Risk of Infective Endocarditis in Patients with End Stage Renal Disease

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Abstract

Background and objectives Endocarditis is a serious complication in patients treated with RRT. The study aimed to examine incidence and risk factors of endocarditis in patients with ESRD.

Design, setting, participants, & measurements The Danish National Registry on Regular Dialysis and Transplantation contains data on all Danish patients receiving renal replacement (hemodialysis, peritoneal dialysis, or kidney transplantation) for ESRD. Incidence of endocarditis was estimated for each RRT modality. Independent risk factors of endocarditis were identified in multivariable Cox regression models.

Results From January 1st, 1996 to December 31st, 2012, 10,612 patients (mean age 63 years, 36% female) initiated RRT (7233 hemodialysis, 3056 peritoneal dialysis, 323 pre-emptive kidney transplantation). Endocarditis developed in 267 (2.5%); of these 31 (12%) underwent valve surgery. The overall incidence of endocarditis was 627 per 100,000 person-years in patients receiving RRT. Incidence was higher in patients receiving hemodialysis compared with those receiving peritoneal dialysis or kidney transplantation (1092 per 100,000 person-years, 212 per 100,000 person-years, and 85 per 100,000 person-years, respectively). Adjusted hazard ratios for endocarditis in patients receiving hemodialysis were 5.46 (95% confidence interval [95% CI], 3.28 to 9.10) and 0.41 (95% CI, 0.18 to 0.91) for kidney-transplanted recipients, respectively, as compared with patients in peritoneal dialysis. The incidence of endocarditis in hemodialysis recipients with central venous catheters was more than two-fold higher as compared with those with arteriovenous fistulas. Overall mortality, subsequent to endocarditis, was 22% in-hospital and 51% at 1 year. The first 6 months in RRT, aortic valve disease, and previous endocarditis were identified as significant risk factors of endocarditis.

Conclusions Patients receiving RRT have a high incidence of endocarditis, in particular during hemodialysis treatment using central venous catheters. The first 6 months in RRT, aortic valve disease, and previous endocarditis are significant risk factors for developing endocarditis.

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Introduction

Infectious diseases including infective endocarditis are serious complications of RRT. Infective endocarditis has been described as a serious contributor to morbidity and mortality (1–12).

Hemodialysis necessitates repeated access to the vascular system *via* an intravenous catheter or a permanent arteriovenous fistula resulting in frequent episodes of bacteremia (1,13). Peritoneal dialysis requires placement of a dialysis catheter into the peritoneal cavity and kidney transplantation involves lifelong immunosuppressive therapy. Thus, all patients receiving RRT are empirically more prone to infections including infective endocarditis.

The type of vascular access in hemodialysis is a well known risk factor for bacteremia (14,15), but no large-scale studies on the risk of infective endocarditis, classified by hemodialysis access type, exist. Most available data on the occurrence of infective endocarditis subgroups by hemodialysis access type are either dated or on the basis of small study populations with samples of 17–69 patients (1,2,8–12,16).

Large-scale studies on the differences in the risk of infective endocarditis between the modalities of RRT are scarce. Available data from a single study reported the incidence of infective endocarditis was significantly higher in patients undergoing hemodialysis compared with patients undergoing peritoneal dialysis (5). The limited studies on the risk of infective endocarditis in kidney transplant recipients have reported infective endocarditis as a serious cause of morbidity and mortality (17–20), but the incidence has never been reported in a nationwide population and it is unclear whether infective endocarditis is more common in peritoneal dialysis than in kidney transplant recipients.

The aims of this study were: (*1*) to review and explore in more detail the incidence of infective endocarditis in patients with ESRD receiving different forms of RRT, (*2*) to compare the relationship between

different forms of hemodialysis access type and the related incidence of infective endocarditis, and (*3*) to determine individual risk factors, including type of vascular hemodialysis access, using data from Danish nationwide registries.

Materials and Methods

Data Sources

In Denmark, all residents are provided with a permanent personal identification number that allows linkage between nationwide administrative registries on the individual level. Four of these registries were accessed to obtain data. The Danish National Patient Registry includes information on all outpatient appointments and hospital admissions including diagnoses and procedural codes in Denmark since 1978. Each outpatient appointment and admission is at end of appointment or discharge coded with one primary diagnosis, and if appropriate one or more secondary diagnoses, according to the International Classification of Diseases—until 1994 the eighth revision (ICD-8) was used and from 1994 the 10th revision (ICD-10) has been applied (21). The codes assessed for comorbidity are considered valid (22). All deaths occurring in Denmark are registered in The National Civil Registry within 2 weeks. The Danish National Prescription Registry was established in 1995 and contains information on every dispensed prescription in Denmark. Dispensed drugs are registered with information on date of purchase and are coded by the Anatomic Therapeutic Classification system. The registry is considered accurate and valid (23). The Danish National Registry on Regular Dialysis and Transplantation was established in 1990 and contains data on all Danish patients being actively treated for ESRD, including changes in treatment modality (24).

Population

All patients with ESRD that initiated RRT in the period from January 1st, 1996 to December 31st, 2012 were identified from The Danish National Registry on Regular Dialysis and Transplantation. RRT was defined as hemodialysis, peritoneal dialysis, or kidney transplantation (transplantation carried out pre-emptively and after maintenance dialysis treatment) for the treatment of ESRD. All changes in renal replacement treatment modality during follow-up were identified and entered (*e.g.*, a patient in hemodialysis could change to kidney transplantation, adding risk time to more than one subgroup), allowing for time-updated exposure. There were no individuals lost to follow-up in the study cohort. Information on heart valve surgery, vascular access including central venous catheter (CVC) access (cuffed and uncuffed), arteriovenous fistula, arteriovenous graft, and peritoneal catheter were obtained from The Danish National Patient Registry. Data from the Danish National Patient Registry was combined with data from The Danish National Registry on Regular Dialysis and Transplantation on primary and changing treatment modalities of hemodialysis, peritoneal dialysis, and kidney transplant, manually assessed on each individual level in collaboration with two independent nephrologists. There were no patients with missing data on any variable.

Thus, all patients were analyzed according to the time spent in each modality of RRT.

Comorbidities

Comorbidities were derived from The Danish National Patient Registry, including a period of 5 years before onset of RRT and until first time of infective endocarditis, death, or study end. Diabetes diagnoses were augmented by including details pertaining to redemption antidiabetic drugs with the Anatomic Therapeutic Classification code A10 from The Danish National Prescription Registry.

Outcome

The endpoint was infective endocarditis, defined according to hospital admission with discharge ICD-10 codes I33 and I38 as recorded in The Danish National Patient Registry. These codes are considered accurate and valid (25,26). Only the first episode of infective endocarditis after initiation of RRT in 1996–2012 was included in the analyses. Subjects were censored at first time of infective endocarditis, death, or study end.

Statistical Analyses

Continuous data were reported as mean with SD. Chi-squared test was used for analysis of differences between discrete variables. The Kruskall–Wallis test was used for differences between continuous variables. The overall incidence was calculated on the basis of the number of events in the cohort divided by the time interval spent in each of the RRT modalities. The relative time spent in CVC was calculated as percentage of the overall time spent in RRT (hemodialysis [CVC (cuffed and uncuffed), arteriovenous fistula, arteriovenous graft], peritoneal dialysis, and kidney transplantation), on the basis of the study population, distributed over each year of study and age beneath and above 70 years, respectively. Multivariable Cox regression was fitted to examine the dependence of infective endocarditis on RRTs (hemodialysis, CVC [cuffed and uncuffed], arteriovenous fistula, arteriovenous graft, peritoneal dialysis, and kidney transplantation) and to identify independent risk factors of infective endocarditis. Age was used as the underlying time-scale. Comorbidity (mitral-, aortic valve disease, and diabetes) was included time dependently by splitting at the time comorbidity was noted. The renal replacement modalities were time-updated at every change in modality, allowing for time-updated exposure. The current calendar year was split in time bands of 5 years for adjustment of the effect of calendar year in multivariable Cox regression. The overall time spent in RRT for each subject was split into three time periods of 183 days, 184–845 days and at least 846 days, representing the first and second quartile of outcome. Multivariable Cox regression was performed being adjusted for comorbidity (mitral-, aortic valve disease, and diabetes), sex, age, calendar year, overall time in RRT, and endocarditis before RRT. Cochran–Armitage time trend test was performed to determine if changes in incidence of patients with ESRD were significant over calendar time. Lack of interaction between RRT and sex, calendar year, mitral-, aortic valve disease, diabetes, overall time in RRT, and endocarditis before RRT was tested and found valid except for age. Stratified age analyses were performed to assess the interaction. The linearity of continuous variables was tested and found valid unless otherwise specified.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Statistical significance was defined as $P<0.05$.

Ethics

This retrospective register-based study was approved by the Danish Data Protection Agency (ref. 2007–58–0015/ internal ref. GEH-2014–015 I-suite no. 02733). Retrospective studies in registries do not require ethical approval in Denmark.

Results

From January 1st, 1996 to December 31st, 2012, a total number of 10,612 patients initiated RRT. The mean age was 63 years (SD±16 years), and 6766 (64%) were male (Table 1). The leading cause of kidney failure was diabetes mellitus (25%). The distributions of comorbidities are shown in Table 1. The primary RRT was hemodialysis in 7233 patients (68%), peritoneal dialysis in 3056 patients (29%), and pre-emptive kidney transplant in 323 patients (3%) (Supplemental Tables 1 and 2).

Heart valve disease diagnosed before initiation of RRT was found in 687 patients (7%). The aortic valve was involved in 435 (4%) subjects followed by the mitral valve in 252 (2%) of the patients (Table 1). The distributions of heart valve disease by subgroups of RRT are shown in Table 1.

Incidence of Infective Endocarditis

In the total cohort of 10,612 patients, 267 events of first-time infective endocarditis occurred after the initiation of RRT (Table 2). Infective endocarditis was diagnosed in 241 patients during hemodialysis treatment, 16 events during peritoneal dialysis treatment and ten events in kidney transplant recipients with a functioning graft. The hemodialysis vascular access at the time of infective endocarditis was arteriovenous fistula in 138 patients, a cuffed CVC in 39, an uncuffed CVC in 39, and an arteriovenous graft in one, whereas there was no information on the hemodialysis vascular access in 24 patients. The causing agent was *Staphylococcus aureus* in 127, coagulase-negative *staphylococci* in 34, *enterococci* in 41, *Streptococcus* in 15, others in eight, blood culture negative in 35, and unavailable

Table 1. Demographic characteristics of patients with incident ESRD according to initial treatment modality in Denmark

Characteristics	Hemodialysis	Peritoneal Dialysis	Kidney Transplant (Pre-Emptive)	Total (=*N*)
Total, *N*	7233 (68)	3056 (29)	323 (3)	10,612 (100)
Age, yr	65±15	60±15	42±16	63±16
Female, *N*	2609 (36)	1119 (37)	118 (37)	3846 (36)
Age, yr	65±15	58±16	43±16	62±16
Male, *N*	4624 (64)	1937 (63)	205 (64)	6766 (64)
Mean age	65±15	60±15	42±16	63±16
Heart valve disease before RRT				
Aortic valve	314 (4)	116 (4)	5 (2)	435 (4)
Mitral valve	182 (3)	64 (2)	6 (2)	252 (2)
Comorbidity				
Myocardial infarction	655 (9)	196 (6)	4 (1)	855 (8)
Diabetes with complication	2057 (28)	819 (27)	57 (18)	2933 (28)
Diabetes	2284 (32)	884 (29)	59 (18)	3227 (30)
Chronic obstructive lung disease	561 (8)	131 (4)	3 (1)	695 (7)
Dementia	1 (0.01)	1 (0.03)	0	2 (0.2)
Peripheral vascular disease	835 (12)	201 (7)	3 (1)	1039 (10)
Cancer	795 (11)	175 (6)	1 (0.3)	971 (9)
Liver disease	188 (3)	36 (1)	4 (1)	228 (2)
AIDS	18 (0.3)	2 (0.1)	0	20 (0.2)
Hemi-/paraplegia	31 (0.4)	4 (0.1)	0	35 (0.3)
Rheumatic disease	199 (3)	91 (3)	8 (2)	298 (3)
Peptic ulcer	569 (8)	152 (5)	3 (1)	724 (7)
Ischemic heart disease	1555 (22)	537 (18)	21 (7)	2113 (20)
Cardiac arrhythmia disorder	963 (13)	239 (8)	11 (3)	1213 (11)
Pulmonary edema	172 (2)	46 (2)	0	218 (2)
Sepsis and cardiogenic shock	594 (8)	92 (3)	3 (1)	689 (7)
Previous atrial fibrillation/Flutter	817 (11)	195 (6)	7 (2)	1019 (10)
Chronic heart failure	1269 (17)	330 (11)	3 (1)	1602 (15)
Cause of kidney disease				
Diabetes mellitus	1793 (24)	762 (25)	52 (16)	2607 (25)
Chronic GN	553 (8)	400 (13)	71 (22)	1024 (10)
Vascular and hypertensive nephropathy	906 (13)	384 (13)	19 (6)	1309 (12)
Polycystic kidney disease	406 (6)	266 (9)	54 (17)	726 (7)
Chronic tubulointerstitial nephropathy	361 (5)	119 (4)	18 (6)	498 (5)
Other	1309 (18)	384 (13)	58 (18)	1751 (17)
Unknown	1905 (26)	741 (24)	51 (16)	2697 (25)

Values are given as mean±SD or *N* (%).

Table 2. Risk factors for infective endocarditis in patients with incident ESRD receiving RRT in Denmark

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 to 25.50)
Cuffed CVC	39	2099	10.03 (5.52 to 18.24)
Arteriovenous fistula	138	874	4.59 (2.73 to 7.73)
Arteriovenous graft	1	570	3.19 (0.42 to 24.26)
Unknown hemodialysis access	24	809	3.67 (1.94 to 6.94)
Hemodialysis	241	1092	5.46 (3.28 to 9.10)
Kidney transplant	10	85	0.41 (0.18 to 0.91)
Peritoneal dialysis	16	212	1.00 (reference)
RRT periods			
RRT period 1[a]	67	1353	1.89 (1.37 to 2.60)
RRT period 2[a]	67	501	0.80 (0.59 to 1.10)
RRT period 3[a]	133	549	1.00 (reference)
Sex			
Male	163	607	0.91 (0.71 to 1.18)
Female	104	663	1.00 (reference)
Comorbidity			
Diabetes mellitus			
1	102	817	1.12 (0.87 to 1.45)
0	165	549	1.00 (reference)
Endocarditis[b]			
1	20	17321	22.24 (13.50 to 36.62)
0	247	581	1.00 (reference)
Aortic valve disease			
1	41	2139	2.65 (1.68 to 4.18)
0	226	556	1.00 (reference)
Mitral valve disease			
1	20	1757	1.38 (0.71 to 2.70)
0	247	596	1.00 (reference)

Model adjusted for sex, age, diabetes, aortic valve disease, mitral valve disease, previous endocarditis, calendar year, renal replacement periods (<183, 184–845, and >845 d in RRT). CVC, central venous catheter.
[a]Renal replacement period 1: first 183 d in renal replacement period; renal replacement period 2: 184–845 d in renal replacement period; renal replacement period 3: >845 d.
[b]Before initiation of RRT.

information in seven. Infective endocarditis reoccurred twice in 28 patients, three times in five patients, and four times in one patient.

During the first year of RRT, 34% of total infective endocarditis cases occurred in hemodialysis and 2% in peritoneal dialysis.

The overall incidence of infective endocarditis was 627 per 100,000 person-years. The incident cases of infective endocarditis increased significantly across the study period (Figure 1). The relative time in CVC increased in the same period, particularly in patients >70 years, across the study period (Figure 2). The incidence of infective endocarditis was substantially higher among patients receiving hemodialysis (1092 per 100,000 person-years) than either patients receiving peritoneal dialysis (212 per 100,000 person-years) or patients who received kidney transplants (85 per 100,000 person-years) (Figure 3). The incidence of infective endocarditis was significantly higher in patients receiving hemodialysis with either uncuffed (3053 per 100,000 person-years) or cuffed CVC (2099 per 100,000 person-years) as compared with patients with an arteriovenous fistula (874 per 100,000 person-years) and the Danish general population (8–10 per 100,000 person-years) (27). The unadjusted incidence rate ratio was 3.5 in uncuffed CVC, 2.4 in cuffed CVC, and 0.7 in arteriovenous graft compared with arteriovenous fistula.

The incidence of RRT for ESRD increased from 466/yr (88.7 per million) in 1996 to 615/yr (110.2 per million) in 2012, corresponding to a 25% increase across the study period when adjusted for the increase in the general population during the same period ($P<0.001$).

Risk Factors of Infective Endocarditis during RRT

As compared with peritoneal dialysis, the hazard ratio for the first episode of infective endocarditis was 5.46 (95% confidence interval [95% CI], 3.28 to 9.10) for patients in hemodialysis, 14.10 (95% CI, 7.76 to 25.50) in uncuffed CVC, 10.03 (95% CI, 5.51 to 18.24) in cuffed CVC, 4.59 (95% CI, 2.73 to 7.73) in arteriovenous fistula, and 0.41 (95% CI, 0.18 to 0.91) for patients receiving kidney transplants with functioning graft, respectively (Table 2). The risk of infective endocarditis was similar in uncuffed CVC compared with cuffed CVC, with a hazard ratio of 1.40 (95% CI, 0.89 to 2.21). The risk of infective endocarditis was 1.89 (95% CI, 1.37 to 2.60) for the

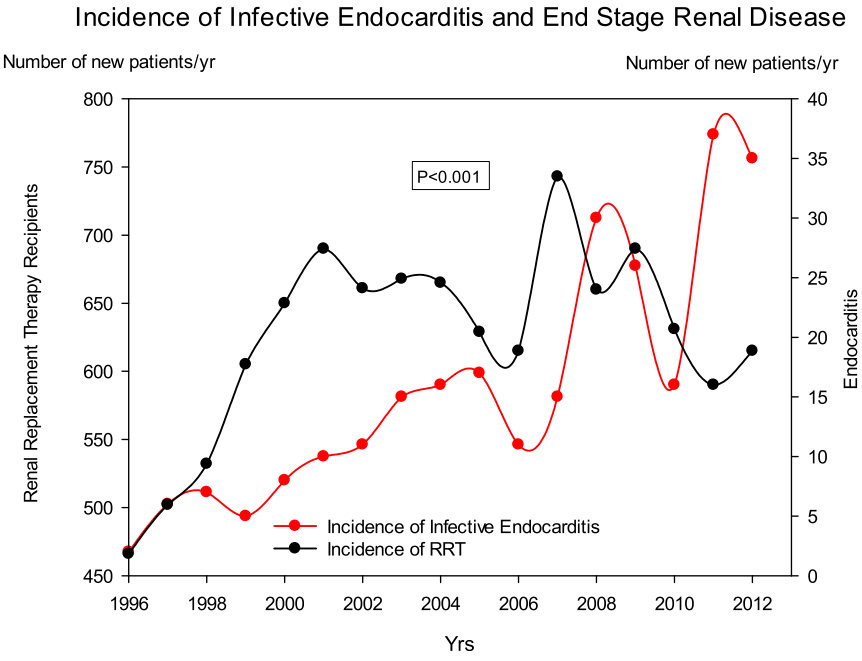

Figure 1. | The incidence of infective endocarditis increased significantly in the ESRD population compared to the increase in incidence of RRT during the period 1996–2012. The *P* value denotes the significant increase in the incidence of infective endocarditis in the ESRD population compared with the increase in the incidence of RRT recipients, adjusted for the background population, across the study period.

first 6 months in RRT and 0.80 (95% CI, 0.59 to 1.10) for the period from 184 to 845 days compared with the period >845 days. Aortic valve disease and previous infective endocarditis were independent risk factors for infective endocarditis during subsequent renal replacement treatment. The risk of infective endocarditis in hemodialysis compared with peritoneal dialysis, median age ≤66 and >66, was significantly different, at 8.61 (95% CI, 4.58 to 16.20) versus 4.40 (95% CI, 2.34 to 8.28), respectively. The risk of infective endocarditis in kidney-transplanted compared with peritoneal dialysis, median age ≤49 and >49, was insignificant, at 0.25 (95% CI, 0.06 to 0.98) versus 0.39 (95% CI, 0.18 to 0.88),

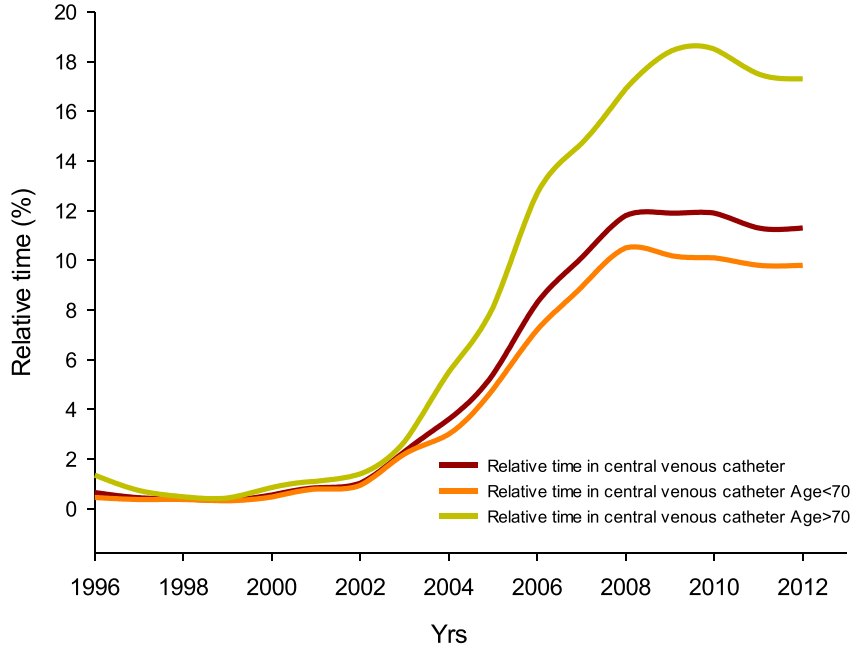

Figure 2. | The relative time in central venous catheter increased during the period 1996–2012. Relative time spent in central venous catheter as proportion of overall time spent in RRT (hemodialysis [central venous catheter (cuffed and uncuffed), arteriovenous fistula, arteriovenous graft], peritoneal dialysis, and kidney transplantation) on the basis of the study population and distributed over each year of study.

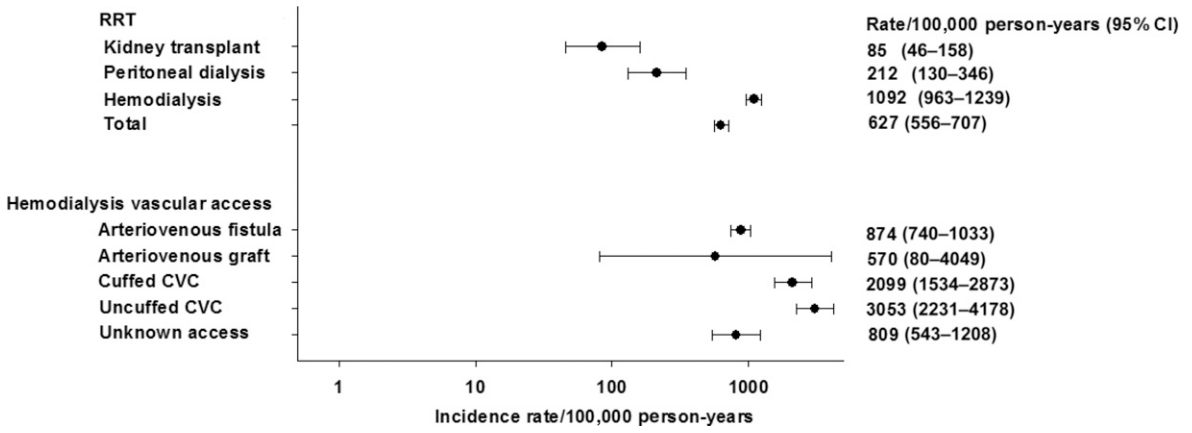

Figure 3. | **The incidence rate of infective endocarditis was high in hemodialysis vascular accesses.** 95% CI, 95% confidence interval; CVC, central venous catheter.

respectively. Sex and diabetes mellitus were not associated with infective endocarditis in our study population, with hazard ratios of 0.91 (95% CI, 0.72 to 1.18) in males compared with females and 1.12 (95% CI, 0.87 to 1.45), respectively.

Table 3 shows the distribution of in-hospital mortality and 1-year mortality subsequent to infective endocarditis in hemodialysis, peritoneal dialysis, kidney-transplanted, and overall.

The patients receiving hemodialysis had the highest in-hospital and 1-year mortality compared with peritoneal dialysis and kidney-transplanted. Table 4 shows the distribution of heart valve surgery subsequent to infective endocarditis. The patients receiving hemodialysis accounted for the highest number of interventions, in particular of the mitral valve. The in-hospital and 1-year mortality rates subsequent to heart valve surgery were highest in hemodialysis.

Discussion

The principal finding of this large nationwide registry study is the high incidence rate of infective endocarditis in ESRD, with the highest rate in hemodialysis followed by peritoneal dialysis and kidney transplant recipients. In addition, the incidence of infective endocarditis in patients receiving hemodialysis with cuffed and uncuffed CVCs as vascular access were significantly greater compared with arteriovenous fistula and arteriovenous graft. The incidence in patients receiving hemodialysis was as high as 1092 per 100,000 person-years, which is >70-fold increased as compared with the general Danish population, where the incidence recently has been reported as eight to ten per 100,000 person-years (27). In peritoneal dialysis and in kidney transplant recipients with functioning graft, we also observed high incidences of 212 per 100,000 person-years and 85 per 100,000 person-years, respectively.

The incidence of infective endocarditis was observed to be higher in patients receiving hemodialysis with CVCs, uncuffed (3053 per 100,000 person-years) and cuffed (2099 per 100,000 person-years), as vascular access than in patients with arteriovenous fistula (874 per 100,000 person-years) and arteriovenous graft (570 per 100,000 person-years).

The risk of infective endocarditis in hemodialysis compared with peritoneal dialysis was significantly higher at median age ≤66 than >66.

The first half-year after initiation of RRT, aortic valve disease, and infective endocarditis before initiation of RRT were independent risk factors of infective endocarditis.

Previous studies of infective endocarditis in patients on RRT have also found a high occurrence of infective endocarditis among patients receiving hemodialysis (3,11,16,28). One large cohort study from the United States, including 327,993 patients registered from 1992 to 1997, reported an incidence of infective endocarditis in patients receiving hemodialysis of 483 per 100,000 person-years and in patients receiving peritoneal dialysis of 248 per 100,000 person-years (5). Our findings are comparable to these data and in line with a previous Danish study on a subgroup of patients receiving chronic hemodialysis (29). We observed a much larger difference in the incidence between these two dialysis modalities. This difference is probably mainly explained by the high incidence of bacteremia in the hemodialysis population (30,31), which might be explained by catheter infections and higher risk of procedure-related bacterial contamination due to repeated access to the vascular system required for hemodialysis (1,13,15,32).

The Fistula First Initiative is a set of guidelines on hemodialysis vascular access, which recommend arteriovenous fistulas or grafts as preferred access modality and a goal of <10% cuffed CVCs. If possible, uncuffed CVCs are

Table 3. In-hospital and 1-yr mortality subsequent to infective endocarditis in patients with incident ESRD in Denmark

RRT	In-Hospital	1-yr 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 4. In-hospital and 1-yr mortality subsequent to heart valve surgery after infective endocarditis in patients with incident ESRD in Denmark

RRT	Heart Valve Surgery					Mortality	
	Total	Aortic Valve	Mitral Valve	Pulmonic Valve	Mitral and Aortic Valve	In-Hospital	1-yr 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; -, None.

to be avoided (33). The penetrance of arteriovenous fistulas in the prevalent hemodialysis population differs between hemodialysis centers in Denmark and ranges from 50% to 90% (34). The Danish National Registry on Regular Dialysis and Transplantation captures the hemodialysis access at initiation of chronic hemodialysis treatment. Thus, to identify the vascular access at the time of infective endocarditis, all cases were tracked individually by procedural codes in The Danish National Patient Registry. To our knowledge this has not been published before. Previous existing reports have been on small numbers of cases and with highly variable distributions of vascular access (1,2,8–12,16).

The findings of this study are consistent with the stated benefits of an arteriovenous fistula as compared with a CVC as vascular hemodialysis access (33). However, we did not find any difference in the risk of infective endocarditis between patients with uncuffed CVCs versus cuffed CVCs (hazard ratio, 1.40; 95% CI, 0.89 to 2.21). The shorter individual period at risk due to the expedient change of all uncuffed CVCs to either cuffed CVCs or an arteriovenous fistula might explain the present result. The incidence of infective endocarditis in the unknown hemodialysis access group was 809 per 100,000 person-years. This incidence might reflect this group as a combination of both cuffed and uncuffed CVCs. The incidence of infective endocarditis in arteriovenous graft recipients was 570 per 100,000 person-years. The utilization of this graft is limited in Denmark and therefore the incidence inconclusive.

Aortic valve disease has shown to increase the risk of developing infective endocarditis subsequent to commencement of renal replacement treatment (35,36). This study confirms this.

A more than ten-fold increase in the incidence of infective endocarditis was observed across the study period, whereas the increase in incidence in the Danish population in the same time period was two-fold (37). The increase in number of patients initiating RRT across the same period cannot explain the increasing incidence because the increase in infective endocarditis was much larger than the increase in patients starting RRT. Improved diagnostics, unrestricted access to chronic dialysis in both the elderly and in frail patients with multiple risk factors, uremia-related impaired immune system (13), and increasing relative time in CVC across the study period in particular in patients $>$ 70 years (Figure 2), are a possible important explanation of this observation. Increased availability of chronic dialysis in elderly patients along with the introduction of cuffed CVCs, enabling hemodialysis in patients with fragile vessels, may explain the increasing relative time in CVCs across the study period (38–40).

One large study analyzed the incidence of infective endocarditis among kidney transplant recipients in 1994–1997. The study reported an increased incidence ratio for infective endocarditis of 7.84 (95% confidence interval, 4.72 to 13.25) compared with the general population (18). This is consistent with this study. The incidence of infective endocarditis is higher in Danish patients who received kidney transplants when compared with the incidence in the general population in Denmark (27). In contrast to hemodialysis, kidney transplant was not a risk factor for infective endocarditis, as compared with peritoneal dialysis. The absence of invasive dialysis procedures and uremia-related immune defects in patients receiving kidney transplants seem to outweigh the infective risks associated with immunosuppressive therapy.

In this study there was an overall demographic difference, according to initial RRT, between hemodialysis, peritoneal dialysis, and pre-emptive kidney transplantation. The hemodialysis population was older with a higher number of comorbidities followed by the peritoneal dialysis group. These differences may contribute to our findings of a higher incidence of infective endocarditis in the hemodialysis group.

This study demonstrates a high risk of infective endocarditis in patients receiving RRT and suggests that increased attention on infective endocarditis in patients with ESRD, especially the hemodialysis group, is warranted. This strongly advocates frequent use of both transthoracic and transesophageal echocardiography in the case of bacteremia or unexplained fever episodes in these patients.

Strengths and Limitations

There are limitations to our present investigation inherent to the observational design of the study. It lacks information concerning type of valve involvement, which is not available due to lack of registration. The positive predictive value of the diagnostic codes for diagnosis of infective endocarditis is approximately 80%. On the other hand, the cohort of patients is large and on the basis of a validated nationwide registry including all patients in Denmark on renal replacement treatment in the study period. The registration of codes denoting the various forms of hemodialysis vascular access are, however, not formally validated, and thus misclassification cannot be excluded (predominantly with regard to differentiation between cuffed and uncuffed CVCs), even though the procedural codes in the registry were reviewed manually for every individual patient. The provided risk estimates are primarily hazard ratios. This is the ratio between the incidence rate of infective endocarditis in patients with a given RRT and the reference treatment at any distinct point in time that the patient has reached without contracting infective endocarditis or dying from other causes. It is the immediate risk ratio and it may not reflect appropriately any long-term risk on a given RRT. Over the long term the competing risk of death from other causes may cause patients with similar hazard ratios to have different long-term risks. Because the clinical situation of RRT is evaluated continuously in patients, we find that the immediate risk is that which is clinically important. In patients with ESRD receiving RRT, the risk of infective endocarditis is considerably higher compared with the general population and is particularly high among patients receiving hemodialysis. CVCs as vascular access had a more than two-fold higher risk as compared with arteriovenous fistulas. The first half-year of RRT, affected aortic valve, and previous infective endocarditis are additional risk factors for subsequent development of infective endocarditis. Increased awareness of the high risk of infective endocarditis in patients with ESRD is warranted.

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Disclosures

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Risk of Infective Endocarditis in Patients with End Stage Kidney Disease

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Supplemental Table 1. Diagnoses- and pharmacotherapy codes used to define comorbidity and aetiology of kidney disease in the study population

Comorbidity	Code
Ischemic heart disease	ICD-8 411-414 ICD-10 DI20, DI23-DI25
Myocardial infarction	ICD-8 410 ICD-10 DI21-DI22
Chronic heart failure	ICD-10 DI517, DI110, DI42-DI43, DI50
Atrial fibrillation/flutter	ICD-8 4273-4276, 4279 ICD-10 DI46-DI49
Cardiac arrythmia	ICD-8 42721-42723, ICD-10 DI44
Pulmonary edema	ICD-8 514 ICD-10 J81-J82
Sepsis and cardiogenic shock	ICD-8 038, 7855 ICD-10 R57, A41
Diabetes mellitus	ICD-8 250 ICD-10 E10-E14 ATC A10
Diabetes with complication	ICD-8 250 ICD-10 E10-E14 excluding E109, E119, E129, E139 ATC A10
Chronic obstructive lung disease	ICD-8 490-492 ICD-10 J42, J44
Liver disease	ICD-8 456, 571-572 ICD-10 B150, B160, B190, K704, K711, K766, K70-K77
Dementia	ICD-8 290 ICD-10 DG311-DG312, DG30
Peripheral vascular disease	ICD-8 443, 1771 ICD-10 DI70-DI74, R02

Cancer	ICD-8 140-209 ICD-10 C00-97
AIDS	ICD-8 042-044 ICD-10 B20-B24
Hemi-/paraplegi	ICD-8 342, 344 ICD-10 G81-G82, G041, T144
Rheumatic disease	ICD-8 725, 7100-7101, 7140-7142, 7148 ICD-10 M05-M06, M32-M34, M353
Peptic ulcer	ICD-8 531-534 ICD-10 K25-K27, K29, K221
Aortic valve disease	ICD-10 DI35
Mitral valve disease	ICD-10 DI34
Aetiology of kidney disease	**Code***
Diabetes mellitus	ICD-10 E10-E11
Chronic glomerulonephritis	ICD-10 N03
Vascular and hypertensive nephropathy	ICD-10 I12
Polycystic kidney disease	ICD-10 Q61
Chronic tubulointerstitial nephropathy	ICD-10 N11
Other	ICD-10 A181, C689, C900, D593, D690, E720, E748, E752, E835, E859, M103, M300, M310, M313, M318, M319, M321, M349, M352, M359, N028, N078, N079, N140, N141, N15, N209, N280, N319, Q605, Q620, Q794, Q878, Q899, S370
Unknown	ICD-10 N171, N18

ICD-8	8th revision of International Classification of Diseases
ICD-10	10th revision of International Classification of Diseases
ATC	Anatomical Therapeutic Classification system
Code*	The Danish National Registry on Regular Dialysis and Transplantation

Supplemental Table 2. Aetiology of kidney disease of the subgroup "other"

Diagnosis	Code* (ICD-10)	(N)	Diagnosis	Code* (ICD-10)	(N)
Tuberculosis of genitourinary system	A181	2	Generalized connective tissue syndrome	M359	15
Malignant neoplasm of urinary organ - unspecified	C689	129	Recurrent and persistent haematuria – unspecified	N028	107
Myelomatosis	C900	176	Hereditary nephropathy with other morphologic lesions	N078	10
Hemolytic-uremic syndrome	D593	33	Hereditary nephropathy - unspecified	N079	9
Allergic purpura	D690	6	Analgesic nephropathy	N140	56
Disorders of amino-acid transport	E720	5	Nephropathy induced by other drugs, medicaments and biological substances	N141	172
Other specified disorders of carbohydrate metabolism	E748	3	Balkan nephropathy	N150	1
Sphingolipidosis	E752	6	Other specified renal tubulo-interstitial diseases	N158	92
Disorders of calcium metabolism	E835	15	Renal tubulo-interstitial disease – unspecified	N159	127
Amyloidosis	E859	87	Urinary calculus – unspecified	N209	57
Arthritis urica	M103	4	Ischemia and infarction of kidney	N280	92
Polyarteritis nodosa	M300	23	Neuromuscular dysfunction of bladder – unspecified	N319	13
Hypersensitivity angiitis	M310	46	Renal hypoplasia – unspecified	Q605	17
Wegener's granulomatosis	M313	156	Congenital hydronephrosis	Q620	41
Other necrotizing vasculopathies	M318	32	Prune belly syndrome	Q794	2
Necrotizing vasculitis	M319	90	Other specified congenital	Q878	21

			malformation syndromes		
Systemic lupus erythematosus with organ involvement	M321	68	Congenital malformation – unspecified	Q899	6
Systemic sclerosis	M349	26	Injury of kidney	S370	2
Behcet's disease	M352	4		Total	1751

Code* The Danish National Registry on Regular Dialysis and Transplantation
ICD-10 10th revision of International Classification of Diseases