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**Author:** Appeldoorn- de Jager, Dina Jezina (Dinanda) van

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# Chapter 8 |

## Cardiovascular and noncardiovascular mortality among patients starting dialysis

Dinanda J. de Jager, Diana C. Grootendorst, Kitty J. Jager, Paul C. van Dijk, Lonneke M.J. Tomas, David Ansell, Frederic Collart, Patrik Finne, James G. Heaf, Johan De Meester, Jack F.M. Wetzels, Frits R. Rosendaal, Friedo W. Dekker

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**Abstract***Context*

Cardiovascular mortality is considered the main cause of death in patients receiving dialysis and is 10 to 20 times higher in such patients than in the general population.

*Objective*

To evaluate if high overall mortality in patients starting dialysis is a consequence of increased cardiovascular mortality risk only or whether noncardiovascular mortality is equally increased.

*Design, setting, and patients*

Using data from between January 1, 1994, and January 1, 2007, age-stratified mortality in a European cohort of adults starting dialysis and receiving follow-up for a mean of 1.8 (standard deviation, 1.1) years (European Renal Association-European Dialysis and Transplant Association [ERA-EDTA] Registry [N=123,407]) was compared with the European general population (Eurostat).

*Main outcome measures*

Cause of death was recorded by ERA-EDTA codes in patients and matching International Statistical Classification of Diseases, 10<sup>th</sup> Revision codes in the general population. Standardized cardiovascular and noncardiovascular mortality rates, their ratio, difference, and relative excess of cardiovascular over noncardiovascular mortality were calculated.

*Results*

Overall all-cause mortality rates in patients and the general population were 192 per 1000 person-years (95% confidence interval [CI], 190-193) and 12.055 per 1000 person-years (95% CI, 12.05-12.06), respectively. Cause of death was known for 90% of the patients and 99% of the general population. In patients, 16,654 deaths (39%) were cardiovascular and 21,654 (51%) were noncardiovascular. In the general population, 7,041,747 deaths (40%) were cardiovascular and 10 183 322 (58%) were noncardiovascular. Cardiovascular and noncardiovascular mortality rates in patients were respectively 38.1 per 1000 person-years (95% CI, 37.2-39.0) and 50.1 per 1000 person-years (95% CI, 48.9-51.2) higher than in the general population. On a relative scale, standardized cardiovascular and noncardiovascular mortality were respectively 8.8 (95% CI, 8.6-9.0) and 8.1 (95% CI, 7.9-8.3) times higher than in the general population. The ratio of these rates, i.e., relative excess of cardiovascular over noncardiovascular mortality in patients starting dialysis compared with the general population, was 1.09 (95% CI, 1.06-1.12). Relative excess in a sensitivity analysis in which unknown/missing causes of death were regarded either as noncardiovascular or cardiovascular varied between 0.90 (95% CI, 0.88-0.93) and 1.39 (95% CI, 1.35-1.43).

*Conclusion*

Patients starting dialysis have a generally increased risk of death that is not specifically caused by excess cardiovascular mortality.

## Introduction

Patients with chronic kidney disease are at higher mortality risk compared with the general population.<sup>1,2</sup> Cardiovascular disease is the most common cause of death in these patients, as noted more than 30 years ago.<sup>3</sup> Several studies have shown that cardiovascular disease accounts for 40% to 50% of deaths in patients with end-stage renal disease.<sup>4-6</sup> Cardiovascular mortality risk in patients receiving hemodialysis or peritoneal dialysis is observed to be 10 to 20 times that in the general population.<sup>4,6</sup>

In addition to mortality, cardiovascular morbidity is highly prevalent in patients receiving dialysis.<sup>7</sup> Approximately 75% of such patients have left ventricular hypertrophy as determined by ultrasound.<sup>8</sup> The prevalence of coronary artery disease or congestive heart failure in patients receiving dialysis is approximately 40%.<sup>9</sup> The high risk of cardiovascular morbidity and mortality in patients receiving dialysis is associated with a high prevalence of known risk factors for cardiovascular disease in the general population (hypertension, diabetes, dyslipidemia). In addition, specific characteristics of the dialysis population play a role, including increased presence of multiple comorbid conditions, volume overload, and disturbed calcium phosphate metabolism.<sup>4,10-13</sup> Moreover, chronic kidney disease has been regarded as a risk factor for cardiovascular disease.<sup>14-17</sup> Therefore, current clinical guidelines recommend that clinicians consider and treat individuals with chronic kidney disease as being at high risk for cardiovascular disease.<sup>18</sup>

The current concept is that the overall high mortality in patients receiving dialysis is largely explained by increased cardiovascular mortality.<sup>18</sup> (pp 58, 59) In many reports on classic or novel cardiovascular risk factors, specific reference is made to high cardiovascular mortality. It is believed that the life span of patients receiving dialysis is reduced mainly as a consequence of premature cardiovascular death.<sup>19</sup> To evaluate whether this is indeed the case, we estimated cardiovascular and noncardiovascular mortality in a large cohort of European patients receiving dialysis and compared these estimates with mortality data from the general European population.

## Methods

### *Study population*

The study cohort consisted of incident patients from the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Registry who were starting hemodialysis and peritoneal dialysis.<sup>20</sup> The ERA-EDTA Registry collects data on renal replacement therapy through national and regional registries in Europe, including date of birth, sex, primary renal disease, date of start of therapy, subsequent changes in treatment modality, and date and cause of death.

Patients were included if they originated from registries reporting less than 25% missing or unknown causes of death. Cause of death was classified by means of the ERA-EDTA coding system for causes of death.<sup>21,22</sup> The inclusion period for the present study was between January 1, 1994, and January 1, 2007. For the present analysis, patients underwent follow-up for a

maximum of 3 years (cumulative survival $\approx$ 50%) from start of dialysis until death or censoring, which occurred at time of recovery of renal function, transplantation, or January 1, 2007 (end of study), whichever occurred first.

#### *Reference Population*

Mortality data from the general populations of the 9 countries from which patients were included were used for reference. Data were obtained from Eurostat, the statistical office of the European Union.<sup>23;24</sup> Eurostat provides cause-specific mortality data, classified by International Statistical Classification of Diseases, 10th Revision (ICD-10) codes, stratified by 5-year age categories and sex.<sup>25</sup>

#### *Definition of Study Outcomes*

Cardiovascular mortality in patients was defined as death attributable to myocardial ischemia and infarction, heart failure, cardiac arrest due to other or unknown cause, or cerebrovascular accident (ERA-EDTA codes 11, 14-16, 18, and 22). Unknown (ERA-EDTA code 0) or missing causes of death were defined as unknown/missing. Noncardiovascular mortality was defined as all other causes of death, i.e. infection, suicide or refusal of treatment, withdrawal, cachexia, malignancies, and miscellaneous (ERA-EDTA codes 12, 13, 17, 21, 23-29, 31-33, 35-39, 41-46, 51-54, 62-64, 66-73, 81, 82, and 99-102).

Cardiovascular mortality in the general population was defined as diseases of the circulatory system, i.e. acute rheumatic fever; chronic rheumatic heart disease; hypertensive diseases; ischemic heart diseases; pulmonary heart diseases and diseases of pulmonary circulation; other forms of heart disease; cerebrovascular diseases; diseases of arteries, arterioles, and capillaries; diseases of veins, lymphatic vessels, and lymph nodes, not elsewhere classified; and other and unspecified disorders of the circulatory system (Eurostat codes ICD-10 I00-I99). ICD-10 codes R96-R99 (ill-defined and unknown causes of mortality) were regarded as unknown/missing cause of death in the general population, while all other codes (thus all causes except ICD-10 I00-I99 and R96-R99) were regarded as noncardiovascular causes of death.

Data were collected in accordance with national and regional laws, which are usually based on European legislation but which may differ slightly between the different countries or regions from which participants were included. For patients starting dialysis, this generally includes requesting informed consent for data collection within the framework of the registries and permission to send these data to the ERA-EDTA registry in an anonymous form.

#### *Statistical analyses*

Data were stratified by 10-year age categories and sex. The lowest age category consisted of patients aged 20 to 24 years, whereas all patients 85 years and older were combined in the highest age category. For each individual patient, person-time at risk was calculated as the time between start of dialysis and censoring or death. Total person-time at risk within the patient populations was calculated as the sum of the individual person-times. Person-time at risk within

the general population was calculated using the demographic large-scale method, a method for calculating person-time within dynamic populations. Using this method, person-time at risk in the 9 general populations of the countries from which patients starting dialysis were included was calculated as the sum of the mean sizes of the general populations in the subsequent calendar years. In addition, the total number of all-cause, cardiovascular, and noncardiovascular deaths during the study period within both populations were determined.

Subsequently, in both populations, age-specific cardiovascular and noncardiovascular mortality rates (per 1000 person-years) were calculated by dividing the total number of deaths by the total person-time lived in an age stratum. Differences between cardiovascular mortality rates in patients and the general population ( $\Delta CV$ ) were calculated by subtracting mortality rates in patients from the rates in the general population. Differences between noncardiovascular mortality rates ( $\Delta non-CV$ ) were calculated in the same manner. Absolute excess cardiovascular mortality over noncardiovascular mortality in patients compared with the general population was calculated as the difference between  $\Delta CV$  and  $\Delta non-CV$ . To correct for age differences between patients and the general population, standardization with weights derived from the age distribution of the general population was used. Standardized mortality rate ratios were calculated by dividing the sum of the stratum-specific standardized mortality rates in patients starting dialysis by the sum of these rates in the general population. Relative excess cardiovascular mortality was defined as the ratio of these 2 rate ratios for cardiovascular and noncardiovascular mortality being higher than 1, to indicate to what extent cardiovascular mortality exceeds noncardiovascular mortality in patients starting dialysis.

Several sensitivity analyses were performed to check the robustness of the results. First, unknown causes of death (either missing or ERA-EDTA code 0) were censored in the analyses. To evaluate the influence of these unknown causes of death, all unknown mortality causes were classified as either cardiovascular or noncardiovascular mortality. Second, to evaluate the effect of censoring at time of transplantation, an analysis was performed in which patients were not censored after transplantation. Third, since follow-up was arbitrarily prespecified at a cumulative survival of approximately 50%, follow-up was censored at 3 years. The effect of maximizing follow-up at 3 years was evaluated in an analysis in which total follow-up of all patients was used instead of only the first 3 years. Fourth, results were obtained using direct standardization, with weights derived from the age distribution of the general population. The influence of the choice of the weighting scheme was assessed in an analysis whereby weights were derived from the patients starting dialysis. If applicable, 2-sided  $p < 0.05$  was regarded as statistically significant. Statistical analyses were performed using SPSS version 14.0.2 (SPSS Inc, Chicago, Illinois).

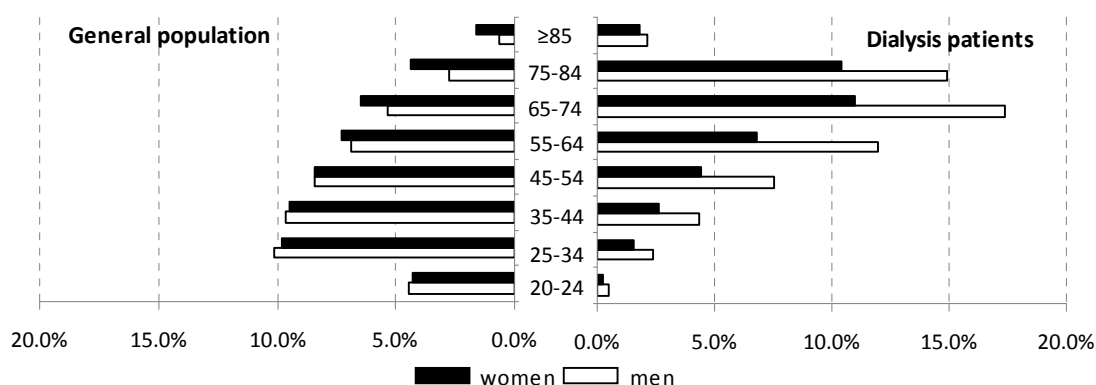
## Results

### *Study population*

Patients (N=123,407) were included from registries in 9 countries: Austria, Belgium (Dutch- and French-speaking), Denmark, Finland, Italy (Basilicata, Emilia-Romagna, Piemonte, Sardegna),

the Netherlands, Norway, Spain (Andalusia, Basque Country, Catalonia), and Sweden. All renal registries had 100% coverage of the general population in the corresponding region. Mean age of the patients at start of dialysis was 63.2 years, and the majority (61.2%) were men (Table 1).

**Figure 1.** Age and sex distribution in the general population (Eurostat, mean size during thirteen-year follow-up period: N=111,190,899: 53,633,232 men and 57,557,667 women, left panel) and dialysis patients (ERA-EDTA Registry, N=123,407 patients: 75,482 men and 47,925 women, right panel).



The general population included 1,445,495,838 person-years over the 13-year observation period. The mean age of patients starting dialysis was higher, and that group included more men than the general population (Figure 1). Follow-up During follow-up, 25,084 patients (20.3%) were censored (withdrawn alive) because of kidney transplantation, and 42,643 (34.6%) died. Cause of death remained missing or unknown for 4,335 patients (10.2%). Characteristics of patients with known and unknown causes of death were not different ( $p>0.05$ ). Noncardiovascular death (21,654 patients [50.8%]) was the most prevalent cause of death, whereas 16,654 patients (39.1%) died of cardiovascular disease. The most common causes of noncardiovascular death were infections (6,220 patients [14.6%]) and malignancies (3,334 patients [7.6%]). The pattern of causes of noncardiovascular death was different across the age groups. Younger patients died relatively often as a consequence of infections, whereas the incidence of “social death” (e.g. refusal of treatment) and cachexia was highest in elderly patients (Table 2). In the general population, 10,183,322 persons (58.4%) died from noncardiovascular causes, 7,041,747 (40.4%) from cardiovascular causes, and 201,050 (1.2%) from unknown causes.

#### *Absolute differences in mortality rates and absolute excess mortality*

The overall all-cause mortality rate was higher in patients starting dialysis (191.7 per 1000 person-years [95% confidence interval, CI, 189.8-193.5]) than in the general population (12.055 per 1000 person-years [95% CI, 12.05-12.06]).

**Table 1.** Baseline description of dialysis patients (N=123,407).

Unless otherwise stated: Mean (SD); CV: cardiovascular; \* At start of follow-up; †During follow-up.

	All patients N=123,407		Age category*									
	20-24 N=1,591	25-34 N=5,471	35-44 N=9,495	45-54 N=16,210	55-64 N=25,051	65-74 N=36,589	75-84 N=26,078	≥85 N=2,922				
Age yr	63.2 (14.9)	22.7 (1.4)	30.6 (2.8)	40.4 (2.9)	50.4 (2.9)	60.3 (2.9)	70.2 (2.9)	79.0 (2.7)	87.6 (2.3)			
Males N (%)	75,482 (61.2)	1,028 (64.6)	3,311 (60.5)	5,975 (62.9)	10,239 (63.2)	15,824 (63.2)	22,267 (60.9)	15,255 (58.5)	1,583 (54.2)			
Renal transplant <sup>†</sup> N (%)	25,084 (20.3)	1,131 (71.1)	3,520 (64.3)	5,236 (55.1)	6,984 (43.1)	6,040 (24.1)	2,080 (5.7)	90 (0.3)	3 (0.1)			
Follow-up yr	1.8 (1.1)	1.8 (1.0)	1.8 (1.0)	1.8 (1.0)	1.9 (1.0)	1.9 (1.0)	1.8 (1.1)	1.6 (1.1)	1.3 (1.1)			

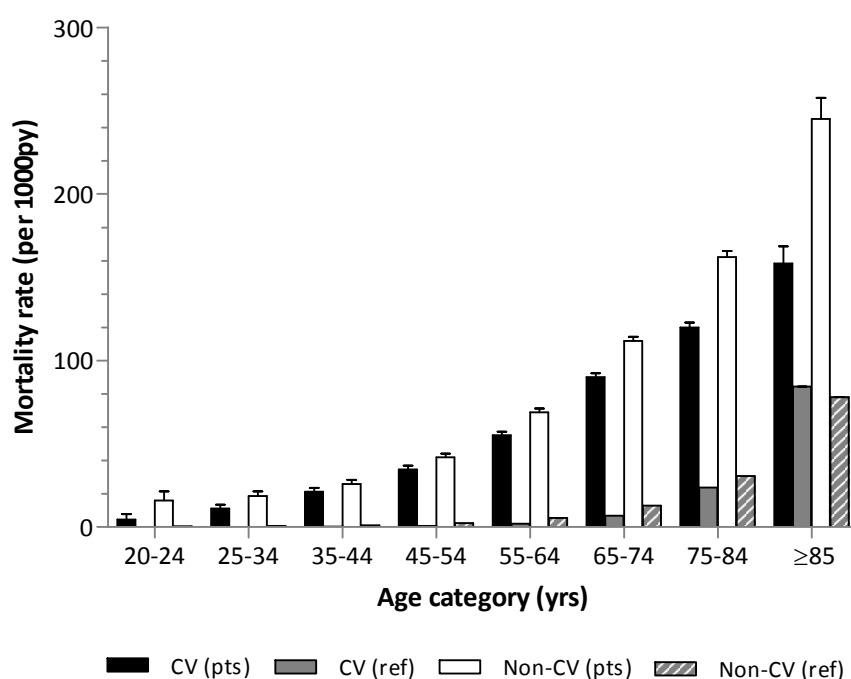
**Table 2.** Causes of death of dialysis patients in the first three years after start of dialysis.

All data are presented as N (%); \* Age at death.

	All patients N=123,407		Age category*									
	20-24 N=977	25-34 N=4,844	35-44 N=8,584	45-54 N=14,713	55-64 N=23,194	65-74 N=35,027	75-84 N=31,211	≥85 N=4,857				
Total deaths	42,643 (34.6)	46 (4.7)	304 (6.3)	880 (10.3)	2,498 (17.0)	6,343 (27.3)	14,779 (42.2)	15,207 (48.7)	2,586 (53.2)			
CV	16,654 (39.1)	8 (17.4)	99 (32.6)	346 (39.3)	1,007 (40.3)	5,973 (40.2)	5,937 (40.2)	5,819 (38.3)	924 (35.7)			
Non-CV	21,654 (50.8)	33 (71.7)	168 (55.3)	422 (48.0)	1,214 (48.6)	7,369 (49.9)	7,369 (49.9)	7,877 (51.8)	1,432 (55.4)			
Infections	6,220 (14.6)	9 (19.6)	65 (21.4)	135 (15.3)	399 (16.0)	979 (15.4)	2,186 (14.8)	2,105 (13.8)	342 (13.2)			
Malignancies	3,334 (7.8)	3 (6.5)	12 (3.9)	58 (6.6)	223 (8.9)	653 (10.3)	1,276 (8.6)	1,012 (6.7)	97 (3.8)			
Cachexia	2,015 (4.7)	0	6 (2.0)	17 (1.9)	70 (2.8)	179 (2.8)	570 (3.9)	913 (6.0)	260 (10.1)			
Withdrawal	2,212 (5.2)	1 (0.1)	5 (1.6)	16 (1.8)	57 (2.3)	202 (3.2)	674 (4.6)	1,012 (6.7)	245 (9.5)			
Suicide/refusal treatment	1,658 (3.9)	1 (0.1)	14 (4.6)	33 (3.8)	57 (2.3)	172 (2.7)	503 (3.4)	722 (4.7)	156 (6.0)			
Miscellaneous	6,215 (14.6)	19 (41.3)	66 (21.7)	163 (18.5)	408 (16.3)	954 (15.0)	2,160 (14.6)	2,113 (13.9)	332 (12.8)			
Unknown	4,335 (10.2)	5 (10.9)	37 (12.2)	112 (12.7)	277 (11.1)	690 (10.9)	1,473 (10.0)	1,511 (9.9)	230 (8.9)			

The cardiovascular and noncardiovascular mortality rates were lowest in young participants and increased with age in both populations. In particular, noncardiovascular mortality rates were higher than cardiovascular mortality rates in patients starting dialysis (Figures 2 and 3). For every age group  $\Delta CV$  and  $\Delta non-CV$  were positive, indicating excess cardiovascular as well as excess noncardiovascular mortality in patients starting dialysis compared with the general population. More important, for almost every age stratum, absolute excess was greater for noncardiovascular than for cardiovascular mortality (Table 3).

**Figure 2.** Absolute cardiovascular (CV) and non-cardiovascular (non-CV) mortality rates (per 1000py, mean with standard error) were higher in dialysis patients (pts) than in the general population (ref) at every age.



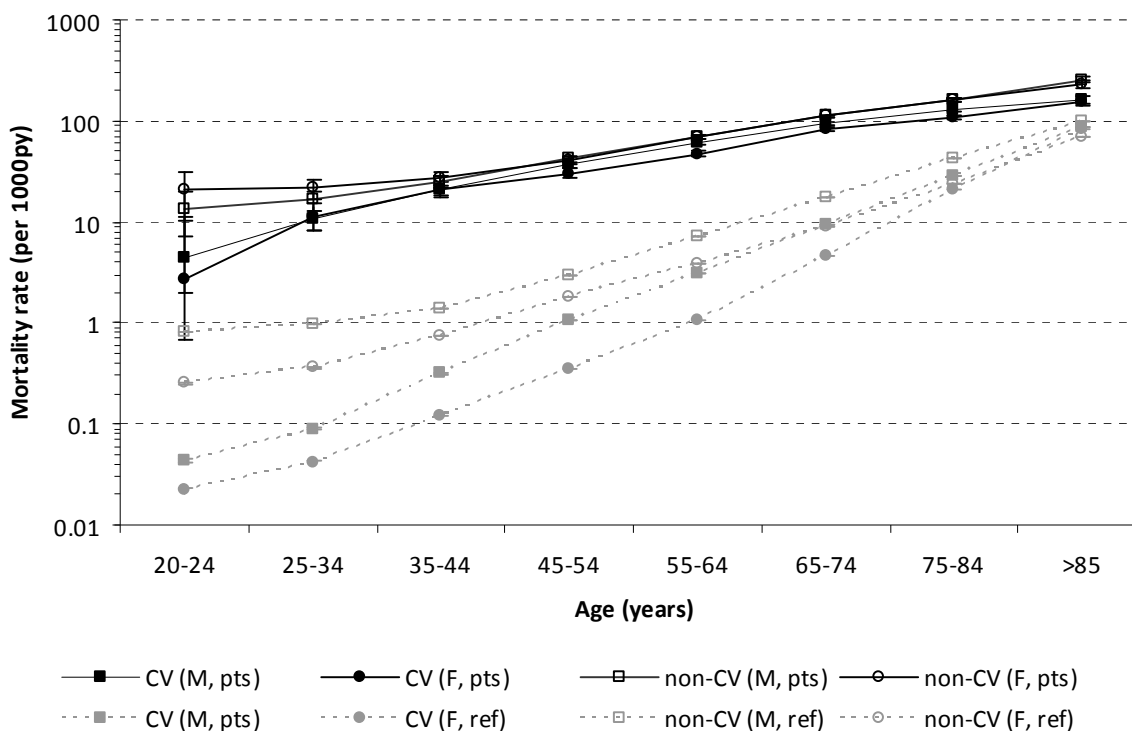
After age standardization, absolute excess noncardiovascular mortality in patients starting dialysis (50.1 per 1000 person-years [95% CI, 48.9-51.2]) was greater than absolute excess cardiovascular mortality (38.1 per 1000 person-years [95% CI, 37.2-39.0]) (Table 3). After age standardization, absolute excess cardiovascular mortality was comparable between men and women (37.3 per 1000 person-years [95% CI, 36.1-38.5] vs. 37.0 per 1000 person-years [95% CI, 35.6-38.5], respectively). However, absolute excess noncardiovascular mortality was greater in women than in men (55.8 per 1000 person-years [95% CI, 53.9-57.7] vs. 44.1 per 1000 person-years [95% CI, 42.7-45.5], respectively).

**Table 3.** Cardiovascular and non-cardiovascular mortality rates (per 1000py), their difference, and the excess risk of cardiovascular mortality over non-cardiovascular mortality in the dialysis population as compared to the general population.

Age	CV <sup>1</sup>		Non-CV <sup>1</sup>		Absolute Excess		
	Pts	Ref	Pts	Ref	ΔCV <sup>2</sup>	Δnon-CV <sup>2</sup>	Excess <sup>3</sup>
20-24	3.9	0.0	16.0	0.5	3.8 (2.2, 5.5)	15.5 (10.0, 20.9)	-11.6 (-17.3, -5.9)
25-34	11.0	0.1	18.7	0.7	10.9 (8.8, 13.1)	18.0 (15.2, 20.8)	-7.1 (-10.6, -3.5)
35-44	21.2	0.2	25.8	1.1	20.9 (18.7, 23.2)	24.7 (22.2, 27.2)	-3.8 (-7.1, -0.5)
45-54	34.6	0.7	41.7	2.4	33.9 (31.8, 36.1)	39.4 (37.0, 41.7)	-5.4 (-8.6, -2.3)
55-64	55.1	2.0	68.8	5.5	53.1 (50.9, 55.2)	63.3 (60.9, 65.7)	-10.2 (-13.5, -7.0)
65-74	90.0	6.8	111.7	12.9	83.3 (81.0, 85.6)	98.8 (96.3, 101.4)	-15.6 (-19.0, -12.1)
75-84	119.8	23.8	162.1	30.6	96.0 (92.9, 99.1)	131.5 (127.9, 135.1)	-35.5 (-40.2, -30.8)
≥85	158.1	84.3	245.1	78.0	73.8 (63.6, 84.0)	167.0 (154.4, 179.7)	-93.2 (-109.5, -77.0)
Unstand. <sup>4</sup>	74.9 (73.7, 76.0)	4.872 (4.87, 4.88)	97.3 (96.0, 98.6)	7.045 (7.04, 7.05)	70.0 (68.8, 71.1)	90.3 (89.0, 91.6)	-20.3 (-22.0, -18.6)
Stand. <sup>5</sup>	42.9 (42.0, 43.8)	4.9*	57.1 (56.0, 58.2)	7.0*	38.1 (37.2, 39.0)	50.1 (48.9, 51.2)	-12.0 (-13.4, -10.5)
20-24	4.5	0.0	13.5	0.8	4.5 (2.4, 6.5)	12.7 (10.6, 14.7)	-8.2 (-11.2, -5.3)
25-34	10.9	0.1	16.5	1.0	10.8 (8.0, 13.6)	15.5 (12.1, 19.0)	-4.8 (-9.2, -0.3)
35-44	21.3	0.3	25.1	1.4	20.9 (18.1, 23.8)	23.7 (20.6, 26.8)	-2.8 (-7.0, 1.4)
45-54	37.4	1.1	42.3	3.0	36.3 (33.5, 39.1)	39.3 (36.3, 42.3)	-3.0 (-7.1, 1.1)
55-64	59.7	3.1	68.2	7.2	56.6 (53.8, 59.4)	61.0 (58.0, 64.1)	-4.4 (-8.6, -0.3)
65-74	95.5	9.5	112.0	17.8	86.0 (83.0, 89.1)	94.2 (90.9, 97.4)	-8.1 (-12.6, -3.7)
75-84	126.6	29.0	161.7	42.0	97.6 (93.5, 101.8)	119.7 (115.1, 124.4)	-22.1 (-28.4, -15.9)
≥85	158.5	87.8	255.1	98.0	70.8 (56.9, 84.6)	157.1 (139.5, 174.6)	-86.3 (-108.7, -64.0)
Unstand. <sup>4</sup>	78.3 (76.8, 79.8)	4.611 (4.61, 4.62)	95.9 (94.2, 97.5)	7.807 (7.80, 7.81)	73.7 (72.2, 75.2)	88.1 (86.4, 89.7)	-14.4 (-16.6, -12.2)
Stand. <sup>5</sup>	41.9 (40.7, 43.1)	4.6*	51.9 (50.5, 53.3)	7.8*	37.3 (36.1, 38.5)	44.1 (42.7, 45.5)	-6.8 (-8.6, -5.0)
20-24	2.8	0.0	20.6	0.3	2.7 (-0.5, 6.0)	20.4 (17.1, 23.6)	-17.6 (-22.3, -13.0)
25-34	11.2	0.0	21.9	0.4	11.2 (7.7, 14.6)	21.5 (16.7, 26.3)	-10.3 (-16.2, -4.4)
35-44	21.0	0.1	26.9	0.8	20.9 (17.3, 24.5)	26.2 (22.1, 30.2)	-5.3 (-10.7, 0.1)
45-54	30.0	0.4	40.8	1.8	29.7 (26.4, 32.9)	39.0 (35.2, 42.8)	-9.4 (-14.3, -4.4)
55-64	47.4	1.0	69.8	3.9	46.4 (43.1, 49.6)	65.9 (61.9, 69.9)	-19.6 (-24.7, -14.4)
65-74	81.7	4.5	111.4	8.9	77.2 (73.7, 80.6)	102.5 (98.5, 106.5)	-25.3 (-30.6, -20.0)
75-84	110.1	20.5	162.7	23.6	89.6 (85.1, 94.2)	139.2 (133.6, 144.7)	-49.5 (-56.7, -42.3)
≥85	157.7	82.9	233.1	69.8	74.7 (59.7, 89.8)	163.3 (145.0, 181.7)	-88.6 (-112.3, -64.8)
Unstand. <sup>4</sup>	69.6 (67.8, 71.3)	5.115 (5.11, 5.12)	99.6 (97.5, 101.7)	6.335 (6.33, 6.34)	64.5 (62.7, 66.2)	93.3 (91.2, 95.3)	-28.8 (-31.5, -26.1)
Stand. <sup>5</sup>	42.2 (40.7, 43.6)	5.1*	62.1 (60.2, 64.0)	6.3*	37.0 (35.6, 38.5)	55.8 (53.9, 57.7)	-18.8 (-21.1, -16.4)

CV: cardiovascular; Δ: difference; <sup>1</sup>Stratum specific mortality rates in patients (Pts) and the general population (Ref); <sup>2</sup>Difference between stratum specific mortality rate in patients and the stratum specific mortality rate in the general population; <sup>3</sup>Excess cardiovascular over non-cardiovascular mortality, calculated as the difference between ΔCV and Δnon-CV; negative values indicate higher non-CV mortality, positive values higher CV mortality; <sup>4</sup>Unstandardized overall mortality rate, their difference and excess; <sup>5</sup>Directly standardized overall mortality rate (for calculation details, see text), their difference and excess; \*Confidence interval similar to unstandardized rate, since weights were based on age-distribution of the reference population.

**Figure 3.** Unstandardized cardiovascular (CV) and non-cardiovascular (Non-CV) mortality rates (per 1000 person-years, mean with 95% CI) of male (M) and female (F) dialysis patients (pts) and the general population (ref).



#### *Relative differences in mortality rates and relative excess mortality*

Overall unstandardized cardiovascular and noncardiovascular mortality rates were respectively 15.4 (95% CI, 14.2-16.5) and 13.8 (95% CI, 12.5-15.1) times higher in patients than in the general population. The directly standardized cardiovascular mortality rate was 8.8 (95% CI, 8.6-9.0) and the noncardiovascular mortality rate was 8.1 (95% CI, 7.9-8.3) times higher in patients starting dialysis than in the general population. The relative excess of cardiovascular over noncardiovascular mortality was 1.09 (95% CI, 1.06-1.12).

Although  $\Delta CV$ ,  $\Delta non-CV$ , and relative excess mortality varied during the calendar period of the study (1994-2007), no change in mortality pattern toward either excess cardiovascular or excess noncardiovascular mortality was present. Minimum and maximum  $\Delta CV$  in the study period were 8.0 (95% CI, 7.4-8.7) and 9.5 (95% CI, 8.1-11.0), respectively; minimum and maximum  $\Delta non-CV$  were 7.6 (95% CI, 7.1-8.0) and 9.4 (95% CI, 8.4-10.5); and minimum and maximum excess were 1.01 (95% CI, 0.82-1.20) and 1.18 (95% CI, 1.08-1.27).

#### *Sensitivity analyses*

To test the robustness of the results, several sensitivity analyses were performed. First, cause of death was unknown in 10.2% of the patients and 1.2% of the general population. To evaluate the

influence of these unknown causes of death, an analysis was performed in which all unknown/missing mortality causes were classified either as noncardiovascular or cardiovascular. In the first extreme, the directly standardized noncardiovascular mortality rate increased to 9.8 (95% CI, 9.6-10.0), resulting in a relative excess cardiovascular mortality of 0.90 (95% CI, 0.88-0.93). For the other extreme, the directly standardized cardiovascular mortality rate increased to 11.2 (95% CI, 11.0-11.5), and the relative excess cardiovascular mortality would be 1.39 (95% CI, 1.35-1.43).

Second, patients were censored at time of transplantation. If not, the directly standardized mortality rate would be 8.1 (95% CI, 8.0-8.3) for cardiovascular mortality and 7.5 (95% CI, 7.4-7.6) for noncardiovascular mortality. This would result in a relative excess cardiovascular mortality of 1.08 (95% CI, 1.05-1.11).

Third, patients in the present analysis underwent follow-up during the first 3 years of dialysis. When patients underwent follow-up during their whole dialysis period, the directly standardized cardiovascular and noncardiovascular mortality rates were 8.6 (95% CI, 8.4-8.7) and 7.9 (95% CI, 7.7-8.0), respectively. This would result in a relative excess cardiovascular mortality of 1.09 (95% CI, 1.06-1.12).

Fourth, since the age distribution was different in patients starting dialysis and in the general population, mortality rates were standardized to the age distribution of the general population. When weights were derived from patients starting dialysis instead of the general population, the directly standardized cardiovascular and noncardiovascular mortality rates would be 7.5 (95% CI, 7.4-7.6) and 6.9 (95% CI, 6.8-7.0), respectively. This would result in a relative excess cardiovascular mortality of 1.09 (95% CI, 1.07-1.11).

### **Comment**

We studied a cohort of 123,407 incident patients starting dialysis, of whom 35% died during 3 years of follow-up. Overall standardized death rates in patients starting dialysis were substantially higher than in the general population. The standardized cardiovascular mortality rate was 38.1 per 1000 person-years (95% CI, 37.2-39.0) higher in patients compared with the general population, and the noncardiovascular mortality rate was 50.1 per 1000 person-years (95% CI, 48.9-51.2). These results suggest that excess mortality in patients receiving dialysis is not specifically the result of increased cardiovascular deaths.

The present study showed that the proportion of cardiovascular and noncardiovascular mortality in patients starting dialysis was approximately 44% (16,654 of 38,308 known causes of death) and 56% (21,654 of 38,308 known causes of death), respectively. This is in accordance with findings from the United States (45% cardiovascular and 55% noncardiovascular, respectively).<sup>26</sup> In addition, the present study showed that the unstandardized cardiovascular mortality risk in patients starting dialysis was 15-fold higher than in the general population. This is in accordance with other studies demonstrating a 10- to 20-fold increased cardiovascular mortality risk for patients receiving dialysis.<sup>4,6</sup> The present analysis added that noncardiovascular mortality was 14-fold higher in such patients than in the general population.

Age-standardized cardiovascular and noncardiovascular mortality were respectively 8.8- and 8.1-fold higher than in the general population, resulting in a relative excess of 1.09 for cardiovascular mortality over noncardiovascular mortality. However, because cardiovascular mortality is lower than noncardiovascular mortality in the general population, these ratios are not easy to compare. Absolute mortality rates show that among patients receiving dialysis, the increased risk of dying from noncardiovascular disease is higher than that for dying from cardiovascular disease (after age standardization, 50.1 extra deaths per 1000 person-years and 38.1 extra deaths per 1000 person-years compared with the general population, respectively). These absolute rates are especially important, because they reflect the burden of disease from a societal perspective. Infections and malignancies were the most important causes of noncardiovascular mortality in patients starting dialysis, which is in line with earlier findings.<sup>27;28</sup> To summarize, the increased risk of cardiovascular mortality in patients starting dialysis goes together with an equally increased risk of noncardiovascular mortality.

Some methodological issues deserve attention. First, mortality data were collected from national and regional registries for patients starting dialysis and from whole countries for the general population. Because it is unlikely that there are national differences in cause-of-death classification, it is not likely that this collection method introduced bias. Furthermore, cause of death was unknown/missing in approximately 10% of the patients and 1% of the general population. This different percentage can be explained by the slightly different method for collecting cause-of-death data between the patients and the general population. Causes of death among patients starting dialysis were recorded by the treating nephrologist. When a patient died at home or elsewhere, the treating physician was dependent on information from others. When cause of death was inconclusive, the nephrologist may have classified the cause as unknown. Causes of death within the general population were, according to law, recorded by the physician who confirmed death and sent to the statistics office, resulting in relatively few missing causes of death. To evaluate the influence of unknown/missing causes of death within the present analysis, a sensitivity analysis was performed in which all unknown/missing mortality causes were classified either as noncardiovascular mortality or as cardiovascular mortality, resulting in a relative excess cardiovascular mortality of 0.90 and 1.39, respectively. This suggests that even in these extreme situations, cardiovascular and noncardiovascular mortality are both markedly increased but more or less to the same extent.

Second, renal failure, which is present in all patients receiving dialysis, is never counted as a cause of death within this group. In contrast, in the general population renal failure may be counted as a cause of death (ICD-10 code N17-N19). However, since renal failure is seldom reported as a cause of death in the general population (<1%), it is unlikely that this has biased the present results.

Third, it can be questioned whether cardiovascular mortality was systematically underestimated or overestimated in one population or the other. Causes of death were determined according to the most plausible cause of death in both populations. Therefore, it is unlikely that a bias was introduced by specific comorbid diagnoses that systematically trumped

other diagnoses in recording the cause of death. Moreover, although the ERA-EDTA coding system is less comprehensive than the ICD-10 coding system, the ERA-EDTA system provides the opportunity to assign a “general cardiovascular” code, such as “cardiac arrest/sudden death, other cause or unknown” or “other causes of cardiac failure” in cases lacking an appropriate code for a specific cause of death certainly related to cardiovascular problems.

Fourth, follow-up was censored at the time of transplantation, because patients are no longer at risk to die while receiving dialysis at that time. It can be argued that such censoring may have influenced the results. However, a sensitivity analysis showed that without censoring for transplantation, relative excess cardiovascular over noncardiovascular mortality was 1.08, indicating that the choice of censoring at time of transplantation did not influence our results. Similarly, maximum follow-up in all patients was restricted to the first 3 years of dialysis to exclude an effect of survivor bias. An additional analysis using total follow-up during dialysis showed that this restriction did not influence the results and conclusion of the study: relative excess cardiovascular over noncardiovascular mortality was 1.09.

Fifth, to correct for age differences, patients were standardized to the age distribution of the general population. The choice for the direct standardization method was based on technical considerations. When the age distribution of patients starting dialysis would have been used, relative excess would have been 1.09.

How can the results of this study be explained? First, the prevalence of risk factors such as hypertension or diabetes for cardiovascular disease is higher in patients starting dialysis than in the general population.<sup>29</sup> In addition, it has been suggested that the uremic milieu in patients receiving dialysis potentiates vascular calcification.<sup>30-32</sup> Although it is unknown whether vascular calcification is a simple risk marker or a causal factor, mortality in patients with cardiac disease who are receiving dialysis is increased compared with that in patients with cardiac disease who are not,<sup>14</sup> suggesting at least some role for vascular calcification in increased cardiovascular mortality in patients receiving dialysis compared with the general population.

Second, uremia in patients receiving dialysis is associated with a state of immune dysfunction characterized by immunoactivation, resulting in inflammation and immunosuppression, which contributes to the high prevalence of infections among such patients.<sup>33</sup> Alterations in the immune system can also be related to excess mortality risk attributable to cancer in patients receiving dialysis. Interestingly, the prevalence of virus-related cancers is higher in patients receiving dialysis than in the general population.<sup>28</sup> Moreover, asymmetric dimethylarginine is considered a full-scale uremic toxin in end-stage renal disease<sup>34</sup> and has been identified as a risk factor for noncardiovascular mortality,<sup>35</sup> further supporting the role of uremia in noncardiovascular mortality. Increased cardiovascular and noncardiovascular mortality risk in patients receiving dialysis can both be explained by the effects of uremia.

Third, end-stage renal disease is associated with conditions including presence of comorbid disease, weight loss, muscle weakness, fatigue, and low physical activity,<sup>36</sup> all of which contribute to a frail phenotype. Frailty itself is associated with a doubling in mortality risk and with 60% increased risk of the combined outcome of death and hospitalization in patients

receiving dialysis.<sup>37</sup> We speculate that frailty is associated with an increase in both cardiovascular and noncardiovascular mortality risk in patients receiving dialysis. Interestingly, certain so-called nontraditional cardiovascular risk factors, such as troponin,<sup>38</sup> fetuin-A,<sup>39</sup> and C-reactive protein<sup>40</sup> are associated with increased cardiovascular as well as noncardiovascular mortality in patients receiving dialysis, which supports this hypothesis.

In summary, the present study shows that cardiovascular and noncardiovascular mortality are equally increased during the first 3 years of dialysis, compared with the general population. This implies that the importance of noncardiovascular mortality in patients receiving dialysis has generally been underestimated. Therefore, research should focus more on methods to prevent noncardiovascular mortality.

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