

# Chapter VI

## Causes of Death

### *Key Words:*

Cardiac deaths

Death rates

Diabetic ESRD

Hemodialysis

Infection in ESRD

Malignancy in dialysis

Peritoneal dialysis

Transplant deaths

Withdrawal from dialysis

Over half a million ESRD patients have died in the United States in the past twenty years. This chapter focuses on the specific causes of mortality and may serve as a source to help decrease the death rates of ESRD patients through further in-depth epidemiological and clinical research. The cause specific death rates for various subgroups of prevalent dialysis and transplant recipients are described. The reasons for withdrawal from dialysis therapy prior to death are also analyzed.

### **Analytical Methods**

The main source of information on causes of death among the ESRD population is the HCFA ESRD Death Notification Form, which was revised in 1990 and contains 59 causes of death. The prior form listed 22 causes of death including “withdrawal from dialysis” as one of the primary causes of death. The new form inquires whether “withdrawal from dialysis” occurred prior to death, as a question separate from “cause of death”. Thus, for each death, the patient’s physician reports both the cause of death and whether the patient withdrew from dialysis prior to death. In this chapter, the USRDS reports on data for deaths that occurred during 1995-1997.

For the purpose of this report, the 59 causes on the HCFA Death Notification Form were collapsed into 8 cause of death categories as shown in Table VI-1. More detailed information is provided in Reference Table D.4, where the causes of death are reported in 22 categories and Reference Table D.5,

where the death rates for all 59 cause of death categories are given by age group.

In past years, the USRDS files included a “missing” cause of death category for those patients who, by means of the Social Security Death Benefits files and hospital discharge records, were known to have died but for whom no Death Notification Form was received. Because of changes in REBUS, a database system described in more detail in the chapter entitled “Analytical Methods” (Chapter XIII), we are no longer able to distinguish between deaths where the physician indicated that the cause of death is unknown and cases where there is no Death Notification Form for the patient (i.e. unknown vs. missing). Thus, the death rates for patients with missing cause are included in the unknown category in Reference Tables D.4-D.6. Prior analyses of these data sources for 1994-1996 reveal that the Death Notification Form was “missing/incomplete” and “unknown” in about 14 and 6 percent of total reported ESRD deaths, 12 and 6 percent of dialysis deaths, and 51 and 4 percent of transplant deaths (USRDS 1998). Using previously reported ratios for each subgroup in this current chapter, the rates of “missing” cause of death have been estimated and are included in the figures presented.

Death rates were analyzed by primary cause of death among patients who were prevalent at the beginning of, or incident (defined as 90 days following start of ESRD) during, the years 1995, 1996 and 1997. Patients were followed through each year and the days at risk were calculated for each

**Collapsed Categories from Causes of Death on Death Notification Form (HCFA-2746)\***

<p><b><u>Acute Myocardial Infarction (Acute MI)</u></b></p> <p><b><u>Cardiac Arrest, cause unknown</u></b></p> <p><b><u>Cardiac, other</u></b>                  Atherosclerotic heart disease                  Cardiac arrhythmia                  Cardiomyopathy                  Pericarditis, including cardiac tamponade                  Pulmonary edema, due to exogenous fluid                  Valvular heart disease</p> <p><b><u>Cerebrovascular (CVD)</u></b>                  Cerebrovascular accident                  Ischemic brain damage</p> <p><b><u>Infection</u></b>                  AIDS                  Fungal peritonitis                  Hepatitis B                  Infection, other                  Other viral hepatitis                  Pulmonary infection, bacterial                  Pulmonary infection, fungal                  Pulmonary infection, other                  Septicemia, due to peritonitis                  Septicemia, due to PVD/gangrene                  Septicemia, due to vascular access                  Septicemia, other                  Tuberculosis                  Viral infection, CMV                  Viral infection, other</p> <p><b><u>Malignancy</u></b>                  Malignant disease, Hx of immunosupp. Rx                  Malignant disease, other</p>	<p><b><u>Other Known Causes</u></b>                  Accident related to treatment                  Accident unrelated to treatment                  Air embolism                  Bone marrow depression                  Cachexia                  Chronic obstructive pulmonary disease                  Cirrhosis                  Complications of surgery                  Dementia                  Diabetic coma, hypo/hyperglycemia                  Drug overdose                  Drug overdose-street drugs                  GI hemorrhage                  Hemorrhage from dialysis circuit                  Hemorrhage from ruptured vascular access                  Hemorrhage from surgery                  Hemorrhage from transplant site                  Hemorrhage from vascular access                  Hyperkalemia                  Liver failure, cause unknown                  Liver-drug toxicity                  Mesenteric infarction/Ischemic bowel                  Other hemorrhage                  Other identified cause                  Pancreatitis                  Perforation of bowel                  Perforation of peptic ulcer                  Polycystic liver disease                  Pulmonary embolus                  Seizures                  Suicide</p> <p><b><u>Unknown</u></b> (Includes cause of death not recorded or no Death Notification Form)</p>
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\* Revised, in use since September 1990

**USRDS 1999**

**Table VI-1**

patient by year, so that patients dying during a year contribute only the days from January 1 (if prevalent) or day 90 of ESRD (if incident) to date of death. On this basis, statistics for patient years at risk were calculated. A patient prevalent at the beginning of 1995, 1996, and 1997 contributed data to all three years. In all analyses, patients were censored at loss-to-followup or end of the calendar year, and in analyses of dialysis groups, patients were censored (removed from the analysis) at transplantation. Patient followup was characterized by age (0-19, 20-

44, 45-64, 65+), race (Asian, Black, Native American, White), sex, and modality (hemodialysis, peritoneal dialysis, transplant) at the beginning of each cohort year for prevalent patients or at 90 days of ESRD for incident patients. This method better reflects the effect of modality, which may change in a given patient from one year to the next. The total number of patient deaths by cause and years at risk for each year were aggregated to enhance the stability of the estimated death rates.

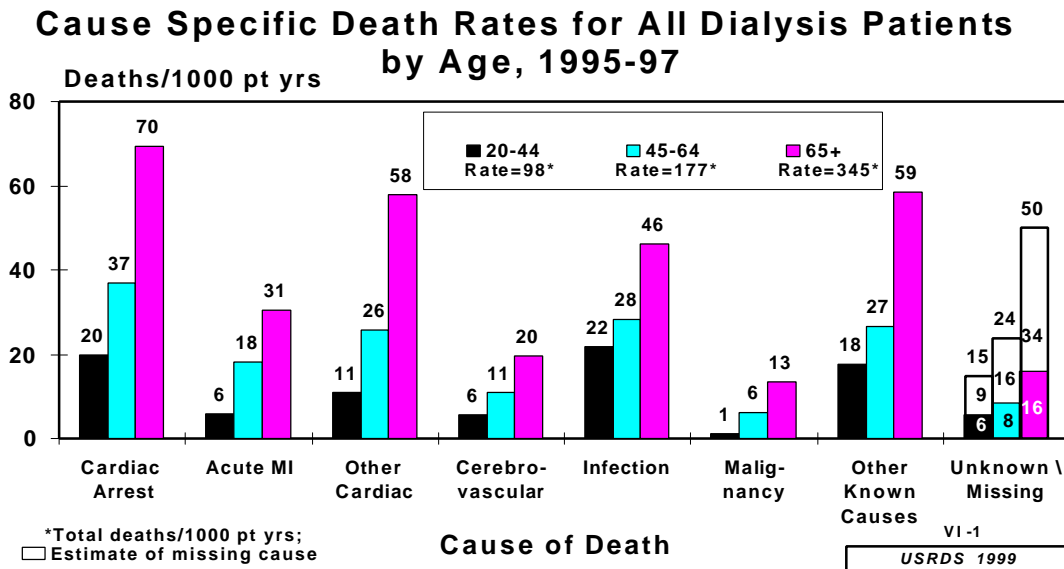


Figure VI-1

Cause specific death rates for all dialysis patients by age, 1995-97. The categories are collapsed from the Death Notification Form as per Table VI-1. Patients < 20 are excluded. Unknown and missing cause are estimated. Patients in Puerto Rico and the U.S. Territories are included. Source: Reference Table D.4.

The figures in this chapter show the unadjusted cause specific death rates for various subgroups of prevalent dialysis and transplant recipients. Numerous other stratified unadjusted death rates by cause of death for a variety of subgroups are presented in the Reference Tables D.4-D.6. Although death rates tend to be more informative, it is also of interest to analyze the distribution of causes of death among patients who died. This also allows comparisons with other studies and data from other registries, which present the percent distribution of cause of death. Percentages can be calculated for various subgroups from death rates in the figures presented in this chapter by dividing the cause specific death rate by the overall or total death rate excluding the missing (estimated) as the denominator. In this report, discussions related to percent distributions of cause specific deaths use this methodology. The cause of death distribution or percent of death is somewhat underestimated when those with missing deaths are included in the denominator.

## Causes of Death Among Dialysis Patients

Death rates by cause of death were analyzed for prevalent and incident ESRD patients treated with

hemodialysis (HD) or peritoneal dialysis (PD). Patients transplanted during the year of observation were censored on day of transplantation. Figure VI-1 shows the actual cause specific death rates for dialysis patients aged 20-44 years, 45-64 years, and 65 years and older. As expected, all rates increase in older age groups, ranging from 98 deaths per 1,000 patient years for patients age 20-44 years to 345 deaths per 1,000 patient years for patients age 65 and older.

As a percent of all deaths, cardiac arrest of unknown cause, acute myocardial infarction and all other cardiac causes account for almost half of the reported causes of dialysis patient deaths in each of the 3 age groups. Death rates due to cardiac causes for 45-64 year-old patients are approximately two fold higher than 20-44 year-old patients. Death rates due to cardiac causes for patients 65 years and older are approximately twice as high as for 44-64 year-old dialysis patients. The high prevalence of cardiac disorders in ESRD patients has been noted previously and has been shown to be associated with an elevated risk of mortality (USRDS 1992; Churchill; Foley). A USRDS study of new and established dialysis patients pointed out that cardiac disorders were already present in a large fraction of patients when they began dialysis (Bloembergen 1997).

**Cause Specific Death Rates\* for All Dialysis Patients  
by Age Groups, 1995-97**

Cause of Death	All	0-19	20-44	45-64	65+
<b>All</b>	<b>231.0</b>	<b>44.4</b>	<b>97.6</b>	<b>176.6</b>	<b>345.3</b>
Cardiac Arrest, Cause Unknown	47.1	7.0	20.0	37.0	69.5
Septicemia	25.2	5.4	11.3	22.5	34.7
Acute Myocardial Infarction	20.8	0.8	5.9	18.1	30.6
Cardiac Arrhythmia	13.4	1.4	5.1	11.0	19.7
Cerebrovascular Accident/Intracranial Hemorrhage	11.1	1.6	4.3	8.8	16.4
Cardiomyopathy	9.8	1.4	2.5	6.7	16.2
Infection (Not Septicemia)	9.0	2.4	10.6	5.9	11.3
Atherosclerotic Heart Disease	8.9	0.4	1.3	5.2	15.8
Malignant Disease	8.2	1.8	1.1	7.3	12.7
Hyperkalemia	4.1	1.8	2.8	2.8	5.9
Cachexia	2.5	0.2	0.6	1.4	4.4
Ischemic Brain Damage/Anoxic Encephalopathy	2.3	0.6	1.2	2.1	3.0
Mesenteric Infarction/Ischemic Bowel	2.3	0.4	0.6	1.6	3.7
Gastro-Intestinal Hemorrhage	2.2	0.8	0.8	1.6	3.4
Pulmonary Edema Due To Exogenous Fluid	2.1	0.8	0.9	1.4	3.4
Valvular Heart Disease	1.6	0.4	0.7	1.2	2.5
Dementia, Incl. Dialysis Dementia, Alzheimers	1.3	0.2	0.1	0.3	2.7
Chronic Obstructive Lung Disease (COPD)	1.1	.	0.1	0.6	2.1
Other Cause (each cause < 1 death per 1000 patient years)	105.1	24.0	47.7	79.1	156.2

\*Death Rates Per 1000 Patient Years at Risk by Cause of Death. Age is on January 1.  
Treatment modality at risk until death, transplant, or end of year.  
Source: Reference Table D.5.

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**Table VI-2**

Infection accounts for almost a quarter of all deaths in the 20-44 year age group, but only 18 percent and 15 percent of deaths in the 45-64 years and 65 years and older age groups, respectively. Septicemia makes up about 50 percent of the infection category in the 20-44-year age group and more than 75 percent of the infection category for the 45-64 and 65 years and older age groups. ESRD patients are known to have a high incidence of infection due to defects in cellular immunity, neutrophil function, and complement activation (Khan; Vanholder). Additionally, dialysis patients have an elevated risk of infection due to the vascular or peritoneal access. Cerebrovascular disease makes up about 6 percent of the deaths in each age group, while 1 to 4 percent of the cause of death for dialysis patients is attributable to malignancy. Previous studies have suggested an increased risk of certain malignancies in the dialysis population compared to the general population (Port 1989a; Kantor; Inamoto). Although this may be due to the effect of

uremia or a side-effect of dialytic therapy, the USRDS Case Mix studies found a prior or current diagnosis of malignancy in 9 percent of patients at initiation of therapy (USRDS 1992), suggesting that acceptance of patients with malignancy is not uncommon. Other known causes account for almost 20 percent of deaths in all three age groups. Table VI-2 provides additional detail for the most prevalent causes of death in the other known cause category by age group. Hyperkalemia, cachexia, and mesenteric infarction/ischemic bowel are the largest causes in the other known category (1-2 percent each).

Figure VI-2 shows the cause specific death rates among all dialysis patients by sex. It is limited to patients aged 45-64 as an example since the pattern varies by age group. The distributions of causes of death for males and females show only small differences. Males have slightly higher death rates due to cardiac causes (83 and 79 deaths per 1,000 patient years for males and females, respectively) and females have higher infection causes (27 deaths per

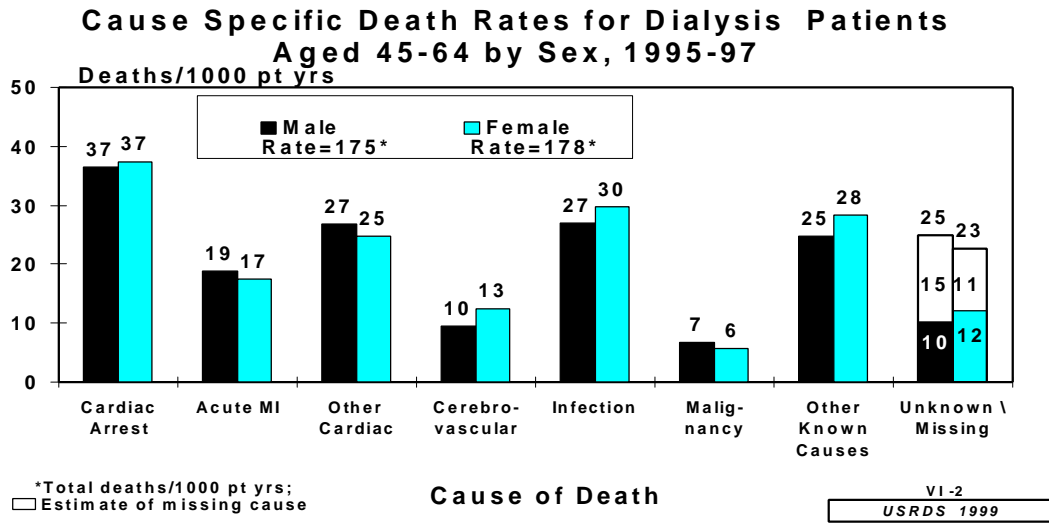


Figure VI-2

Cause specific death rates for all dialysis patients aged 45-64 by sex, 1995-97. The categories are collapsed from the Death Notification Form as per Table VI-1. Unknown and missing cause are estimated. Patients in Puerto Rico and the U.S. Territories are included. Source: Reference Table D.4.

1,000 patient years for males and 30 deaths per 1,000 patient years for females) and cerebrovascular disease (10 deaths per 1,000 patient years for males and 13 deaths per 1,000 patient years for females). Malignancy deaths show minor differences by sex. The total death rate is somewhat higher for males

(175 deaths per 1,000 patient years) than females (171 deaths per 1,000 patient years) in the 45-64-year age group.

The cause specific death rates for Blacks and Whites, limited to patients aged 45-64, is shown in

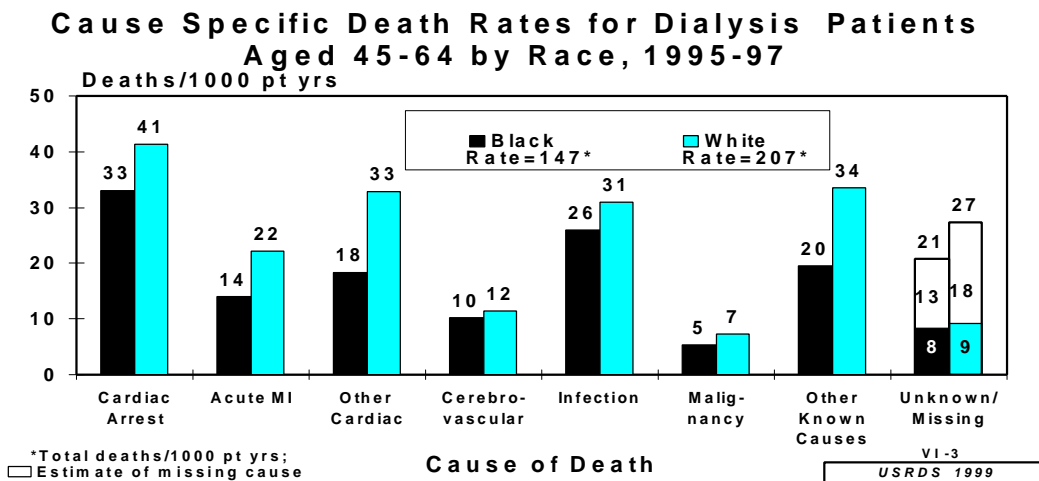


Figure VI-3

Cause specific death rates for all dialysis patients aged 45-64 by race, 1995-97. The categories are collapsed from the Death Notification Form as per Table VI-1. Black and White patients only. Unknown and missing cause are estimated. Patients in Puerto Rico and the U.S. Territories are included. Source: Reference Table D.4.

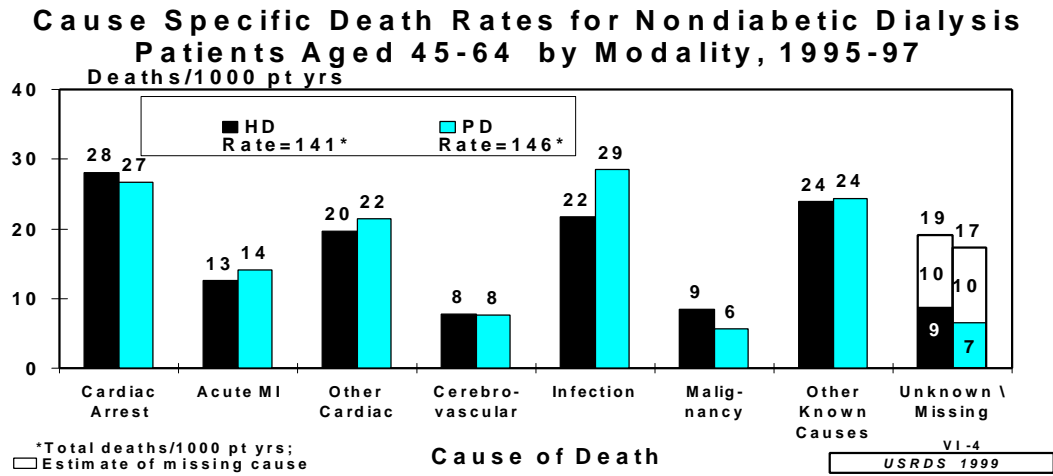


Figure VI-4

Cause specific death rates for all nondiabetic dialysis patients aged 45-64 by treatment modality, 1995-97. The categories are collapsed from the Death Notification Form as per Table VI-1. HD and PD patients only. Unknown and missing cause are estimated. Patients in Puerto Rico and the U.S. Territories are included. Source: Reference Table D.4.

Figure VI-3. Whites have an almost 40 percent higher death rate than Blacks (207 and 147 deaths per 1,000 dialysis patient years in this unadjusted analysis). This has previously been shown to be attributed to an increased risk of death due to acute myocardial infarction, all other cardiac causes, withdrawal from dialysis, and infection (Bloembergen 1994). The largest excess risk is for “other cardiac causes”, acute MI, and cardiac arrest. The death rates

for all cardiac causes combined are 96 and 65 deaths per 1,000 patient years for Whites and Blacks, respectively. The minor differences in death rates are smaller for cerebrovascular, and malignancy causes. Whites have higher rates of death for each cause category than Blacks.

Figures VI-4 and VI-5 show the cause of death for dialysis patients aged 45-64 by dialytic modality for

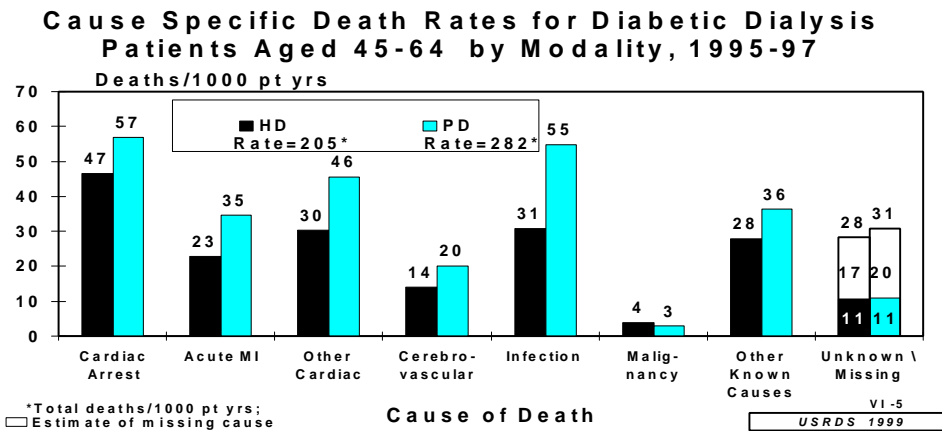
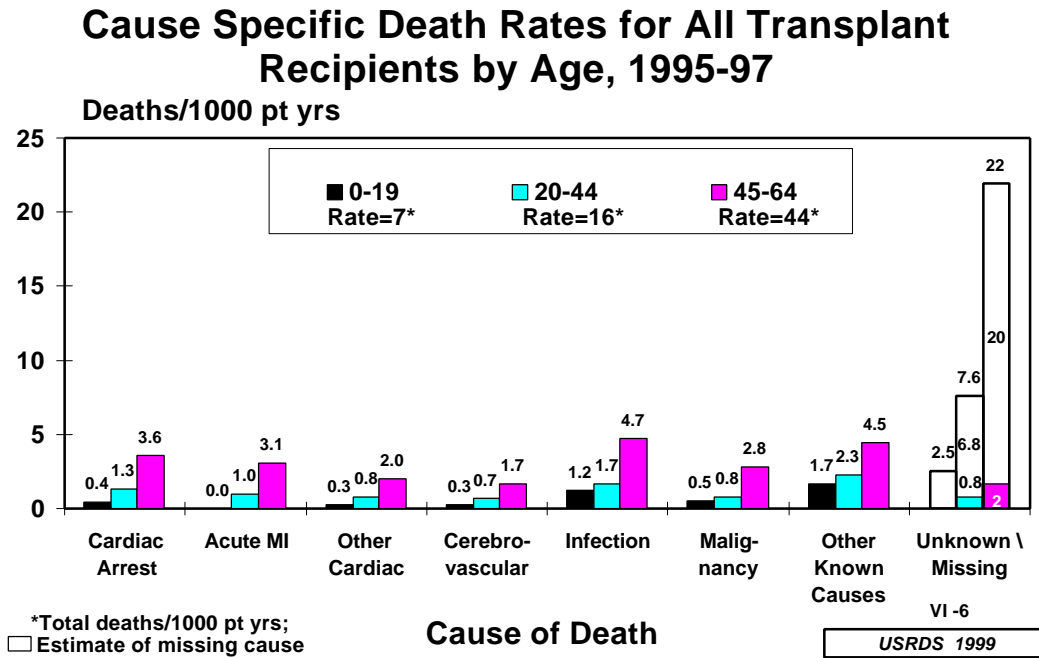


Figure VI-5

Cause specific death rates for all diabetic dialysis patients aged 45-64 by treatment modality, 1995-97. The categories are collapsed from the Death Notification Form as per Table VI-1. HD and PD patients only. Unknown and missing cause are estimated. Patients in Puerto Rico and the U.S. Territories are included. Source: Reference Table D.4.



Cause specific death rates for all transplant patients by age, 1995-97. The categories are collapsed from the Death Notification Form as per Table VI-1. Patients  $\geq 65$  are excluded. Unknown and missing cause are estimated. Patients in Puerto Rico and the U.S. Territories are included. Source: Reference Table D.4.

nondiabetic and diabetic patients, respectively. There is a small difference in the death rates of nondiabetic HD and PD patients. Nondiabetic HD patients have a death rate of 141 per 1,000 patient years and nondiabetic PD patients have a death rate 146 per 1,000 patient years. However, diabetic PD patients have a substantially higher death rate than diabetic HD patients (282 and 205 deaths per 1,000 patient years, respectively). Nondiabetic HD and PD patients have similar proportions for all cardiac causes combined (61 and 63 deaths per 1,000 patient years, respectively). However, diabetic PD patients have higher death rates due to cardiac causes than diabetic HD patients (138 and 100 deaths per 1,000 patient years, respectively). PD patients have substantially higher death rates due to infection than HD patients for both nondiabetics and diabetics. Further discussion of the distribution of specific cardiac and infectious causes among all deaths are presented in the USRDS 1997 Annual Data Report. Nondiabetic patients have higher death rates due to malignancy among patients on HD (9 deaths per 1,000 patient years at risk) and PD (6 deaths per 1,000 patient years at risk) than do diabetic patients on HD (4 deaths per 1,000 patient years at risk) and

PD (3 deaths per 1,000 patient years at risk). Of note is the higher fraction of HD patient deaths due to malignancy than the fraction for PD patients. Among nondiabetics, there are similar death rates for other and unknown causes of death among HD patients and PD patients. Diabetic PD patients have a much higher death rate for other causes than diabetic HD patients.

In general, the differences in cause specific mortality among PD and HD treated patients may be due to the technical differences of these dialysis modalities, differences in compliance, medical care, or dose of dialysis. Differences in case-mix severity among these patient groups may also play a role, although a recent study has shown overall somewhat greater comorbidity among new ESRD patients initiating PD than HD (Held 1997a). Possible explanations for the observed differences in cause specific mortality have been discussed previously (USRDS 1998). It should be noted that the results presented here refer mostly to prevalent patients. Overall mortality during the first year of ESRD has been shown to be very similar for HD and PD patients (Held 1997b). Recent studies also emphasize

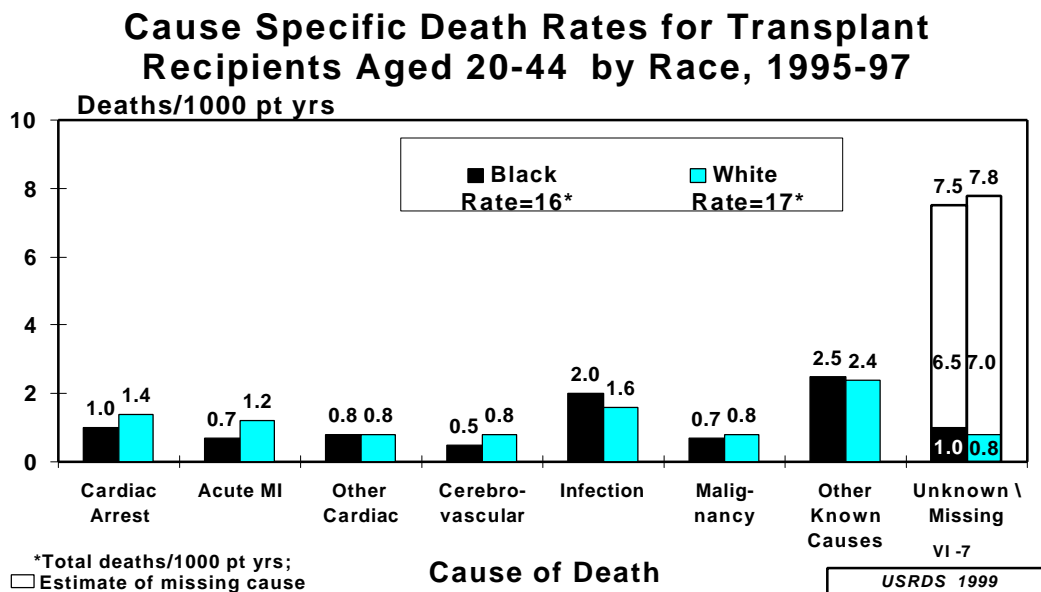


Figure VI-7

Cause specific death rates for all transplant patients aged 20-44 by race, 1995-97. The categories are collapsed from the Death Notification Form as per Table VI-1. Black and White patients only. Unknown and missing cause are estimated. Patients in Puerto Rico and the U.S. Territories are included. Source: Reference Table D.4.

the differences between analyses of incident and prevalent patients (Vonesh).

### Causes of Death among Transplant Recipients

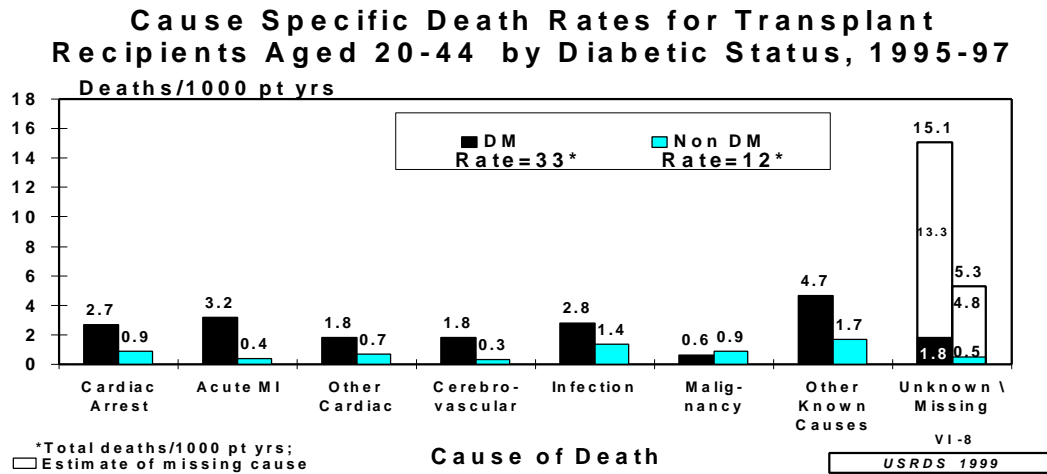
Prevalent patients with a functioning transplant on January 1 of 1995, 1996, or 1997 were classified as such and are followed through the remainder of each year independent of transplant failure that may have occurred in some patients during the year. The cause specific death rates for all patients with a functioning transplant aged 0-19, 20-44 and 45-64 years are given in Figure VI-6. The death rate for pediatric transplant recipients (age 0-19 years) was more than two fold lower than adult transplant recipients aged 20-44-years and about 6 times lower than adult transplant recipients aged 45-64 years. In contrast to dialysis patients, cardiac causes accounted for a smaller proportion of deaths for transplant recipients with approximately 16 to 36 percent of all deaths for each age group. About a quarter of all pediatric transplant recipient deaths were due to infection, whereas 18 and 20 percent of transplant recipient deaths in the 20-44 and 45-64 year age groups were due to infection. Malignancy accounted for 11 percent, 9

percent, and 12 percent of transplant recipient deaths in the 0-19, 20-44, 45-64 year age groups, respectively. Previous studies have suggested an increased risk of certain malignancies in the transplant population (Penn) compared to the general population. Other known causes make up a large proportion of transplant recipient deaths. The most common known causes were hyperkalemia and GI hemorrhage.

A comparison of patients with similar age reveals a substantially lower death rate for transplant recipients than for dialysis patients. Transplant recipients aged 20-44 years had a sixth of the death rate of dialysis patients aged 20-44 years, while transplant recipients aged 45-64 years had a quarter of the death rate of dialysis patients aged 45-64 years. This is likely due, in part, to selection of healthier patients to transplantation (Gaylin; Port 1993; Wolfe). In addition to patient selection, other factors such as the greater level of renal functional replacement with transplantation may be playing a role in the better long-term outcomes with transplantation.

Figure VI-7 shows the cause specific death rates by race for transplant recipients aged 20-44 years.

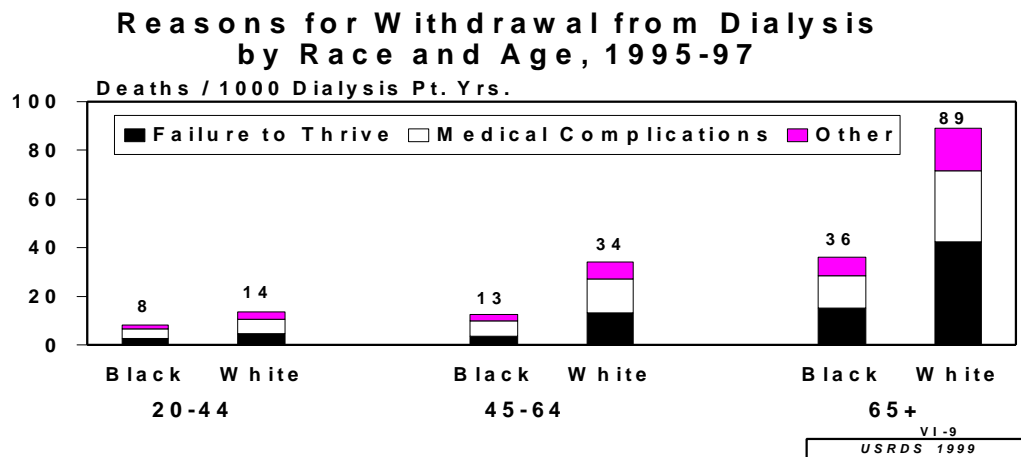




Cause specific death rates for all transplant patients aged 20-44 by diabetic status, 1995-97. The categories are collapsed from the Death Notification Form as per Table VI-1. Unknown and missing cause are estimated. Patients in Puerto Rico and the U.S. Territories are included. Source: Reference Table D.4.

Black transplant recipients aged 20-44 years have a slightly lower death rate than White transplant recipients aged 20-44 (16 and 17 deaths per 1,000 patient years, respectively). The death rate due to cardiac arrest, acute MI and cerebrovascular disease for Black transplant recipients is lower than White transplant recipients, while Blacks had higher rates of infectious causes than Whites. Blacks and Whites have similar rates of other cardiac, malignancy, and other known causes. In the older age groups, Black

transplant recipients have a higher rate of death than White transplant recipients (see Reference Table D.4) which is in contrast to the dialysis population where death rates due to most causes were higher among Whites. Despite these higher death rates among Black transplant recipients the benefit of cadaveric renal transplantation for dialysis patients on the transplant waiting list is large and similar to that observed in Whites (Ojo).



Reasons for withdrawal from dialysis by race and age, 1995-97. Patients with missing cause of withdrawal are excluded. Black and White patients only. Patients < 20 are excluded. Patients in Puerto Rico and the U.S. Territories are included. Source: Reference Table D.6.

### Reasons for Withdrawal from Dialysis by Sex and Age, 1995-97

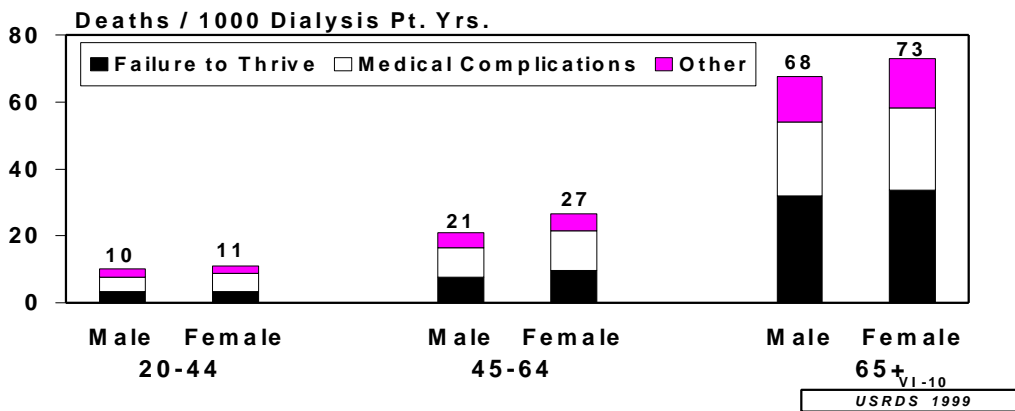


Figure VI-10

Reasons for withdrawal from dialysis by sex and age, 1995-97. Patients with missing cause of withdrawal are excluded. Patients < 20 are excluded. Patients in Puerto Rico and the U.S. Territories are included. Source: Reference Table D.6.

The distribution of causes of death for transplant recipients aged 20-44 years by diabetic status is shown in Figure VI-8. Death rates were generally 2 to 3 times higher among diabetic than nondiabetic transplant recipients among all causes, with the exception of deaths due to malignancy, which were slightly higher among nondiabetic transplant recipients in this age group. A relatively high fraction of diabetic transplant recipients died of acute myocardial infarction.

### Withdrawal from Dialysis

Approximately 1 out of 5 dialysis patients withdraws from dialysis before death. (This does not include patients who have stopped dialysis because of a return of renal function.) The overall withdrawal rate was 41 deaths per 1,000 dialysis patient years. Discussion of the rate of withdrawal from dialysis by age, diabetic status, sex, and race is presented in the USRDS 1998 Annual Data Report.

The reported reasons for withdrawal from dialysis by race and age and by sex and age are shown in Figures VI-9 and VI-10. Overall, older patients have a much higher rate of withdrawal than do younger patients. The increase in withdrawal rate with age may be the result of increasing severity of comorbid

conditions which may lessen the quality of life of a dialysis patient to the extent that further dialysis may reach questionable benefits (Port 1989b; Mailloux; Nelson). Rates for death preceded by withdrawal were approximately two to three fold higher in Whites compared to Blacks for all age categories over age 20. This is consistent with previous studies which have shown that withdrawal from dialysis is over twice as commonly reported for White patients than for Black patients (Port 1989b; Nelson; Bloembergen 1994; Leggat 1997a). These differences are likely due to sociocultural reasons (Leggat 1997b). Blacks and Whites have similar proportions of reasons in the 20-44 group. Blacks have higher proportions of withdrawal due to medical complications and lower proportions of withdrawal due to failure to thrive than do Whites in the 45-64 and 65+ age groups.

Females withdrew at a slightly higher rate than males (11 versus 10 deaths per 1,000 patient years) in the 20-44 group and at a moderately higher rate than males in the 45-64 (27 versus 21 deaths per 1,000 patient years) and 65+ (73 versus 68 deaths per 1,000 patient years) groups. Females tended to have higher rates of withdrawal due to medical complications than males in all age groups.

It has been stated that withdrawal from dialysis reflects, on one hand, failure of renal replacement

therapy, and on the other hand, maintenance of patient autonomy (Leggat 1997a). In addition, the high rates of withdrawal in the United States (Sehgal) may be due to acceptance of patients for whom benefits from therapy may have been uncertain at initiation of ESRD therapy. As individual patient outcome is not predictable, some have advocated an approach of liberal acceptance policies combined with a willingness to support patients in their decision to withdraw from dialysis (Port 1994).

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