Chapter 7

Mortality due to pulmonary embolism, myocardial infarction, and stroke among incident dialysis patients

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J Thromb Haemost. 2012; 10(12): 2484-2493

ABSTRACT

Background: It has been suggested that dialysis patients have lower mortality rates for pulmonary embolism than the general population, because of platelet dysfunction and bleeding tendency. However, there is limited information whether dialysis is indeed associated with a decreased mortality risk from pulmonary embolism. The aim of our study was to evaluate whether mortality rate ratios for pulmonary embolism were lower than for myocardial infarction and stroke in dialysis patients compared with the general population.

Methods: Cardiovascular causes of death for 130 439 incident dialysis patients registered in the ERA-EDTA Registry were compared with the cardiovascular causes of death for the European general population.

Results: The age- and sex-standardized mortality rate (SMR) from pulmonary embolism was 12.2 (95%CI 10.2-14.6) times higher in dialysis patients than in the general population. The SMRs in dialysis patients compared with the general population were 11.0 (95% CI 10.6-11.4) for myocardial infarction, 8.4 (95% CI 8.0-8.8) for stroke, and 8.3 (95% CI 8.0-8.5) for other cardiovascular diseases. In dialysis patients, primary kidney disease due to diabetes was associated with an increased mortality risk due to pulmonary embolism (HR 1.9; 95% CI 1.0-3.8), myocardial infarction (HR 4.1; 95% CI 3.4-4.9), stroke (HR 3.5; 95% CI 2.8-4.4), and other cardiovascular causes of death (HR 3.4; 95% CI 2.9-3.9) compared with patients with polycystic kidney disease.

Conclusion: Dialysis patients were found to have an unexpected highly increased mortality rate for pulmonary embolism and increased mortality rates for myocardial infarction and stroke.

INTRODUCTION

End-stage renal disease patients who receive dialysis treatment have a markedly increased risk of death with a cardiovascular mortality risk that is 8-20 times higher than in the general population.[1-6] However, there is limited information on the contribution of various specific causes of cardiovascular death such as pulmonary embolism, myocardial infarction and stroke to the excess risk. It has been suggested that dialysis patients have a lower risk for pulmonary embolism than the general population, because of platelet dysfunction and bleeding tendency.[7,8] In support of this notion, autopsy studies have shown pulmonary embolism to be less common in dialysis patients than in non-dialysis patients.[9-12] However, epidemiological studies investigating the risk of mortality due to pulmonary embolism in dialysis patients are lacking. While studies in dialysis patients have shown an increased risk for myocardial infarction[13] and stroke,[14,15] the specific mortality risks due to these causes have not been adequately dissected.

Based on the previous autopsy studies on pulmonary embolism, we hypothesized that mortality rate ratios for pulmonary embolism would be lower than those for myocardial infarction and stroke in dialysis patients compared with the general population. Therefore, our aim was to assess the rates of mortality from myocardial infarction, stroke, and pulmonary embolism in a large cohort of incident dialysis patients and compare them with those in the general population. Finally, we set out to investigate the risk factors for death from these specific cardiovascular causes in the dialysis population.

METHODS

Dialysis patients

The study cohort consisted of incident dialysis patients derived from the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry.[16] This cohort included patients from national and regional registries in 11 European countries: Austria, Dutch- and French-speaking Belgium, Denmark, Finland, Greece, Iceland, Calabria (Italy), the Netherlands, Norway and the autonomous communities of Andalusia, Asturias, Basque country, Catalonia, Castile-La Mancha, Castile and Leon, Extremadura, and Valencian region in Spain, and Sweden. The ERA-EDTA Registry collects data on renal replacement therapy, including date of birth, sex, primary kidney disease, date of start of renal replacement therapy, dialysis modality at baseline and during follow-up, and date and cause of death. Primary kidney disease was classified according to the coding system of the ERA-EDTA.[17] We grouped patients into nine classes of primary kidney disease: polycystic kidney disease, glomerulonephritis, pyelonephritis, hypertension, renal vascular disease, diabetes, multi-system disease (renal

vascular disease due to polyarteritis, granulomatous polyangiitis, glomerulonephritis related to liver cirrhosis, cryoglobulinaemic glomerulonephritis, myelomatosis, amyloidosis, systemic lupus erythematosus, Henoch-Schoenlein purpura, Goodpasture's syndrome, and systemic sclerosis), miscellaneous, and missing/unknown. Patients were included if they originated from registries reporting less than 25% missing or unknown causes of death. We included patients who initiated dialysis between January 1, 1994, and December 31, 2005, and followed them for a maximum of 3 years from onset of dialysis until December 31, 2008, or until death or censoring (i.e. recovery of renal function, kidney transplantation or loss to follow-up).

Mortality in dialysis patients

We classified the causes of death according to the coding system of the ERA-EDTA, which is a standardized classification of causes of death in dialysis patients.[17] Cardiovascular mortality was defined as a death attributable to pulmonary embolism (ERA-EDTA code 21), myocardial infarction (ERA-EDTA code 11), stroke (ERA-EDTA code 22), and other cardiovascular causes [cardiac arrest / sudden death (ERA-EDTA code 15), fluid overload / pulmonary edema (ERA-EDTA codes 18), hypertensive cardiac failure (ERA-EDTA codes 16), other causes of cardiac failure (ERA-EDTA codes 14)]. Unknown (ERA-EDTA code 0) and missing causes of death were defined as unknown. All other causes of death were defined as non-cardiovascular.

Mortality in the general population

Mortality data obtained from the general population in the corresponding 11 countries (or regions) that contributed data on dialysis patients were used as reference. These mortality data, derived from the national cause of death statistics, were obtained from the World Health Organization (WHO). The WHO provides mortality data coded according to the International Statistical Classification of Diseases (ICD), stratified by age categories, sex, and calendar year.

Cardiovascular mortality in the general population was defined as death from diseases of the circulatory system (ICD-9 codes 390-459; ICD-10 codes I00-I99),[3] i.e. pulmonary embolism (ICD-9 codes 415.1; ICD-10 codes I26),[18] myocardial infarction (ICD-9 code 410; ICD-10 codes I21-I22),[19] stroke (ICD-9 codes 430-434, 436; ICD-10 codes I60-I64)[20], and other causes of cardiovascular death (ICD-9 codes 390-459, except 415.1, 410, 430-434, and 436; ICD-10 codes I00-I99, except I26, I21-I22, and I60-I64). Ill-defined and unknown causes of mortality (ICD-9 codes 797-799; ICD-10 codes R96-R99) were regarded as unknown cause of death in the general population, while all other codes (all ICD-9 codes except 390-459 and 797-799 and all ICD-10 codes except I00-I99 and R96-R99) were regarded as non-cardiovascular causes of death.

Statistical analysis

Continuous variables are presented as means with standard deviation (SD). Data were stratified by age-categories (20-24 years, 25-34 years, 35-44 years, 45-54 years, 55-64 years, 65-74 years, 75-84, and ≥85 years) and sex.

The rates of mortality from all causes and specific cardiovascular causes (pulmonary embolism, myocardial infarction, stroke, and other) in each age category were calculated by dividing the number of patients who died due to cardiovascular causes by the total observation time at risk in each age stratum, for both the dialysis patients and the general population. The time at risk in the general population was calculated using the demographic large-scale method.[3] Using this method, person-time at risk in the general population of the 11 countries from which dialysis patients were included, was calculated as the sum of the mean size of the general population in the subsequent calendar years.

Furthermore, we calculated crude mortality rate ratios with 95% CIs by dividing the mortality rates in dialysis patients by the mortality rates in the general population. In addition, age- and sex-standardized mortality rate ratios were calculated using direct standardization with the general population as reference. We also did a sensitivity analysis in which age- and sex-standardized mortality rate ratios with 95% CIs were calculated for pulmonary embolism, myocardial infarction, and stroke after changing all unknown codes of death in the general population into pulmonary embolism, myocardial infarction, or stroke, respectively. Finally, among incident dialysis patients, we calculated hazard ratios (HRs) with 95% CIs to evaluate the effect of age, sex, and primary kidney disease at baseline on death due to pulmonary embolism, myocardial infarction, stroke, and other cardiovascular diseases using Cox regression. We also used Cox regression to evaluate the effect of dialysis modality (hemodialysis or peritoneal dialysis) at 3 months after the beginning of renal replacement therapy on death due to pulmonary embolism, myocardial infarction, stroke, and other cardiovascular diseases. SPSS statistical software (version 18.0; SPSS, Chicago, Illinois) was used for the analysis.

RESULTS

In this study, we included 130 439 dialysis patients from 11 countries who began dialysis between January 1, 1994, and December 31, 2005. The mean age of the dialysis patients was 63.1 years, 61.0% were male, in 22.3% diabetes was the cause of kidney disease, and 84.1% started hemodialysis as the initial dialysis modality (Table 1). The mean follow-up of dialysis patients was 2.0 years resulting in a total observation time of 260 772 years. During the observation period, 23.7% of the patients underwent renal transplantation.

Table 1. Baseline characteristics of dialysis patients

Characteristic	Age category at onset of dialysis, n (%)								
	All (n=130,439)	**20-24 y (n=1,686)**	**25-34 y (n= 5,738)**	**35-44 y (n=9,932)**	**45-54 y (n=17,189)**	**55-64 y (n=26,405)**	**65-74 y (n=40,030)**	**75-84 y (n=26,737)**	**≥85 y (n=2,722)**
Age, mean (SD), y	63.1 (14.7)	22.7 (1.4)	30.5 (2.8)	40.4 (2.9)	50.4 (2.8)	60.4 (2.9)	70.2 (2.8)	78.9 (2.6)	87.5 (2.3)
Sex (%)									
Female	39.0	35.3	39.3	36.1	36.8	37.1	39.7	41.7	44.0
Male	61.0	64.7	60.7	63.9	63.2	62.9	60.3	58.3	56.0
Primary kidney disease (%)									
Polycystic kidney disease	5.9	0.5	2.1	9.8	13.4	7.9	3.9	2.4	1.3
Pyelonephritis	7.2	16.8	11.4	7.3	6.4	6.3	7.0	7.4	7.5
Glomerulonephritis	13.5	31.9	29.5	24.7	19.0	13.5	9.7	7.7	5.3
Hypertension	11.0	3.1	5.2	6.8	7.8	9.4	11.9	16.0	18.5
Renal vascular disease	6.8	0.7	0.8	1.2	2.7	4.8	8.3	11.9	15.2
Diabetes	22.3	3.0	17.3	21.0	22.4	27.0	25.4	17.1	8.7
Miscellaneous	8.5	17.4	10.4	8.8	8.5	9.3	8.2	7.2	6.6
Multisystem disease	7.0	12.2	8.8	6.9	6.6	6.9	7.2	6.6	4.6
Unknown	17.8	14.5	14.6	13.4	13.1	14.9	18.3	23.8	32.2
Dialysis modality (%)									
Peritoneal dialysis	15.9	20.6	24.6	25.1	22.1	17.7	12.9	9.8	7.6
Hemodialysis	84.1	79.4	75.4	74.9	77.9	82.3	87.1	90.2	92.4
Renal transplantation* (%)	23.7	80.7	75.1	65.2	50.1	28.4	6.3	0.4	0.1
Follow-up, mean (SD), y	2.0 (1.1)	1.9 (1.1)	1.9 (1.0)	2.0 (1.0)	2.1 (1.0)	2.1 (1.0)	2.0 (1.1)	1.8 (1.1)	1.4 (1.1)

*transplantation during follow-up

The general population yielded an observation time of 1140.2 million person-years. The mean age of the general population was lower than the mean age of the dialysis patients. There were fewer men in the general population than in the dialysis patients.

During follow-up, 50 765 of the 130 439 dialysis patients died (Table 2). Among the deceased patients, cardiovascular diseases were the cause of death in 39.8% of cases: pulmonary embolism 0.7%, myocardial infarction 11.4%, stroke 7.3%, and other cardiovascular cause of death 20.3% (including cardiac arrest/ sudden death 12.3% and other than cardiac arrest/ sudden death 8.0%). Death from non-cardiovascular causes occurred in 46.5% of the patients, while the cause of death was unknown in 13.8%. There was a similar pattern of cardiovascular causes of death (pulmonary embolism, myocardial infarction, stroke, and other cardiovascular cause of death) across the age groups. In the general population, 13 739 478 persons died during the study period. Of those, 40.1% died from cardiovascular diseases (pulmonary embolism 0.5%, myocardial infarction 8.6%, stroke 9.0%, and other cardiovascular cause of death 21.9%), 57.9% from non-cardiovascular diseases, and 2.0% from unknown causes.

Both in the general population and the dialysis population, the mortality rates for pulmonary embolism, myocardial infarction, stroke, and other cardiovascular causes of death increased with age (Figure 1).

Table 3 shows the mortality rates for total and cause specific (pulmonary embolism, myocardial infarction, stroke, and other) cardiovascular mortality in different age categories stratified by sex. In both the dialysis patients and the general population, mortality rates due to myocardial infarction and due to other cardiovascular causes of death were higher in men than in women, while women were at higher risk of death due to stroke and pulmonary embolism than men. The total cardiovascular mortality rate was 77.4 per 1000 person-years in dialysis patients and 4.8 per 1000 person-years in the general population. The age- and sex-standardized cardiovascular mortality rate was 8.9 (95% CI 8.7-9.1) times higher in dialysis patients than in the general population.

Table 2. Causes of death in the first three years of dialysis treatment

Dialysis patients	All (n=130,439)		Age category at death, N (%)															
			20-24 y (n=1,008)		25-34 y (n=5,039)		35-44 y (n=8,845)		45-54 y (n=15,415)		55-64 y (n=24,075)		65-74 y (n=38,064)		75-84 y (n=33,080)		≥85 y (n=4,913)	
Total deaths, n (%)	**50,765**	**(100)**	**57**	**(100)**	**346**	**(100)**	**1,009**	**(100)**	**2,918**	**(100)**	**7,371**	**(100)**	**17,759**	**(100)**	**18,359**	**(100)**	**2,946**	**(100)**
CV*, n (%)	**20,187**	**(39.8)**	**11**	**(19.3)**	**110**	**(31.8)**	**411**	**(40.7)**	**1,185**	**(40.6)**	**2,981**	**(40.4)**	**7,231**	**(40.7)**	**7,185**	**(39.1)**	**1,073**	**(36.4)**
Pulmonary embolism	365	(0.7)	1	(1.8)	1	(0.3)	8	(0.8)	18	(0.6)	51	(0.7)	136	(0.8)	137	(0.8)	13	(0.4)
Myocardial infarction	5,812	(11.4)	0	(0.0)	16	(4.6)	97	(9.6)	341	(11.7)	960	(13.0)	2,165	(12.2)	2,032	(11.1)	201	(6.8)
Stroke	3,699	(7.3)	2	(3.5)	41	(11.9)	107	(10.6)	253	(8.7)	520	(7.4)	1,254	(7.1)	1,288	(7.0)	234	(7.9)
Other	10,311	(20.3)	8	(14.0)	52	(15.0)	199	(19.7)	573	(19.6)	1,450	(19.7)	3,676	(20.7)	3,728	(20.3)	625	(21.2)
Cardiac arrest/ sudden death	6,235	(12.3)	5	(8.8)	37	(10.7)	144	(14.3)	382	(13.1)	903	(12.3)	2,200	(12.4)	2,163	(11.8)	401	(13.6)
Other than cardiac arrest/ sudden death	4,076	(8.0)	3	(5.3)	15	(4.3)	55	(5.5)	191	(6.5)	547	(7.4)	1,476	(8.3)	1,565	(8.5)	224	(7.6)
Non-CV*, n (%)	**23,597**	**(46.5)**	**35**	**(61.4)**	**185**	**(53.5)**	**447**	**(44.3)**	**1,321**	**(45.3)**	**3,397**	**(46.1)**	**8,113**	**(45.7)**	**8,639**	**(47.1)**	**1,460**	**(49.6)**
Unknown, n (%)	**6,981**	**(13.8)**	**11**	**(19.3)**	**51**	**(14.7)**	**151**	**(15.0)**	**412**	**(14.1)**	**993**	**(13.5)**	**2,415**	**(13.6)**	**2,535**	**(13.8)**	**413**	**(14.0)**

*CV, cardiovascular disease

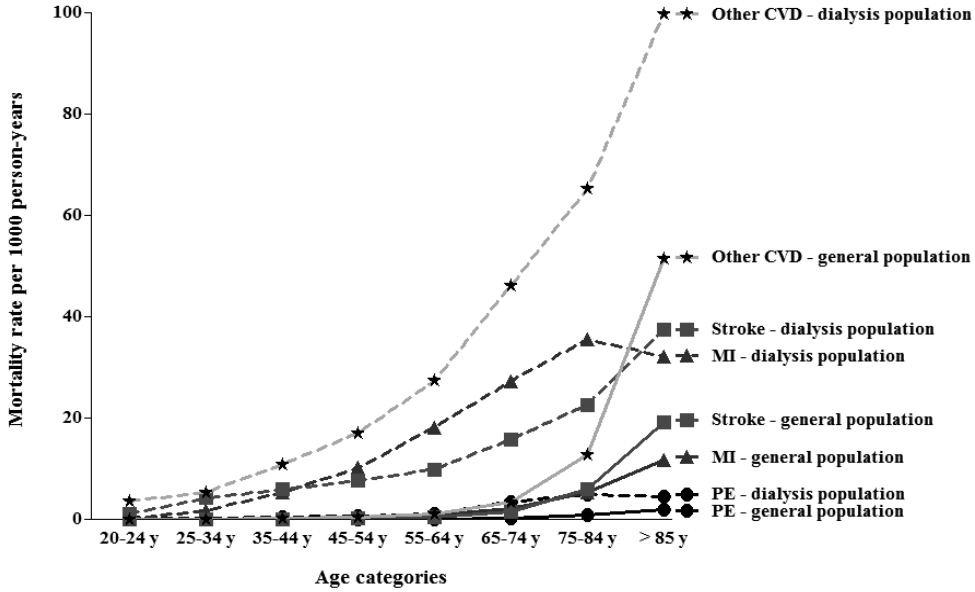

Figure 1. Mortality rates due to pulmonary embolism, myocardial infarction, stroke, and other cardiovascular diseases in dialysis patients and in the general population for different age categories

PE, pulmonary embolism; MI, myocardial infarction; CVD, cardiovascular disease; y, years

Compared with the general population, the age- and sex-standardized mortality rate ratios in dialysis patients were 12.2 (95% CI 10.2-14.6) for pulmonary embolism (1.4 among dialysis patients versus 0.1 among the general population per 1000 person-years, respectively), 11.0 (95% CI 10.6-11.4) for myocardial infarction (22.3 versus 1.0 per 1000 person-years, respectively), 8.4 (95% CI 8.0-8.8) for stroke (14.2 versus 1.1 per 1000 person-years, respectively), and 8.3 (95% CI 8.0-8.5) for other cardiovascular causes of death (39.5 versus 2.6 per 1000 person-years, respectively). The mortality rates for all cardiovascular causes of death were highest in the first 6 months after initiation of dialysis: mortality rate 1.9 per 1000 person-years for pulmonary embolism, 26.2 per 1000 person-years for myocardial infarction, 15.5 per 1000 person-years for stroke, and 51.6 per 1000 person-years for other cardiovascular causes of death.

In a worst case scenario, in which we changed all unknown codes of death in the general population into pulmonary embolism, myocardial infarction, or stroke, age- and sex-standardized mortality rate ratios were still increased for respectively pulmonary embolism (2.7; 95% CI 2.3-3.3), for myocardial infarction (8.4; 95% CI 8.0-8.8) and stroke (6.8; 95% CI 6.5-7.2).

Table 3. Total and cause-specific mortality rates per 1000 person-years in dialysis patients compared with the general population

		Age category, N (%)								
Characteristic		**All**	**20-24 y**	**25-34 y**	**35-44 y**	**45-54 y**	**55-64 y**	**65-74 y**	**75-84 y**	**≥85 y**
Total cardiovascular mortality										
Dialysis patients	Male	80.5	5.5	9.9	22.9	38.2	60.6	95.6	131.8	176.6
	Female	72.6	3.6	12.9	20.9	30.1	48.7	83.5	116.9	164.1
	Total	77.4	4.8	11.1	22.1	35.2	56.2	90.7	125.6	171.1
General	Male	4.6	0.0	0.1	0.3	1.1	3.2	9.7	28.9	86.0
Population	Female	5.0	0.0	0.0	0.1	0.4	1.1	4.7	21.0	82.0
	Total	4.8	0.0	0.1	0.2	0.7	2.1	7.0	24.1	83.2
Unstandardized mortality rate ratio 16.0 (95% CI 15.8-16.3)					**Age- and sex-standardized mortality rate ratio 8.9 (95% CI 8.7-9.1)**					
Pulmonary embolism										
Dialysis patients	Male	1.1	0.0	0.2	0.2	0.6	0.9	1.4	2.0	1.7
	Female	1.8	1.2	0.0	0.9	0.5	1.1	2.2	3.0	2.6
	Total	1.4	0.4	0.1	0.4	0.5	1.0	1.7	2.4	2.1
General	Male	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.3	0.9
Population	Female	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.4	0.9
	Total	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.4	0.9
Unstandardized mortality rate ratio 20.2 (95% CI 18.3-22.4)					**Age- and sex-standardized mortality rate ratio 12.2 (95% CI 10.2-14.6)**					
Myocardial infarction										
Dialysis patients	Male	25.2	0.0	1.3	5.3	11.8	21.1	30.6	41.0	37.4
	Female	17.8	0.0	2.0	5.1	7.2	13.0	22.1	27.9	25.2
	Total	22.3	0.0	1.6	5.2	10.1	18.1	27.2	35.5	32.1
General	Male	1.2	0.0	0.0	0.1	0.5	1.2	3.1	7.1	14.6
Population	Female	0.9	0.0	0.0	0.0	0.1	0.3	1.2	4.0	10.5
	Total	1.0	0.0	0.0	0.1	0.3	0.7	2.0	5.2	11.7
Unstandardized mortality rate ratio 21.5 (95% CI 21.0-22.1)					**Age- and sex-standardized mortality rate ratio 11.0 (95% CI 10.6-11.4)**					
Stroke										
Dialysis patients	Male	13.2	1.4	3.7	5.6	8.3	9.3	14.7	20.8	33.4
	Female	15.7	0.0	4.8	6.0	6.1	10.6	17.2	25.0	42.3
	Total	14.2	0.9	4.1	5.8	7.5	9.8	15.7	22.5	37.3
General	Male	0.9	0.0	0.0	0.1	0.2	0.5	1.7	6.2	18.4
Population	Female	1.3	0.0	0.0	0.0	0.1	0.3	1.2	5.6	19.3
	Total	1.1	0.0	0.0	0.0	0.1	0.4	1.4	5.8	19.0
Unstandardized mortality rate ratio 13.1 (95% CI 12.7-13.5)					**Age- and sex-standardized mortality rate ratio 8.4 (95% CI 8.0-8.8)**					
Other Cardiovascular disease										
Dialysis patients	Male	41.0	4.1	4.7	11.7	17.4	29.3	48.9	68.0	104.0
	Female	37.3	2.4	6.1	9.0	16.3	23.9	42.0	61.1	94.1
	Total	39.5	3.5	5.2	10.7	17.0	27.3	46.1	65.2	99.7
General	Male	2.4	0.0	0.0	0.1	0.5	1.4	4.7	15.2	52.2
Population	Female	2.9	0.0	0.0	0.1	0.2	0.5	2.3	11.0	51.2
	Total	2.6	0.0	0.0	0.1	0.3	1.0	3.4	12.7	51.5
Unstandardized mortality rate ratio 15.0 (95% CI 14.7-15.3)					**Age- and sex-standardized mortality rate ratio 8.3 (95% CI 8.0-8.5)**					

In dialysis patients, older age at the beginning of dialysis (≥85 years) was associated with an increased risk of pulmonary embolism (HR 7.8; 95% CI 3.3-18.6), myocardial infarction (HR 9.6; 95% CI 7.5-12.3), stroke (HR 8.9; 95% CI 7.2-11.2), and other cardiovascular causes of death (HR 12.3; 95% 10.6-14.3) when compared with patients who were younger at onset of dialysis (20-44 years) (Table 4). Male sex was associated with an increased risk of myocardial infarction (HR 1.4; 95% CI 1.3-1.5) and other cardiovascular causes of death (HR 1.1; 95% 1.1-1.2), whereas males had a decreased risk of death due to pulmonary embolism (HR 0.6; 95% CI 0.5-0.8) and stroke (HR 0.9; 95% CI 0.8-0.9). Both diabetes and multi-system diseases were associated with an increased risk of pulmonary embolism (HR 1.9; 95% CI 1.0-3.8 and HR 3.2; 95% CI 1.6-6.4, respectively), myocardial infarction (HR 4.1; 95% CI 3.4-4.9 and HR 2.2; 95% CI 1.7-2.7, respectively), stroke (HR 3.5; 95% CI 2.8-4.4 and HR 2.8; 95% CI 2.1-3.6, respectively), and other cardiovascular causes of death (HR 3.4; 95% CI 2.9-3.9 and HR 3.4; 95% CI 2.9-4.0, respectively), as compared with polycystic kidney disease. Dialysis modality was not associated with specific cardiovascular causes of death. Risk factors were the same for different causes of death in the other cardiovascular causes of death group.

Table 4. Risk factors for mortality due to specific cardiovascular diseases in dialysis patients

	Hazard ratio (95% CI) Pulmonary embolism		Hazard ratio (95% CI) Myocardial infarction		Hazard ratio (95% CI) Stroke		Hazard ratio (95% CI) Other CV	
Age categories at onset of dialysis*								
20-44	1	(reference)	1	(reference)	1	(reference)	1	(reference)
45-54	1.6	(0.8-3.4)	2.6	(2.1-3.1)	1.5	(1.2-1.8)	1.9	(1.7-2.2)
55-64	3.1	(1.6-5.8)	4.6	(3.8-5.5)	2.2	(1.8-2.6)	3.2	(2.8-3.6)
65-74	5.1	(2.8-9.4)	7.4	(6.2-8.8)	3.4	(2.9-4.0)	5.3	(4.7-6.0)
75-84	8.0	(4.3-14.8)	9.4	(7.9-11.3)	5.0	(4.2-5.9)	7.7	(6.9-8.7)
≥85	7.8	(3.3-18.6)	9.6	(7.5-12.3)	8.9	(7.2-11.2)	12.3	(10.6-14.3)
Sex								
Female	1	(reference)	1	(reference)	1	(reference)	1	(reference)
Male	0.6	(0.5-0.8)	1.4	(1.3-1.5)	0.9	(0.8-0.9)	1.1	(1.1-1.2)
Primary kidney disease†								
Polycystic kidney disease	1	(reference)	1	(reference)	1	(reference)	1	(reference)
Glomerulonephritis	1.3	(0.7-2.7)	1.3	(1.1-1.7)	1.6	(1.3-2.1)	1.5	(1.3-1.8)
Pyelonephritis	1.7	(0.8-3.5)	1.3	(1.1-1.7)	1.6	(1.2-2.1)	1.6	(1.3-1.9)
Hypertension	1.2	(0.6-2.4)	2.5	(2.1-3.1)	2.3	(1.8-2.9)	2.3	(2.0-2.7)
Renal vascular disease	1.8	(0.9-3.8)	2.9	(2.3-3.5)	2.7	(2.1-3.4)	3.1	(2.7-3.7)
Diabetes	1.9	(1.0-3.8)	4.1	(3.4-4.9)	3.5	(2.8-4.4)	3.4	(2.9-3.9)
Miscellaneous	1.9	(0.9-3.8)	1.6	(1.3-1.9)	2.1	(1.6-2.7)	2.0	(1.7-2.3)
Multisystem disease	3.2	(1.6-6.4)	2.2	(1.7-2.7)	2.8	(2.1-3.6)	3.4	(2.9-4.0)
Unknown	1.6	(0.8-3.1)	1.9	(1.6-2.4)	2.2	(1.8-2.8)	2.3	(2.0-2.7)
Dialysis modality‡								
Peritoneal dialysis	1	(reference)	1	(reference)	1	(reference)	1	(reference)
Hemodialysis	0.8	(0.6-1.1)	1.0	(0.9-1.1)	1.0	(0.9-1.1)	1.0	(0.9-1.1)

CV, cardiovascular disease; *Adjusted for sex, calendar year, and country; †Adjusted for age, sex, calendar year, and country; ‡Adjusted for age, sex, primary kidney disease, calendar year, and country

DISCUSSION

We found an unexpected highly increased risk of pulmonary embolism in dialysis patients as compared with the general population and an elevated risk of myocardial infarction and stroke in dialysis patients as compared with the general population. The total cardiovascular mortality rate in the 130 439 dialysis patients was 77.4 per 1000 person-years of which 1.4 per 1000 person-years could be attributed to pulmonary embolism, 22.3 per 1000 person-years to myocardial infarction, 14.2 per 1000 person-years to stroke, and 39.5 per 1000 person-years to other cardiovascular causes. The age- and sex-standardized mortality rates in dialysis patients were 12.2-fold increased for pulmonary embolism, 11.0-fold increased for myocardial infarction, 8.9-fold increased for stroke, and 8.3-fold increased for other cardiovascular causes of death compared with the general population.

The previous studies have investigated the total cardiovascular mortality risk in dialysis patients compared with the general population,[1,3,6] but there is limited information on the contribution of the various specific causes of cardiovascular death to the excess risk. The age- and sex-standardized mortality rates in dialysis patients as compared with the general population were comparable to a previous European study.[21] While two previous studies suggested an increased incidence of pulmonary embolism in the first year of dialysis,[22,23] there is limited information on the mortality associated with pulmonary embolism and whether it contributes to the increased cardiovascular mortality risk in dialysis patients. Our results contradict the findings of autopsy studies on pulmonary embolism.[9-12] These studies showed that pulmonary embolism was less common in dialysis patients (prevalences ranging from 0% to 6.5%) than in non-dialysis patients (prevalences ranging from 8.2% to 16.0%). In our study, 0.7% of deaths in dialysis patients were caused by pulmonary embolism compared with 0.5% in the general population. Comparison of our findings with those from the aforementioned autopsy series is hampered for several reasons. First, the use of autopsy series to investigate pulmonary embolism could lead to selection bias caused by different indications for autopsy in dialysis patients and non-dialysis patients. Moreover, postmortem diagnosis often provides little information about the clinical significance of pulmonary embolism and information on whether it contributed to death is often lacking.

Our finding that the mortality rate ratio was highest for pulmonary embolism was a surprise. Although pulmonary embolism as a cause of death is less common, clinicians should be aware of the increased risk of this disorder in dialysis patients, since it is the most common preventable cause of hospital death.[24] In contrast to myocardial infarction and stroke, pulmonary embolism can be prevented by administering prophylactic anticoagulation therapy in patients considered to be at increased risk.[25] Especially high-risk groups, including elderly dialysis patients with diabetes or multi-system disease as shown in our study, could benefit from thromboprophylaxis. Nevertheless, further studies are needed to show whether thromboprophylaxis is cost-effective and safe in high-risk dialysis patients, given the increased bleeding risk associated with anticoagulation and given its potential role in the generation of vascular calcification. The increased mortality rate for myocardial infarction,[2,13,26,27] stroke,[14,15,27,28] and other cardiovascular diseases[2,4,5] in our cohort of dialysis patients is in line with previous studies that showed an increased incidence of myocardial infarction, stroke, and other cardiovascular events.

Our results show that death due to pulmonary embolism was associated with increased age, female sex, and diabetes. Female sex and increased age are also important risk factors for pulmonary embolism in the general population.[29] Studies on the association between diabetes and pulmonary embolism in the general population have shown conflicting results,[30,31] but our

data show that diabetes is a risk factor in dialysis patients. We did not find an association between treatment modality (hemodialysis or peritoneal dialysis) and mortality due to pulmonary embolism. It could be suggested that the mortality risk of pulmonary embolism should be theoretically lower for hemodialysis patients than for peritoneal dialysis patients, because of anticoagulation use during hemodialysis sessions to prevent clot formation. However, peritoneal dialysis patients could have less comorbidities than hemodialysis patients at baseline explaining the similar mortality rates for hemodialysis and peritoneal dialysis patients. We had no information about comorbidities to investigate this. Our findings that older age, male sex, and diabetes as cause of end-stage renal disease were associated with an increased risk of myocardial infarction in dialysis patients is consistent with previous studies.[1,13] The association between stroke and increased age, female sex, and diabetes as cause of end-stage renal disease in our study was also in agreement with previous studies in dialysis patients.[14,15,27,32]

The unexpected increased mortality risk of pulmonary embolism could reflect an increased incidence of pulmonary embolism in dialysis patients.[22,23] Furthermore, an increased fatality rate of pulmonary embolism in dialysis patients could lead to an increased mortality risk due to pulmonary embolism.[33] A previous study showed that patients with a severely decreased kidney function (glomerular filtration rate <30 ml/min) had a 5.5-fold increased mortality risk within 2 weeks after an initial pulmonary embolism as compared with persons with a filtration rate ≥30 ml/min.[33] The investigation of non-fatal events and fatality rates was beyond our scope, since we focused on mortality rates. However, based on the higher prevalence of pulmonary embolism as a cause of death in dialysis patients (0.7%) than in the general population (0.5%), the 12.2-fold increased mortality risk due to pulmonary embolisms is probably not only a reflection of higher mortality rates in dialysis patients than in the general population.

Several explanations for an increased incidence of pulmonary embolism in dialysis patients are possible. An explanation could be the higher rate of hospitalization, surgery, and immobilization in dialysis patients than in the general population. Furthermore, several studies have demonstrated a hypercoagulable state in dialysis patients.[34,35] Hypercoagulability due to vasculitis could also explain the increased risk of pulmonary embolism in patients with multi-system disease, including patients with systemic lupus erythematosus or granulomatous polyangiitis,[36-38] while nephrotic-range proteinuria could explain the increased risk in patients with diabetes as both diabetes and pulmonary embolism have been associated with the nephrotic syndrome.[39] However, the nephrotic syndrome probably plays a less important role in the development of pulmonary embolisms in dialysis patients than in other kidney disease patients, since the nephrotic syndrome is less common in dialysis patients because

of the fast loss of residual renal function. Another plausible explanation for the increased risk of venous thrombosis in dialysis patients could be thrombus formation associated with catheters and arteriovenous accesses for dialysis which may cause pulmonary embolisms through dislodgement of thrombi.[40,41] We had no information about type of access in this study. Moreover, anticoagulation could be withheld in dialysis patients, because of the increased bleeding risk. We also had no information about anticoagulation use.

Several explanations for the highly increased mortality risk of myocardial infarction and stroke are possible. The high risk of myocardial infarction and stroke could be explained by the much higher prevalence of traditional risk factors for cardiovascular diseases, such as diabetes, hypertension, and left ventricular hypertrophy in the dialysis population than in the general population.[14,15,27,32,42] In addition, chronic kidney disease has been shown to be associated with inflammation and accelerated atherosclerotic vascular disease that subsequently could increase the mortality risk from myocardial infarction or ischemic stroke.[43,44] Moreover, anticoagulation of patients combined with uremic bleeding diathesis, may cause an increased risk of hemorrhagic stroke. Unfortunately, our data did not allow the calculation of mortality rate ratios for ischemic and hemorrhagic stroke separately.

A potential limitation of our study was that the cause of death was unknown in approximately 13.8% of the dialysis patients compared with 2.0% of the general population. This difference can be explained by the slightly different method for assigning the cause of death in dialysis patients as compared with the general population. For example, the autopsy is performed less commonly in dialysis patients than in the general population. Causes of death among patients on dialysis were recorded by the primary nephrologist. When a patient died at home or elsewhere outside the hospital, the nephrologist will have been dependent on information from others, and may more likely report a cause of death as unknown. Conversely, causes of death within the general population are, according to law, recorded by the physician who confirmed the death and thereafter sent the data to the statistics office, resulting in relatively fewer missing causes of death. Since the proportion of missing causes of death is greater in dialysis patients than in the general population, it is likely that this study underestimated the mortality rate ratios for total and specific cardiovascular mortality in dialysis patients as compared with the general population due to misclassification of cardiovascular death as unknown. Furthermore, misclassification may have become even worse due to the potential attribution of the code sudden cardiac death to dialysis patients who in reality may have died from pulmonary embolism, myocardial infarction, or stroke. In a highly unlikely worst case scenario, in which we change all unknown codes of death in the general population into pulmonary embolism, myocardial infarction, or stroke, we would still observe increased age- and sex-standardized mortality rate ratios for pulmonary embolism (2.7; 95% CI 2.3-3.3),

and also for myocardial infarction (8.4; 95% CI 8.0-8.8) and stroke (6.8; 95% CI 6.5-7.2), respectively.

In conclusion, dialysis patients have an unexpected highly increased mortality risk due to pulmonary embolism, and an increased mortality risk due to myocardial infarction, stroke, and other cardiovascular diseases as compared with the general population.

ACKNOWLEDGEMENTS

We would like to thank the patients and staff of all the dialysis and transplant units who have contributed data via their national and regional renal registries. Furthermore, we gratefully acknowledge the following registries and persons for their participation in the data collection: P. Castro de la Nuez and J. M. Munoz Terol (Andalusian Renal Registry); A. Magaz, J. Aranzabal, I. Lampreabe and J. Arrieta (Basque Country RenalRegistry); E.Arcos, J. Comas,R.Deulofeu and J. Twose [Catalan Renal Registry (RMRC) and Catalan Transplant Organization (OCATT)]; A. Hemke [Dutch End-Stage Renal Disease Registry (RENINE)]; C. Gro¨ nhagen-Riska (Finnish Registry for Kidney Diseases); G. A. Ioannidis (Greek National Renal Registry); M. Postorino (Italian Renal Registry: Calabria); S. Schon, A. Seeberger, L. Backman and B. Rippe [Swedish Renal Registry (SNR)]; J. Haef (Danish Renal Registry); J.M. des Grottes and F. Collart (French-Speaking Belgium Registry); R. Kramar (Austrian Registry); and O. Zurriaga [Registro de Enfermos Renales de la Comunidad Valenciana (REMRENAL)] for providing data. The ERA–EDTA Registry is funded by the European Renal Association–European Dialysis and TransplantAssociation (ERA–EDTA).

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