICD-8), replaced by ICD-10 from 1994 onwards (66). The codes used to assess Charlson comorbidities are considered valid (67). The surgical procedural codes are registered in accordance to the Nordic-Medical Statistical Committee's Classification of Surgical Procedures (NCSP).
2) The Register of Medicinal Product Statistics contains information on every purchased prescription since 1995 on date of purchase, content and amount coded by the Anatomical Therapeutic Classification system (ATC). Redeemed prescriptions are partially reimbursed and therefore an incentive to record purchased pharmacotherapy at individual level is present. The data quality of the registry is considered high (68).
3) The Danish National Registry on Regular Dialysis and Transplantation holds information on all Danish ESKD patients in RRT (HD, PD and KT) including change in treatment modality, since 1990. ESKD patients are registered after at least three months in RRT. The registry has a completeness of more than 97% compared with the Danish National Patient Registry as reference standard (69).
4) The Danish Registry of Cause of Death includes information on each occurring death in Denmark on individual level since 1970, coded according to the ICD-10 from 1994 onwards (70).
5) The Danish Civil Registration System was established in 1968 and includes information on birth date, gender and vital status on individual level (65).

6) The East Danish Database on Endocarditis enrolled patients diagnosed with IE prospectively from October 1st, 2002 to December 31st, 2012 at two referral tertiary heart centers (Rigshospitalet and Gentofte Hospital). The diagnosis of IE was based on the revised Duke criteria (71). The database contains more than 250 variables (e.g. microbiology, echocardiography, and clinical data) (72).
7) The SAB Database is nationwide and located at Statens Serum Institut. This database was established in 1956 and contains information on more than 94% of SAB cases in Denmark, referred from all Danish Departments of Microbiology (44).
8) The Departments of Microbiology provided information on the causative microorganism of IE.

Ethics and data protection

The studies were approved by the Danish Data Protection Agency (ref. 2007-58-0015 / internal ref. GEH-2014-015 I-suite no. 02733). Ethical approval is not required for registry based studies in Denmark. The data is encrypted and accessed via a secured server located at Statistics Denmark.

Study population

Paper I & Paper III

From The Danish National Registry on Regular Dialysis and Transplantation, we identified all ESKD patients initiating and changing RRT (HD, PD, pre-emptive KT, KT) between January 1st 1996 and December 31st 2012. In paper III, the cohort was only followed until December 31st 2011.

To allow changes in treatment modalities during follow-up, procedural codes pertaining HD vascular access and peritoneal catheter were obtained from The Danish National Patient Registry, Table 1. In addition in paper I, procedural codes for heart valve surgery were retrieved, Table 1. The Danish National Registry on Regular Dialysis and Transplantation and the procedural codes extracted from The Danish National Patient Registry on RRT modalities were merged, enabling patients to change treatment modality during follow-up (e.g. patients in PD could change to KT

during follow-up and add risk time to more than one RRT modality). Patients receiving RRT with PD and HD concurrently before switching to HD permanently were treated as HD patients. These data were assessed manually in cooperation with two independent nephrologists.

From The Danish National Patient Registry, we assessed comorbidities up to 5 years prior to index until event of interest, death or study end, whichever came first. The purchase of glucose-lowering drug prescriptions obtained from The Register of Medicinal Product Statistics was used as a proxy for a diabetes mellitus diagnosis (Appendix I, Supplemental Table I). The ATC codes of glucose-lowering drugs have been applied as a proxy for the diagnosis of diabetes mellitus in a recent study (73).

Paper II

We retrospectively identified a HD population from The Danish National Registry on Regular Dialysis and Transplantation between January 1st, 1996 and December 31st, 2012 and included each patient at the first episode of IE with *S. aureus* after initiation of RRT. The diagnosis of IE was identified in The Danish National Patient Registry with the ICD-10 codes I33 and I38. Data on microbiology was collected from Departments of Microbiology. Information on valve involvement and echocardiography was obtained from medical records.

From The East Danish Database on Endocarditis, we identified a non-ESKD population with *S. aureus* endocarditis. Patients receiving temporary HD following acute kidney failure during admission were not excluded, Table 1.

Comorbidities were identified from The Danish National Patient Registry in a period of 5 years before inclusion.

Table 1. List of procedural codes

	*NCSP
Hemodialysis vascular access	BMBZ51A, BMBZ51B, BMBZ51D, BMBZ51F, BMBZ61, BMBZ61A, BMBZ71, BMBZ71A, KBPL, KBPL10, KBPL10A, KBPL20, KBPL20A, KBPL30, KBPL30A, KBPL99
Peritoneal catheter	BJFZ45
Acute dialysis	BFJD00, BJFD01, BJFD02
Heart valve surgery	KFG, KFK, KFM, KFJE, KFJF

*NCSP Nordic-Medical Statistical Committee's Classification of Surgical Procedures

Outcome

The thesis was based on following end points

Paper I

The first episode of IE after initiation of RRT was the end point of interest in paper I (ICD-10 codes I33 and I38).

Paper II

The main outcome in paper II was all-cause mortality, subdivided into cardiovascular- and non-cardiovascular death (Appendix II, Supplemental Table III). The cause of death was considered cardiovascular, if at least one of the diagnoses on the death certificate were cardiovascular (ICD-10 I-diagnoses).

Paper III

The end point in paper III was first time SAB after initiation of RRT.

Statistical analyses

In all papers, continuous variables were reported as mean±standard deviation. Differences in continuous variables and categorical variables were tested with Kruskall-Wallis test and Chi-squared test, respectively. Fisher's exact test was applied when expected frequency in the cells was <5 in paper II.

SAS version 9.4 (SAS institute, Cary, NC, USA) was applied for statistical analyses. Two-sided p-value <0.05 was considered statistically significant.

Paper I

The incidence rate of IE was estimated for the entire cohort of ESKD patients and each RRT modality based on number of events divided by risk time added to each respective RRT modality /100,000 person-years. The relative time in CVC was calculated based on the proportion of time spent in CVC divided by the entire time spent in RRT in time band of one year by calendar year. The Cox regression model was used in a time dependent manner to assess the association between each RRT modality and the outcome, IE, and to identify independent risk factors. The RRT modality was time-updated, allowing patients to change treatment modality during follow-up and add risk time to more than one treatment subset. Comorbidity (mitral-, aortic valve disease and diabetes) entered this model and was updated as noted. Diabetes was updated as glucose-lowering drug was purchased. Furthermore, this model was adjusted for calendar year, which was split in bands of five years. Time spent in RRT was added to the model and split in three time periods at 183 days- and at 845 days after initiation of RRT, according to the first two quartile distribution of outcome. Gender and IE prior to RRT was applied and age was used as the underlying time-scale. Interaction was assessed between RRT modalities and the covariates added to the model and found valid except from age. Age-stratified analysis was performed to assess the interaction.

Cochrane-Armitage time trend test was used to assess the trend in the incidence of ESKD patients and IE across the study period.

Paper II

Cox regression model was applied to examine time from *S. aureus* endocarditis until death (all-cause mortality, cardiovascular death and non-cardiovascular death) or study end. The hazard ratio between the exposures (HD and non-ESKD) varied over time (violation of proportional hazard assumption) and entered therefore the model in categorical time periods of below 20 days, 20-70 days and at least 71 days for the outcome, all-cause mortality, and in time periods of below 26 days, 26-81 days and at least 82 days for the outcome, cardiovascular death. These periods represented the first- and second quartile distribution of outcome. The model was adjusted for gender, age and diabetes mellitus. Time from *S. aureus* endocarditis to death or study end was applied as the underlying time-scale in the model. The cumulative incidences were assessed for all-cause mortality and for each of the end points; cardiovascular- and non-cardiovascular death accounting for competing risks of death.

Ten HD patients changed RRT modality during the study period. Sensitivity analyses were performed excluding these patients. The hazard ratios and cumulative incidences remained unaltered.

Paper III

The incidence rate of SAB was calculated for the entire cohort of ESKD patients and for each RRT modality. The number of cases in each RRT modality was divided by the time spent in the RRT treatment groups. Poisson regression was used to determine the association between the various modalities of RRT and SAB. The RRT modalities entered the analysis time-updated, enabling patients to change treatment group and add risk time to more than one group during follow-up. Age, gender and comorbidity (diabetes mellitus, mitral- and aortic valve disease) were included in the model. Comorbidity was split at the time it was noted. Diabetes mellitus was noted at redemption of prescription. Age was split in bands of one year and calendar time entered the model in time-bands of five years. The time spent in RRT was split in time bands of three periods at 90 days- and at >270 days after initiation of RRT. The second split represented the second quartile distributed according to outcome. Test for interaction between RRT modalities and the covariates were found valid except from time spent in RRT. Stratified analysis of time spent in RRT

was performed to assess the interaction. Moreover, trend test was performed to examine the incidence of SAB during the study period.

Main results

Summary of main results and conclusions from the studies are presented in the subsequent section of the thesis. For further details, the papers I-III on which the thesis is based, are referred in appendix I-III.

Paper 1

A total of 10,612 ESKD patients initiated RRT in the period January 1st 1996 to December 31st 2012. The initial population comprised 7233 HD patients (68%), 3056 PD patients (29%), and 323 pre-emptive KT (3%). First time IE during ESKD treatment with RRT occurred in 267 patients across the study period, Table 1. The incidence rate of IE was remarkably higher in HD patients than PD- and KT patients, Table 1. The incidence rate of IE was highest in patients with CVC (cuffed and uncuffed) as vascular accesses in HD, Table 1. The risk of IE was increased in patients receiving HD especially with CVC compared with PD patients, Table 1. There was no difference in the risk of IE between uncuffed CVC compared with cuffed CVC, HR 1.40 (95% CI 0.89-2.21). The first six months in RRT, aortic valve disease and IE prior to RRT were independently associated to IE, Table 1.

The in-hospital mortality and one-year mortality subsequent to IE and heart valve surgery was elevated in HD patients compared with PD- and KT patients, Tables 2 & 3.

The increase in incident cases of IE during the period 1996 to 2012 in patients with ESKD compared with the increase in the incidence of ESKD patients, adjusted for the general population, was significant, Figure 1.

The proportion of time spent in CVC increased across the study period. Patients above 70 years comprised a larger percentage of the relative time in CVC, Figure 2.

In conclusion, we observed an increased risk of IE in HD patient compared with PD patients. The risk of IE was in particular increased in HD patients treated with CVC. We identified the first six months in RRT, aortic valve disease and IE prior to RRT as independent risk factors of IE.

Table 1. Risk factors of infective endocarditis in end-stage kidney disease patients receiving renal replacement therapy

Parameter	Number of events	Unadjusted incidence rate/100,000 person-years	Hazard Ratio (95% Confidence Interval)
Renal replacement modality			
[*] Uncuffed CVC	39	3053	14.10 (7.76-25.50)
[*] Cuffed CVC	39	2099	10.03 (5.52-18.24)
Arteriovenous fistula	138	874	4.59 (2.73-7.73)
Arteriovenous graft	1	570	3.19 (0.42-24.26)
Unknown hemodialysis access	24	809	3.67 (1.94-6.94)
Hemodialysis	241	1092	5.46 (3.28-9.10)
Kidney transplant	10	85	0.41 (0.18-0.91)
Peritoneal dialysis	16	212	1.00 (reference)
Renal replacement therapy periods			
[†] Renal replacement therapy period 1	67	1353	1.89 (1.37-2.60)
[†] Renal replacement therapy period 2	67	501	0.80 (0.59-1.10)
[†] Renal replacement therapy period 3	133	549	1.00 (reference)
Comorbidity			
Diabetes mellitus			
1	102	817	1.12 (0.87-1.45)
0	165	549	1.00 (reference)
[‡] Endocarditis			
1	20	17321	22.24 (13.50-36.62)
0	247	581	1.00 (reference)
Aortic valve disease			
1	41	2139	2.65 (1.68-4.18)
0	226	556	1.00 (reference)
Mitral valve disease			
1	20	1757	1.38 (0.71-2.70)
0	247	596	1.00 (reference)

** CVC central venous catheter*

† Renal replacement period 1: First 183 days in renal replacement period, Renal replacement period 2: 184-845 days in Renal replacement period, Renal replacement period 3: >845 days

‡ Before initiation of renal replacement therapy

§ Model adjusted for sex, age, diabetes, aortic valve disease, mitral valve disease, previous endocarditis, calendar year, renal replacement periods (<183 days-, 184-845 days- and >845 days in renal replacement therapy).

Table 2. Mortality subsequent to infective endocarditis

Renal replacement therapy	In-hospital	1-year including in-hospital
Overall	58 (22%)	135 (51%)
Hemodialysis	53 (20%)	124 (46%)
Peritoneal dialysis	4 (2%)	8 (3%)
Kidney transplant	1 (0.3%)	3 (1%)

**Values are given as N (%)*

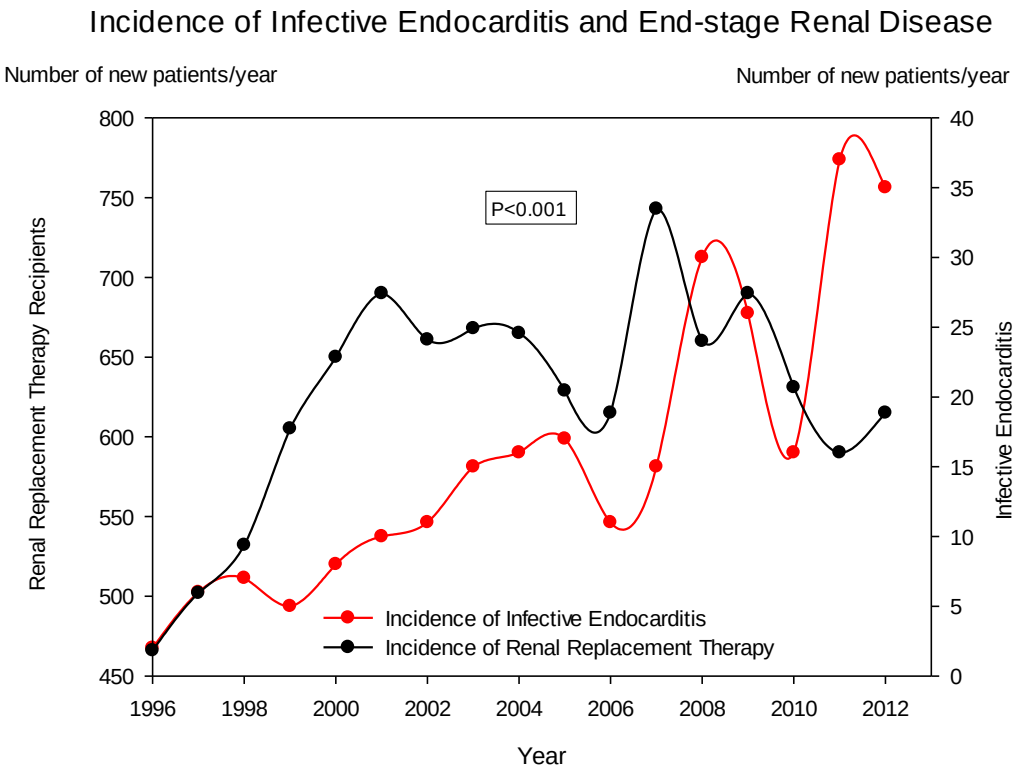
Table 3. Heart valve surgery and mortality

	Heart valve surgery					Mortality	
Renal replacement therapy	**Total**	**Aortic valve**	**Mitral valve**	**Pulmonic valve**	**Mitral- and aortic valve**	**In-hospital**	**1-year including in-hospital**
Total	31	11	15	1	4	5 (16%)	12 (39%)
Hemodialysis	28	10	17	1	3	4 (14%)	10 (36%)
Cuffed CVC	1	-	1	-	-	-	-
Uncuffed CVC	7	2	5	-	-	-	-
Arteriovenous fistula	17	8	7	1	1	-	-
Unknown vascular access	3	-	1	-	2	-	-
Peritoneal dialysis	1	-	1	-		-	1 (100%)
Kidney transplant	2	1		-	1	1 (50%)	1 (50%)

**Values are given as N (%)*

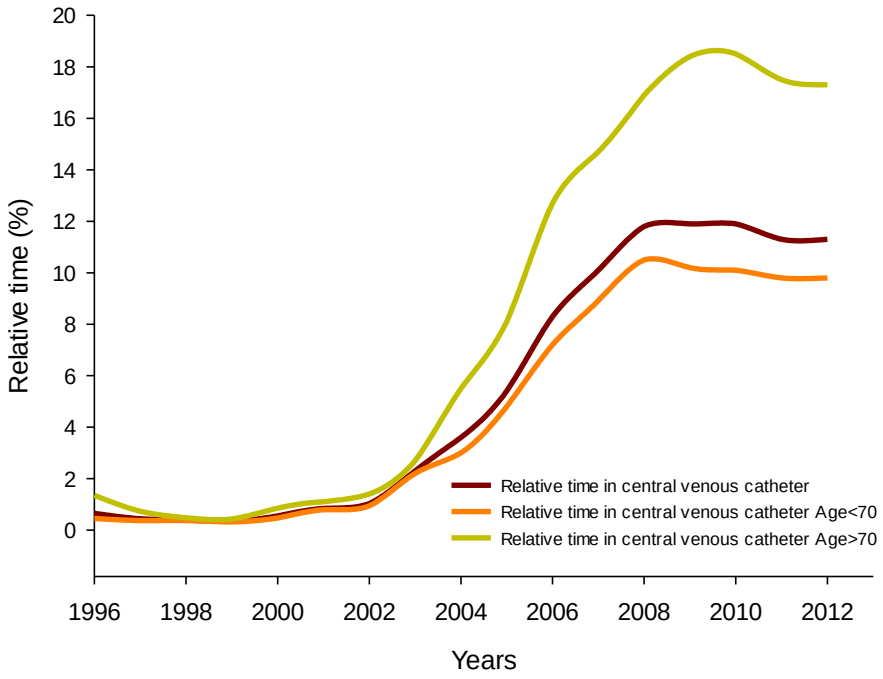
†CVC central venous catheter

Figure 1.



**The p-value refers to the significant increase in incidence cases of IE compared with the increase in incidence of ESKD patients, adjusted for the general population.*

Table 3. Relative time in central venous catheter across the study period 1996-2012



**Relative time in CVC as percentage of time in RRT by calendar year*

Paper 2

A total number of 121 HD patients with first time IE after initiation of RRT, if *S. aureus* endocarditis, were identified from 8791 patients in HD. From the East Danish database on Endocarditis, 190 non-ESKD patients with *S. aureus* endocarditis were identified among 977 patients with IE. During admission, 31 non-ESKD patients developed acute kidney failure and received temporarily HD.

The all-cause in-hospital mortality subsequent to *S. aureus* endocarditis was similar in HD and non-ESKD patients, whereas the one-year mortality was significantly higher in the HD- compared with non-ESKD patient, Table 1.

After an initial period of similar all-cause mortality, cardiovascular death and non-cardiovascular death in HD- and non-ESKD patients, the risk of all-cause mortality and cardiovascular death in HD patients exceeded the risk in non-ESKD patients, Figure 1 & 2.

The risk of all-cause mortality increased significantly in HD patients compared with non-ESKD patients >70 days after admission, Figure 3. Age and diabetes mellitus were identified as independent risk factors. The cardiovascular risk of death was significantly elevated >81 days after admission in HD patients compared with non-ESKD patients, Figure 4. Age and diabetes mellitus were associated to cardiovascular death.

In conclusion, the all-cause in-hospital mortality for S. aureus IE in HD patients is similar to non-ESKD patients, whereas the one-year mortality is significantly higher in HD patients compared with non-ESKD patients. All-cause mortality and cardiovascular death increased significantly in HD patients compared with non-ESKD patient more than 70 days and 81 days after admission with S. aureus endocarditis, respectively.

Table 1. In-hospital- and one-year mortality subsequent to *Staphylococcus aureus* endocarditis

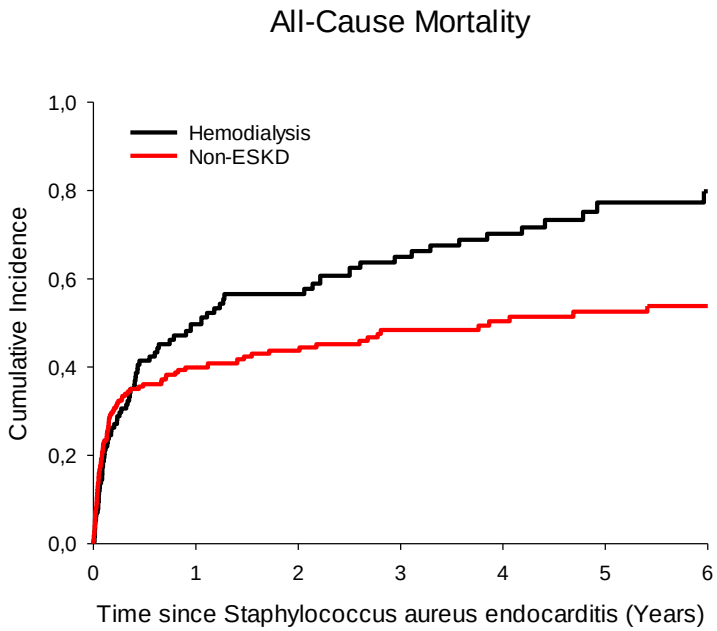
	In-hospital			1-year excluding in-hospital		
Cause of Death	**Hemodialysis**	**Non-ESKD**	**P value**	**Hemodialysis**	**Non-ESKD**	**P value**
	(n = 121)	**(n = 190)**		**(n = 121)**	**(n = 190)**	
All-cause	27 (22.3%)	47 (24.7%)	0.683	32 (26.4%)	29 (15.3%)	0.023
Cardiovascular	14 (11.6%)	26 (13.7%)	0.729	18 (14.9%)	17 (8.9%)	0.123
Heart failure	2 (1.7%)	7 (3.7%)		4 (3.3%)	10 (5.3%)	
Myocardial infarction	-	2 (1.1%)		2 (1.7%)	1 (0.5%)	
Stroke	3 (2.5%)	4 (2.1%)		4 (3.3%)	4 (2.1%)	
†Other	9 (7.4%)	5 (2.6%)		13 (10.7%)	3 (1.6%)	
Non-cardiovascular	13 (10.7%)	21 (11.1%)	0.932	11 (9.1%)	11 (5.8%)	0.298
Sepsis	10 (8.3%)	14 (7.4%)		5 (4.1%)	3 (1.6%)	
Respiratory failure	3 (2.5%)	2 (1.1%)		3 (2.5%)	1 (0.5%)	
ESKD	-	-		2 (1.7%)	-	
Diabetes mellitus	-	-		2 (1.7%)	1 (0.5%)	
Gangrene	-	-		-	1 (0.5%)	
Unknown	-	5 (2.6%)		-	5 (2.6%)	

**Values are given as N (%), - None*

†Aortic valve disease, mitral valve insufficiency, ventricular fibrillation, vascular hypertension, cardiac arrest, atrial fibrillation, unclassified cardiovascular cause of death subsequent to S. aureus endocarditis

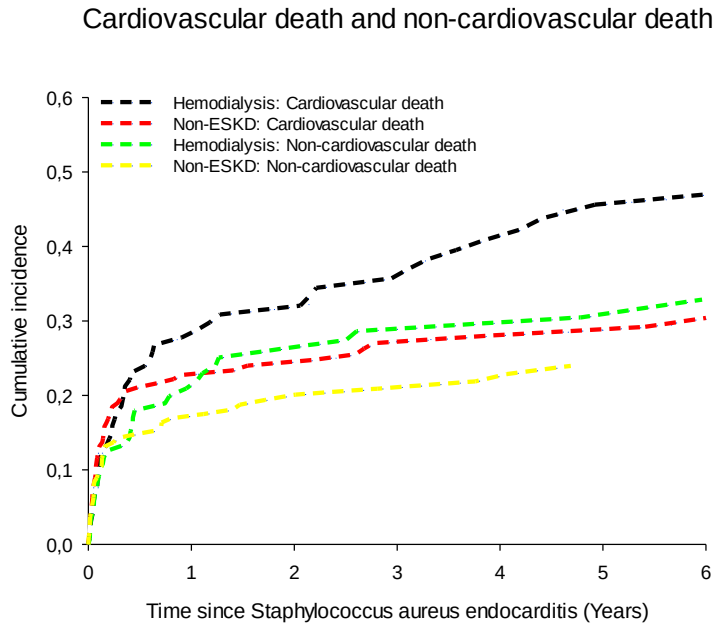
‡ESKD end-stage kidney disease

Figure 1. Cumulative incidence of all-cause mortality in hemodialysis- and non-ESKD patients



**Non-ESKD non-end-stage kidney disease*

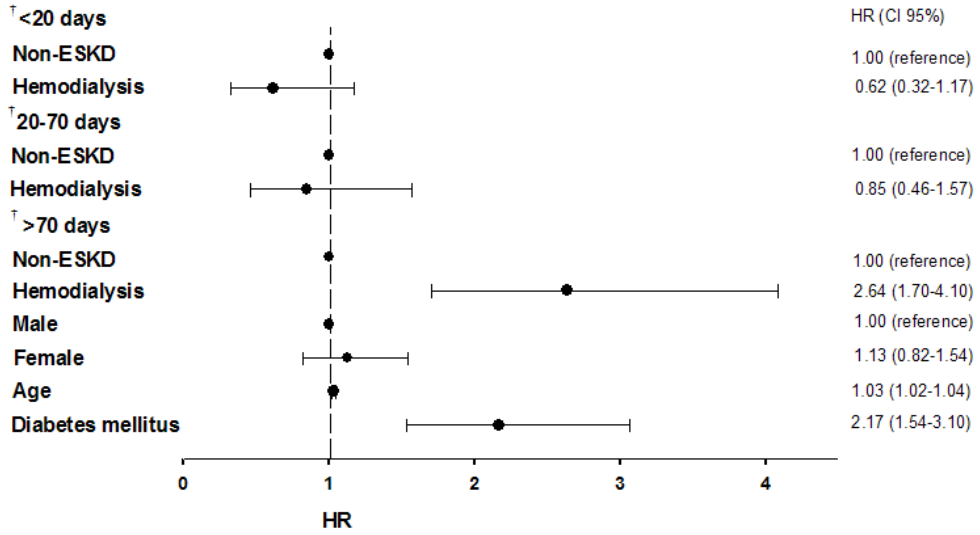
Figure 2. Cumulative incidence of cardiovascular- and non-cardiovascular death in hemodialysis- and non-ESKD patients



** The model is taking competing risks of death into account for each outcome*

† Non-ESKD non-end-stage kidney disease

Figure 3. Risk of all-cause mortality

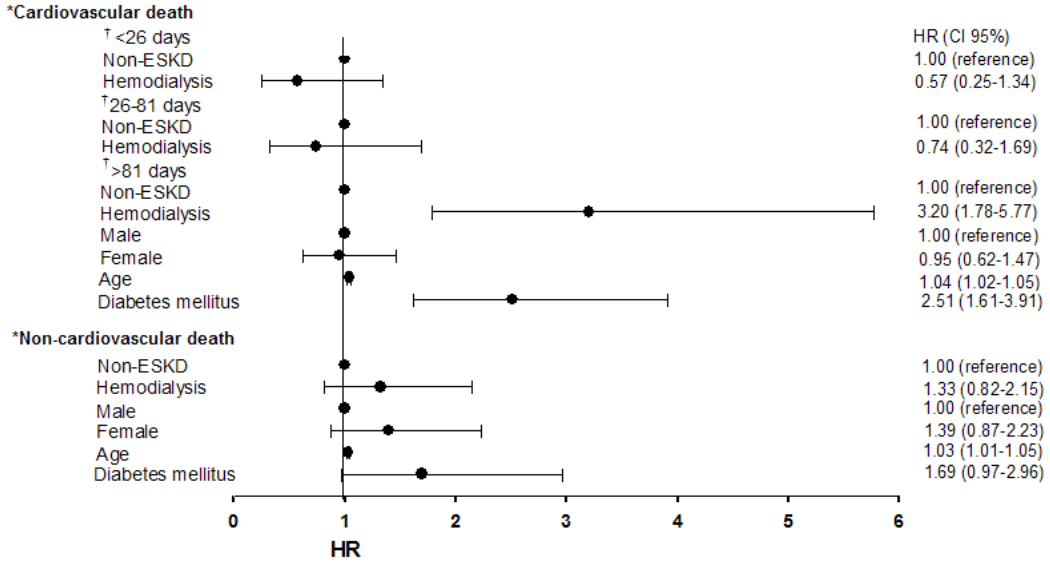


** Model adjusted for sex, age, diabetes mellitus and time since endocarditis to event or study end*

† Days after admission with S. aureus endocarditis

‡ HR Hazard Ratio, CI confidence interval, Non-ESKD non-end-stage kidney disease

Figure 4. Risk of cardiovascular death and non-cardiovascular death



* Models adjusted for sex, age, diabetes mellitus and time since endocarditis to event or study end

† Days after admission with *S. aureus* endocarditis

‡ HR Hazard Ratio, CI confidence interval, Non-ESKD non-end-stage kidney disease

Paper 3

In the period from 1996 to 2011, a total number of 9997 patients initiated RRT. HD patients represented 6826, PD patients 2882 and pre-emptive KT 289. A first SAB episode occurred 1278 times during the study period. The incidence of SAB was substantially higher in patients in HD than in PD and KT during the first 90 days of RRT. The incidence of SAB was highest in patients with CVC (uncuffed and cuffed) during the initial 90 days of RRT. The incidence rates continued to decline after 90 days in RRT and leveled off after 270 days, Figure 1.

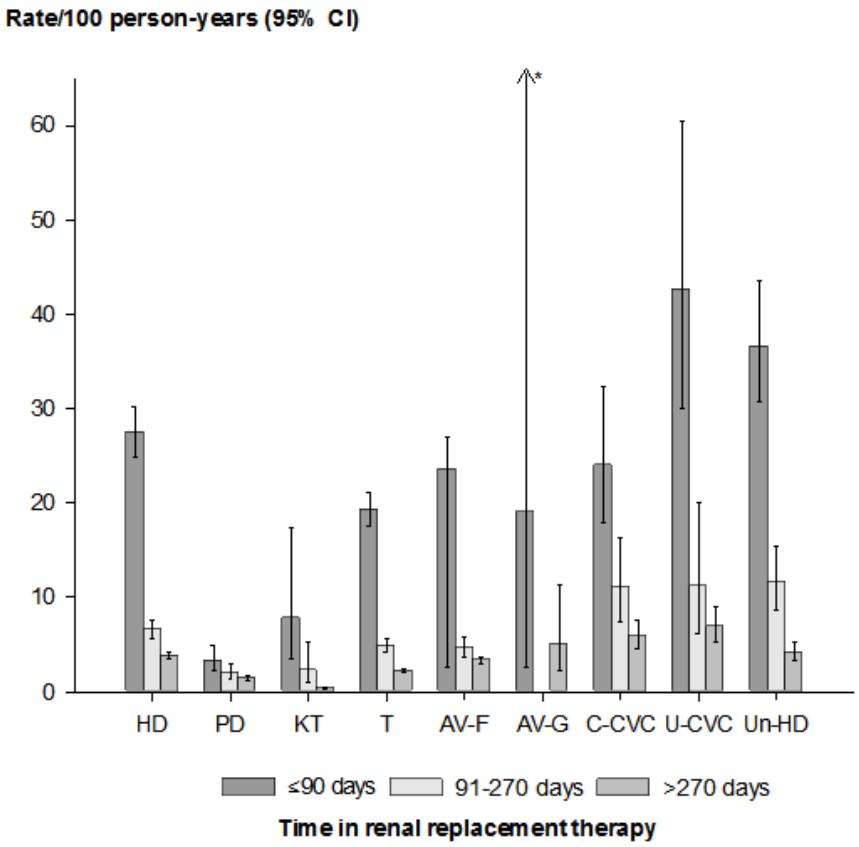
The risk of SAB was increased in HD patients particularly in patients with CVC compared with patients in PD. The difference in the rate ratio between uncuffed CVC compared with cuffed CVC was insignificant (RR 1.29 95% CI 0.99-1.69). The first three months in RRT, gender and diabetes mellitus were independently related to SAB, Figure 2.

The risk of SAB was increased in patients receiving HD. Patients with CVC (uncuffed and cuffed) carried the highest risk compared with PD patients during the first 90 days in RRT, Figure 2. The risk of SAB continued to decrease after 90 days in RRT**,** Figure 3.

The mortality in the initial 90 days was 5.6% and in the period between 91-270 days, 9.2%, in the ESKD patients after commencement of RRT.

In conclusion, the incidence rate of SAB was highest in patients with CVC (uncuffed and cuffed) among HD vascular accesses. The difference in risk of SAB was insignificant between uncuffed CVC compared with cuffed CVC. The first three months in RRT comprised a high risk period of SAB, especially in CVC. Diabetes mellitus and gender were identified as independent risk factors of SAB.

Figure 1. Incidence rate of *Staphylococcus aureus* bacteremia in end-stage kidney disease patient receiving renal replacement therapy modalities



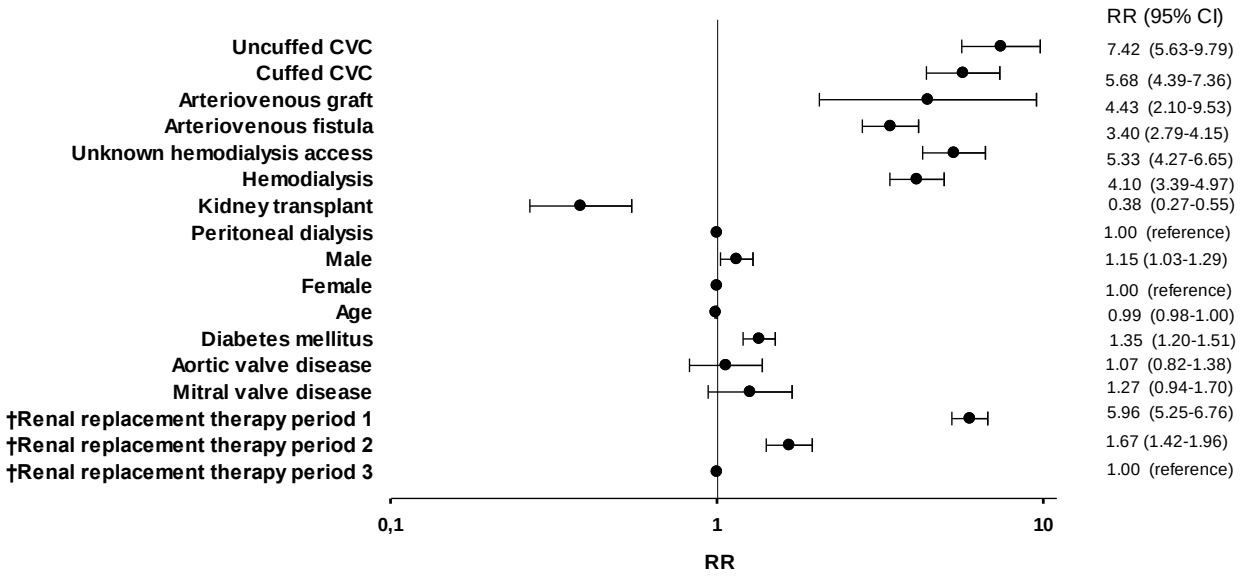
Rate/100 person-years

	HD	PD	KT	T	AV-F	AV-G	C-CVC	U-CVC	Un-HD
≤90 days	27.4	3.3	7.8	19.3	23.6	19.0	24.0	42.6	36.5
91-270 days	6.6	2	2.2	4.8	4.7	0	11	11.1	11.5
>270 days	3.8	1.4	0.3	2.2	3.4	5.1	5.8	6.9	4.1

**134.6/100 person-years*

HD Hemodialysis; PD Peritoneal dialysis; KT Kidney transplantation; T Total; AV-F Arteriovenous fistula; AV-G; Arteriovenous graft; C-CVC Cuffed central venous catheter; U-CVC Uncuffed central venous catheter; Un-HD Unknown hemodialysis; 95% CI 95% Confidence interval

Figure 2. Risk factors for *Staphylococcus aureus* bacteremia in patients receiving renal replacement therapy

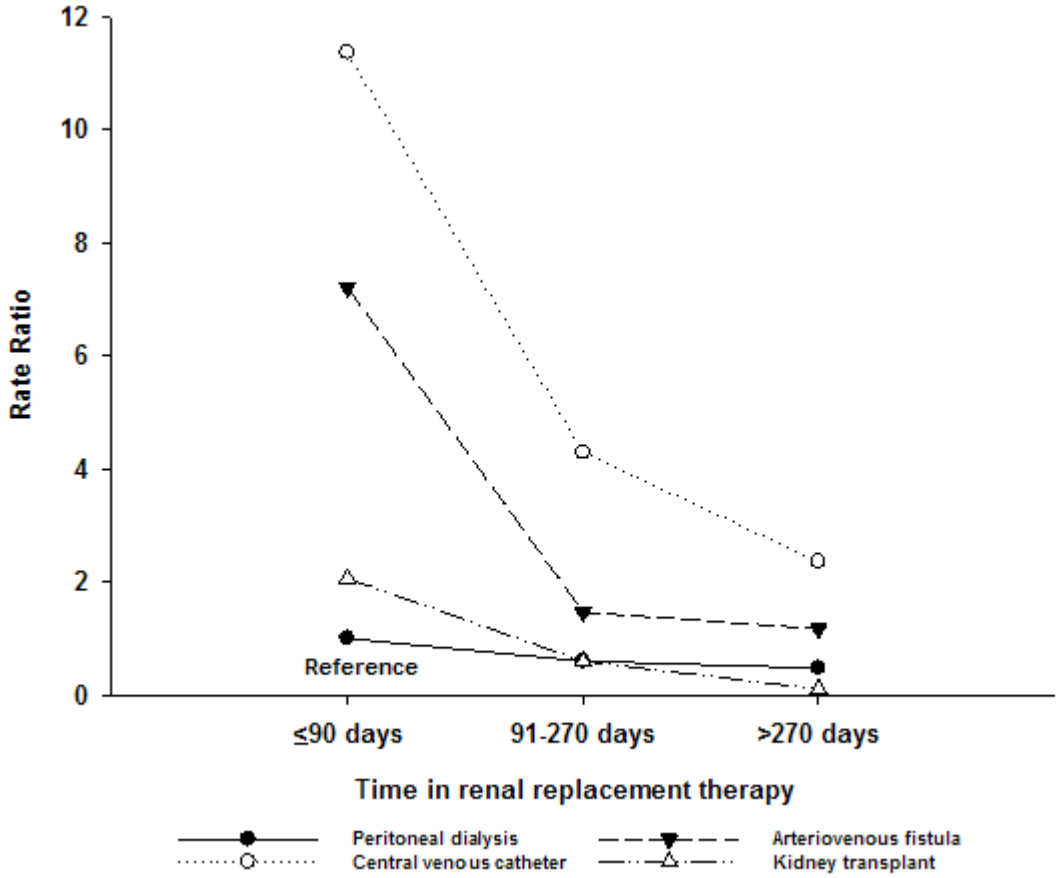


**Model adjusted for sex, age, diabetes mellitus, aortic valve disease, mitral valve disease, calendar time, renal replacement therapy periods (≤90 days-, 91-270 days- and >270 days in renal replacement therapy).*

†Renal replacement therapy period 1: First 90 days in renal replacement therapy, Renal replacement therapy period 2: 91-270 days in renal replacement therapy, Renal replacement therapy period 3: >270 days in renal replacement therapy to event, death or study end

‡ CVC central venous catheter, RR Rate ratio, 95% CI 95% Confidence Interval

Figure 3. Risk of *Staphylococcus aureus* in end-stage kidney disease patients receiving renal replacement therapy according to time in renal replacement therapy



Rate ratio (95% CI)

	Peritoneal dialysis	Central venous catheter	Arteriovenous fistula	Kidney transplant
≤90 days	1.00 (reference)	11.37 (7.09-18.22)	7.22 (4.69-11.10)	2.07 (0.84-5.08)
91-270 days	0.60 (0.34-1.06)	4.29 (2.53-7.27)	1.46 (0.92-2.33)	0.60 (0.23-1.57)
>270 days	0.48 (0.30-0.77)	2.36 (1.50-3.72)	1.17 (0.76-1.78)	0.11 (0.06-0.19)

**Model adjusted for sex, age, diabetes mellitus, aortic valve disease, mitral valve disease and calendar time*

95% CI 95% confidence interval

Methodological considerations

General considerations

The nationwide Danish registries have been maintained through decades. A number of these registries including diagnosis codes have been validated with useful results underscoring the applicability. Observational studies are based on these registries to investigate associations between defined exposure- and outcome variables. However, randomized clinical trials (RCT) remain the gold standard for establishing the causal relationship between cause and effect. The RCT is designed to eliminate bias if conducted appropriately. Although, RCT is the study design of choice, the research questions are limited to ethics. Moreover, strict selection criteria applied in RCT limit the generalizability. Conversely, observational studies are less expensive, easy to undertake, reflect natural settings and have a high generalizability. In addition, observational studies can be used to generate hypotheses and complement RCTs (74).

Multivariable regression models

Cox regression and Poisson regression are widely used to analyse time-updated data. The risk estimates provided from Cox regression and Poisson regression are hazard ratios and rate ratios, respectively. The Cox regression model is based on the hazard rate, which is the instantaneous incidence rate of an event of interest at any distinct point in time a subject has reached without contracting the event of interest or died of other causes. The hazard ratio is the ratio between the incidence rate of an event of interest of a treatment group relative to the reference group at any distinct point in time without contracting the event of interest or death and expresses the magnitude of difference between the groups. The hazards may change over time, but it is a basic assumption that the hazard ratio is constant – the proportional hazard assumption. The Poisson regression model is based on a basic assumption of constant incidence (hazard) in intervals of time. The length of time intervals can vary. The rate ratio is then the ratio between the rates in time intervals defined by a parameter of interest and reference time intervals. Cox- and Poisson regression are therefore rather similar. In the studies of this thesis, Cox regression model and

Poisson regression model were applied in a time-updated manner that allowed patients to change exposure variable during follow-up and add risk time to more than one exposure variable. Technically, this was performed by "splitting" the data for patients such that a new record was generated at each shift in exposure variable before entering the record into the regression models. Thus, the contributed risk time in each exposure variable was treated independently for each patient. Confounders, age and calendar year etc. were time-updated likewise during follow-up and each patient record was split at alterations in these variables as well resulting in a new patient record. These records were entered the regression models. Each patient record in a treatment group of interest is compared with a patient in the reference group with comparable characteristics in the regression models in order to adjust for confounders. However, residual confounding remains. The Cox regression model treats time-scales differently in the model, if more than one time-scale is investigated. In case of several time-scales, only one of the time-scales enters the regression model non-parametric, while additional time-scales are treated parametrical. The Poisson regression model treats all time-scales equally. The time-scales are split into discrete values and entered into the regression model. The regression models provide similar estimations and were applied in papers I-III.

Analyses of cumulative incidences

The probability of an event of interest at a certain point in time in living subjects can be analysed in several ways. The Kaplan-Meier estimates are widely used in survival analyses and provide estimations on the probability of an event in living subjects under the assumption that the remaining subjects in the analyses represent the censored observations. Thus, it is assumed that the censored subjects have the same survival possibility as those who remain in the analyses. Patients with competing risks are censored in the Kaplan-Meier estimator, which is inappropriate as the competing risk might be death – and it is unlikely that patients dying would have had the same risk as survivors had they stayed alive. Moreover, the rate of a competing risk has an impact on the probability of an event of interest. For this reason, the Kaplan-Meier estimates are up-ward biased and the results over-estimated, when substantial competing risk is present. Conversely, the Aalen-Johansen estimator calculates the cumulative risk of the event of interest while not having

the competing risk. This estimator provides a more likely estimation of the possibility of contracting the event of interest in living subjects as it is capable of accounting for competing risks. The risk of outcome variables was assessed with the Aalen-Johansen estimator accounting for competing risks of death in paper II.

Bias and confounding

Observational studies are susceptible to selection bias. This bias is a systematic error related to the initial study phase and introduced during selection of a study population different from the study population of interest. In the present thesis, all ESKD patients with established RRT were included in the study. ESKD patients are noted in the Danish National Registry on Regular Dialysis and Transplantation after a thorough review of each patient record by nephrologists affiliated to any given department of nephrology all over Denmark. The selection of eligible ESKD patients for heart valve surgery was based on individual evaluation by the present physicians as no guideline exists for such intervention in patients with ESKD. The presumed differences in selection of eligible ESKD patients might impact the mortality rate in the intervened- and non-intervened ESKD patients. Moreover, observational studies are subject to information bias that arises from measurement errors of exposure, covariate or outcome variables. The detecting of IE may have changed across the study period as imagination techniques have become more available and physician awareness has increased. ESKD patients with possible IE, who died before admission, were unable or refuted to undergo the necessary diagnostic examination might not have been registered with the IE diagnosis. As a result of this, the possibility of under-reporting might be present and therefore the rates of IE could be higher in patients with ESKD. In paper II, we applied the acute dialysis codes in order to find non-ESKD patients with acute kidney failure subsequent to *S. aureus* endocarditis, but the accuracy of these codes is unknown. We used discharge codes up to five years before index as the baseline characteristics. The accuracy of this method is uncertain as well.

A confounder is associated to the exposure and the outcome without being an intermediate in the causal pathway between exposure and outcome. In RCT, the randomly assignment of subjects to any given treatment arm, minimizes the imbalance of known and unknown confounders between the study groups. However, in observational studies, it is only possible to assess known

confounders, and residual confounding by unknown- and unmeasured confounders remains. There are various ways to reduce confounding in observational studies, i.e. restriction and matching. We adjusted for confounders by multivariable regression models.

Confounding by indication is inevitable in observational studies. It is introduced during selection of treatment based on preceding patient characteristic, which enacts as a confounder. The confounder is unmeasured and cannot directly be adjusted for. Therefore, RCT remains the superior methodology to manage this confounder by proper randomization.

Discussion

The present thesis investigated the occurrence of IE and SAB in patients with ESKD and outcome using nationwide Danish registries and the East Danish database on Endocarditis. The main findings were 1) Increased risk of IE in patients receiving RRT with HD and primarily in patients with CVC. In addition, the risk of IE was increased in the initial six months of RRT 2) Increased one-year mortality rate in HD patients with *S. aureus* endocarditis compared with non-ESKD patients with *S. aureus* endocarditis and 3) Increased risk of SAB in HD patients particularly in patients with CVC. Moreover, the risk of SAB was primarily increased during the initial 90 days of RRT. We consider these findings contribute to the present knowledge in the field of infective diseases in patients with ESKD.

In paper I, we investigated the relation between various modalities of RRT and IE. The major findings of the study were a higher incidence rate of IE in HD- and PD patients than in KT patients. The high incidence rate of IE in HD- and PD patients is in agreement with previous studies showing elevated occurrence of IE in HD- and PD patients (31;32;39;40;42). Abbott et al demonstrated in a historical cohort of 327,993 dialysis patients from 1992-1997, an incidence rate of IE in patients receiving HD of 483/100,000 person-years and in patients treated with PD of 248/100,000 person-years (31). In a recent study, Jones et al identified 42 episodes of IE in a retrospective cohort of 1500 dialysis patients at a single center during 1998-2011 (37). However, the association between RRT modalities and IE has not been established before with time-updated exposure variables, allowing patients to change treatment group not only at the level of RRT modalities (e.g. PD and KT), but also at the level of HD vascular accesses.

In the present study, patients treated with CVC carried the highest risk and incidence rate of IE among HD vascular accesses. This is in accordance with common belief, but this association has not been investigated in a large study previously (32-38;40). The present body of literature on the distribution of IE cases, on more than one HD vascular access, is limited to 17-69 cases of IE. The distribution of IE cases on HD vascular access has been reported at center level and varies according to center and location (32-38;40).

The observed high risk of IE in patients treated with HD and CVC in this study might be related to frequent bacteremia as a consequence of catheter infections and repeated access to the vascular

system (34;45;56;75-77). Taken together, these results advocate for arteriovenous fistula instead of CVC as the primary vascular access, which is in agreement with the guidelines from The Fistula First Initiative (78). These set of guidelines recommend arteriovenous fistula as the preferred vascular access for HD and reduced use of CVC to less than 10%.

In this study, we found no significant difference between cuffed- and uncuffed CVCs. This finding has not been presented before. Additionally, aortic valve disease was identified as an independent risk factor of IE subsequent to initiation of RRT in line with other studies (24;79). Moreover, we found that the first six months of RRT and IE prior to RRT were independently related to IE. We demonstrated an increase in IE across the study period concomitant with a progressively use of CVC among the elderly population. This might be a result of unrestricted access to RRT in the elderly population across the study period combined with fragile vessels (80)

The principal results of paper II demonstrated a similar all-cause in-hospital mortality rate in HD patients compared with non-ESKD patients subsequent to *S. aureus* endocarditis. The difference in mortality at one-year follow-up was significant between HD- and non-ESKD patients. The one-year mortality rate in HD remained high, whereas it decreased by one-third in non-ESKD patients. The risk of all-cause mortality and cardiovascular death in HD exceeded the risk in non-ESKD within three months after admission.

The in-hospital mortality in HD patients confirmed the in-hospital and thirty day mortality in previous smaller and larger studies concerning HD populations (32;34;37;40;43). Our result was slightly higher than a previous Danish study (39). One explanation might be that they included IE cases regardless of bacterial etiology. Importantly, neither of these studies were based on an isolated nationwide HD population of *S. aureus* endocarditis.

In a recent study, Hsiao et al found an equal, but higher rate of in-hospital mortality between HD- and non-ESKD patients diagnosed with IE (81). Hsiao et al included patients with TTE or TEE detected vegetation on heart valves, but only TTE results were presented. TEE remains superior in detecting small vegetations and complicated pathology as perivalvular abscesses (30;82). TEE has a sensitivity of detecting vegetations on native valves of up to 96%, whereas the sensitivity to identify vegetations for TTE is only 70%. Furthermore, the outcome in patients with complicated IE is lethal if treated conservatively (83). In our study, the percentage of TEE was high and a possible

difference in the proportion of TEE in the study by Hsiao et al could explain the deviation in mortality rate.

The annual mortality in the general Danish dialysis population was 15% in 2016 (2). The mortality is primarily related to cardiovascular death as the leading cause followed by infections, mainly due to HD vascular accesses (12;13). Despite of the high annual mortality rate in the general Danish dialysis patients, the mortality in HD patients subsequent to *S. aureus* IE was higher at one-year follow-up.

In the present study, HD patients were associated with increased risk of all-cause mortality and cardiovascular death at more than 70- and 81 days after admission compared with non-ESKD patients. Diabetes mellitus and age were independently associated with all-cause mortality, which is consistent with previous studies (35;43). In this study, ten HD patients switched treatment modality from HD to either PD or KT during the follow-up period. For this reason, sensitivity analyses were performed to validate these associations, which remained consistent.

The mortality was high at one-year follow-up in HD patients subsequent to *S. aureus* endocarditis compared with non-ESKD patients with *S. aureus* endocarditis. The risk of all-cause- and cardiovascular mortality increased in HD patients within three months after admission compared with non-ESKD patients.

In paper III, we assessed the relation between the different modalities of RRT with special focus on HD vascular accesses and SAB. The main findings were a high incidence rate of SAB in patients treated with HD compared with the other modalities of RRT and an increased risk of SAB during the initial 90 days compared with more than 270 days in RRT. The risk of SAB was increased in patients with CVC followed by patients with arteriovenous fistula in the first 90 days of RRT compared with PD patients. The risk decreased steadily within the first year of RRT.

The overall incidence rate of SAB in patients with RRT remained high during the initial 90 days of RRT (19.3/100 person-years) and after the initial 270 days of treatment with RRT (2.2/100 person-years). These rates of SAB are far above the incidence rate of SAB in the general Danish population (0.026/100 person-years) (44). This could be explained by circumstances characterizing ESKD patients in RRT. These patients have an impaired immune system possibly related to retained

uremic toxins, the vascular system is assessed repeatedly in HD patients, PD patients have a permanent catheter with daily access to the peritoneal cavity and KT patients are in continuous immunosuppressive therapy. Thus, this patient category is prone to infections (12-16;45;46).

The distribution of the incidence rate of SAB in patients with HD and PD was accordant with the distribution of the incidence rate of bacteremia in previous studies (84;85). Wang et al included retrospectively 366 HD- and 532 PD patients from a single hospital during 2003-2008 and identified 191 episodes of bacteremia. Wang et al found a higher incidence rate of bacteremia in HD patients than in PD patients, which is consistent with our findings for SAB (85). In a recent large US HD population, Nguyen et al found the highest incidence rate of bacteremia in CVCs and the lowest in arteriovenous fistula, which is in line with our distribution of SAB on HD vascular access (84). Conversely, neither of these studies included time-updated exposure variables or investigated bacteremia with primary focus on SAB.

Existing studies have shown ambiguous results on the risk of infection with cuffed- and uncuffed CVC, respectively (61;86;87). Two previous multicentre studies on outpatient HD patients, proposed a lower risk of infection in patients with cuffed CVC versus uncuffed CVC (86;87). Contrary to these studies, Taylor et al found no markedly difference between cuffed- and uncuffed CVCs in a multicentre population including 527 patients during 1998-1999 with 6 months follow-up for each patient (61). The present study found no significant difference in the risk of SAB between cuffed- and uncuffed CVC with time-updated follow-up of exposure variables.

The mortality rate after initiation of HD is generally high and decreases after the first few months of HD (88). We found a high initial mortality in the ESKD patients that decreased steadily within the first nine months of RRT. In patients initiating HD, cardiovascular disease and infections are the major causes of death (89). This might explain the decline in the risk of SAB in CVC and arteriovenous fistula within the first year of RRT as a possible result of continuous selection of less comorbid patients.

Strengths and limitations

The strengths of the studies in this thesis were the unselected ESKD population based on a validated registry, the high data quality of the pharmacotherapy and the outcome measure, SAB, and comorbidity codes from the maintained nationwide registries. In addition, all medical records for the HD population were reviewed in paper II to obtain information on microbiology, echocardiography and heart valve involvement. Furthermore, the non-ESKD population in paper II was based on a prospectively collected database. The establishment of a prospective database is time consuming and expensive, but the quality of the data is high and the collected variables are targeted towards the population of interest. The study populations in paper I, III and the HD population in paper II in the present thesis are historical and are limited to the observational design. The relation of causality cannot be established between exposure and outcome in observational studies, but it can be approached. Residual confounding remains. The confounder related to the treatment indication in observational studies is not measureable and cannot be adjusted for. However, observational studies are less expensive, reflects natural settings, easy to conduct and generalizable. In paper I, the incidence of ESKD patients in the last study years differed from the annual registry reports of The Danish Society of Nephrology. These reports are updated annually as new data are collected and available for preceding years. In paper I and III, we used procedural codes to obtain information on RRT accesses. These codes are not validated and misclassification especially concerning the cuffed- and uncuffed CVC cannot be avoided even though the codes were reviewed manually. We were not able to identify the HD vascular accesses in the unknown HD subset. This subgroup may likely reflect unclassified CVCs, since surgical procedure is required for arteriovenous graft and arteriovenous fistula, misclassification is less likely. The application of arteriovenous graft is limited in Denmark, which unfortunately leaves the estimations inconclusive. In paper II, we compared the HD population with a non-ESKD population. The non-ESKD population was enrolled at two tertiary referral heart centers, which limits the generalizability of the results. In paper I, we used codes to retrieve the outcome variable, IE. These codes have recently been validated with a positive predictive value of 82% (90). Finally, the end point (cause of death) in paper II was not validated in the Danish Registry of Cause of Death and in the meanwhile, the numbers of autopsies in Denmark have been on a decline and was less than 10% in 2011 (70).

Conclusion

The findings of the included studies in this thesis contribute to the present evidence in the field of IE and SAB in patients with ESKD receiving RRT.

Paper I and III concluded that the risk of IE and SAB was increased in patients with HD and CVC in a nationwide population of ESKD patients. The difference between cuffed- and uncuffed CVC was comparable for both of the outcomes. The risk of IE was increased in the initial six months of RRT and the risk of SAB in the first 90 days after initiation of RRT. In the stratified analysis, the risk of SAB decreased continuously after 90 days and was highest in CVC followed by arteriovenous fistula. These studies emphasize the importance of arteriovenous fistula as initial HD vascular access.

The main findings in paper II, were the increased 1-year mortality in HD patients compared with non-ESKD patients subsequent to *S. aureus* endocarditis and the increased risk of all-cause mortality and cardiovascular death in the HD- compared with the non-ESKD patients more than 70 days and 81 days after admission, respectively.

Future research

In paper II, we decided to investigate the outcome between HD- and non-ESKD patients subsequent to *S. aureus* endocarditis. The mortality rate between a matched baseline HD- and the HD *S. aureus* population could be investigated further in order to clarify whether *S. aureus* IE has a long-term impact on the baseline mortality rate in this population.

HD patients are in contact with the health care system at least thrice weekly, which disposes this population to health care related infections. Research covering the genotypes of *S. aureus* in the HD patients compared with community acquired SAB in a non-ESKD population need to be explored to identify the possible differences in virulence related to the genotypes and their impact.

The access and availability of a wide number of biochemical markers might allow investigation of possible associations between various pharmacotherapies applied in chronic kidney disease patients and their impact on biochemical markers. Relations between biochemical markers and

various end points are as well an area of future research with special focus on different stages of chronic kidney disease.

The path towards ESKD varies in patients with chronic kidney disease on individual level. The severity of complications in patients with ESKD is also patient dependent. In addition, the underlying cause of ESKD remains unknown in a large proportion of patients progressing towards ESKD. For these reasons, a national bio bank with blood samples of ESKD patients might assist in investigating different genetic traits and associations related to the adverse outcomes and complications of ESKD patients on individual level.

Dansk resumé

Patienter med kronisk nyresvigt i renal erstatningsterapi er i høj risiko for udvikling af infektioner blandt andet som følge af de forskellige behandlingsmodaliteter.

Denne afhandling havde til formål at kortlægge incidens og risikofaktorer for endokardit og *Staphylococcus aureus* bakteriæmi hos de danske kroniske nyresvigtspatienter i renal erstatningsterapi med udgangspunkt i landsdækkende registre.

Det første studie undersøgte incidens og risikofaktorer for endokardit i de forskellige typer af renale erstatningsterapier fra 1996-2012 blandt 10,612 patienter. Det primære fund var øget risiko for endokardit hos patienter i hæmodialyse behandling ved sammenligning med patienter, der modtog peritoneal dialysebehandling. Den højeste risiko for endokardit blev observeret blandt de patienter der blev hæmodialyseret med central venøse katetre efterfulgt af arteriovenøse fistler. Der var ingen signifikant forskel mellem patienter der blev hæmodialyseret med tunnellerede- og ikke-tunnellerede venøse katetre. Risikoen for udviklingen af endokardit var højest i de første 6 måneder af renal erstatningsterapi perioden.

Det andet studie fokuserede på at undersøge mortaliteten og dødsårsagerne i en hæmodialyse population og i en population uden patienter i renal erstatningsterapi med *S. aureus* endokardit. Hovedfundet var en øget dødelighed det første år efter *S. aureus* endokardit i hæmodialyse populationen sammenlignet med populationen uden renal erstatningsterapi patienter. Risikoen for død af alle årsager og kardiovaskulær død i hæmodialyse gruppen steg indenfor de første tre måneder efter indlæggelsen med *S. aureus* endokardit ved sammenligning med populationen uden renal erstatningsterapi patienter.

Det tredje studie undersøgte incidensen og risikoen for *Staphylococcus aureus* bakteriæmi med fokus på de forskellige hæmodialyse karadgangsveje fra 1996-2011 blandt 9997 patienter. Risikoen for *Staphylococcus aureus* bakteriæmi var højest i hæmodialyse patienter sammenlignet med peritoneal dialysepatienter. Risikoen var særlig høj blandt patienter, der blev dialyseret med centrale venøse katetre. *Staphylococcus aureus* bakteriæmi risikoen var højest de første 90 dage af renal erstatningsterapi perioden, særlig blandt patienter der blev dialyseret med centrale venøse katetre efterfulgt af arteriovenøse fistler.

Afhandlingen sætter primært fokus på den høje risiko for endokardit og *Staphylococcus aureus* bakteriæmi hos patienter i renal erstatningsterapi. Hovedfundene understreger vigtigheden af øget opmærksomhed blandt sundhedspersonale særligt i den initiale periode efter opstart af renal erstatningsterapi.

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Appendices

Appendix 1

Appendix 2

Appendix 3

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