chapter four

cardiovascular disease in patients with end-stage renal disease

Everyday it's a gettin' closer
Goin' faster than a roller coaster
Love like yours will surely come my way
A hey, a hey hey

Buddy Holly & Norman Petty, "Everyday"

04

This year's contribution from the USRDS Cardiovascular Special Studies Center focuses on two broad areas: long-term temporal trends related to cause-specific mortality, and pharmacologic interventions for cardiovascular conditions.

Over the past decade there has been a notable decline in the proportion of dialysis patient deaths related to cardiovascular disease. While withdrawal from dialysis was recognized as a cause of death during this time, this recognition was not accompanied by any abrupt change in cause-specific cardiovascular mortality rates; the rates have, instead, been declining steadily. In the prevalent dialysis population, the percentage of deaths due to cardiac disease has fallen from 45 in 1997–1999 to 39 in 2007–2009; the percentage attributable to cardiovascular disease has declined from 50 to 42. Some deaths classified as being due to withdrawal might be cardiovascular in origin (particularly those related to frailty or cognitive decline, both of which may reflect cardiovascular disease burden). Nevertheless, the overall decline in attributable cardiovascular mortality closely parallels that seen in the cause-specific rates shown in Table 4.a.

The percentage of deaths due to acute myocardial infarction has also fallen, from 8.8 to 5.1 — a noteworthy finding, given that the advent of more sensitive cardiac troponin assays for use in detecting AMI would, if anything, be expected to increase the number of AMI-related deaths.

It is worth taking a look back at the 2002 Annual Data Report, the first USRDS report to include data on Healthy People 2010 (HP2010) objectives. We reported that the rate of death from cardiovascular disease in all ESRD patients was 82.6 per 1,000 patient years at risk, considerably higher than the initial HP2010 target of 52. In the 2010 ADR, the actual rate of 64.1 in 2008 was close to the revised HP2010 target of 62.1. The Healthy People program has now set goals for 2020, and new objective CKD-14.3 targets a cardiovascular mortality rate for dialysis patients of 81.3. As shown in our HP2020 chapter, this modest target is already close to being achieved, with a rate in 2009 of 82.6.

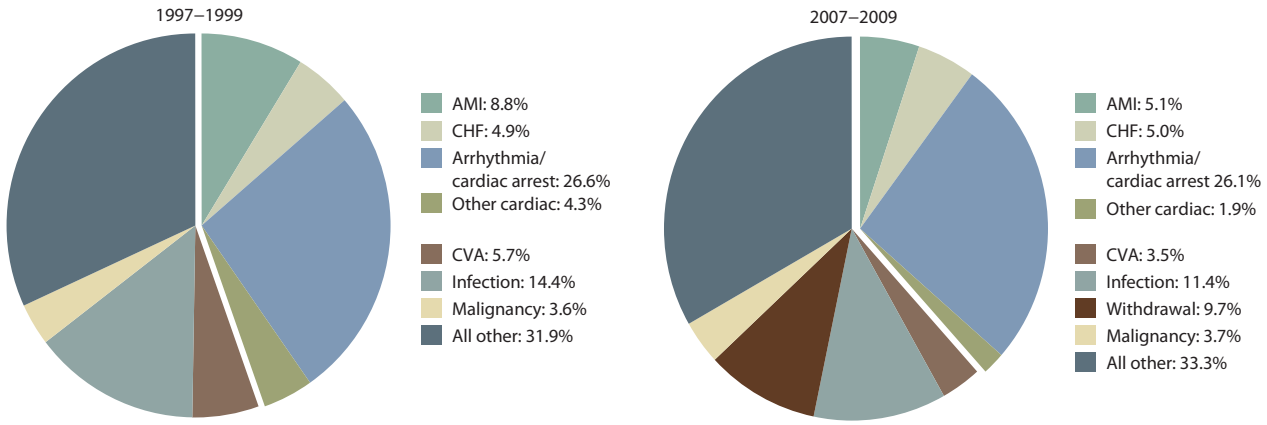
Unadjusted cardiovascular mortality rates showed a progressive increase during the late 1990s, peaking in 1999 at 121.5 deaths per 1,000 patient years. This has been followed by a decrease of 2–6 percent each year since 2001. This steady change appears to be the primary reason for the decline in all-cause mortality rates in U.S. dialysis patients.

INTRODUCTION

Much attention has been directed in past publications to the "underutilization" of evidence-based therapies in dialysis patients, and to a general perception of "therapeutic nihilism" (Herzog, 1999; Winkelmayer, 2006). Even in the earlier part of this decade, evidence-based therapies were underused; earlier publications, for example, suggested that beta blockers were not used in more than one-third of the dialysis patients who were potential candidates for these agents. In a relatively short time, however, there has been a virtual sea change in clinical practice related to treatment of cardiovascular disease in ESRD patients. Two in three dialysis patients with diagnosed CHF, and three in four transplant patients with CHF, received beta blockers in 2008. From a cardiologist's perspective, this rapid expansion in beta blocker use is perhaps the most impressive aspect of the recent change, and it is tempting, in part, to attribute the progressive decline in cardiovascular mortality to the use of these and other evidence-based therapies.

>> **Figure 4.1;** see page 384 for analytical methods. *Prevalent dialysis patients, 1997–1999 & 2007–2009.*

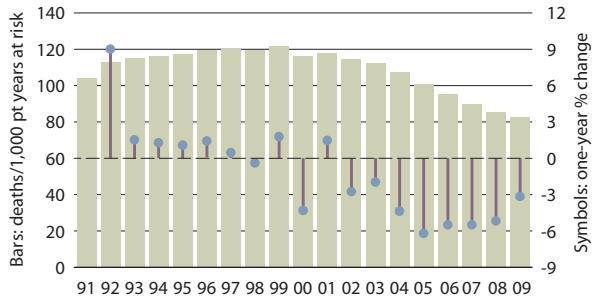
4.1ii **Causes of death in prevalent dialysis patients, 1997–1999 & 2007–2009**



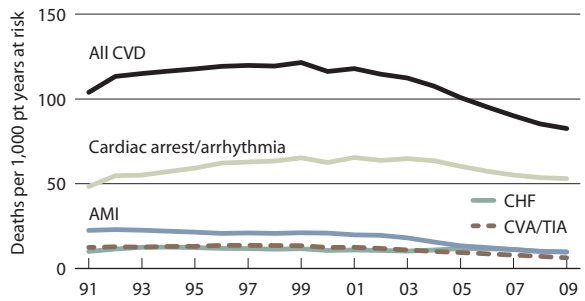
4 aii Unadjusted cardiovascular mortality rates in prevalent dialysis patients (deaths per 1,000 patient years)

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Patients with cardiovascular disease																			
Age: 20-44	37.9	42.4	41.6	41.7	44.9	43.3	43.0	41.9	39.8	39.5	40.5	41.7	39.9	38.8	37.5	35.7	33.0	31.3	31.2
45-64	86.6	94.2	93.6	93.4	93.7	95.1	94.6	91.4	93.9	88.5	89.3	86.3	84.6	81.3	75.6	73.4	68.6	65.4	63.7
65-74	145.3	156.1	155.8	159.7	156.3	156.9	157.5	155.7	156.7	148.8	149.8	143.0	139.2	133.1	123.5	114.8	108.1	104.5	101.2
75+	197.8	208.7	216.4	213.0	216.3	220.3	218.3	220.6	223.5	213.2	214.1	207.3	201.6	190.4	179.8	166.9	160.6	149.4	142.5
Male	107.2	115.3	117.0	117.5	118.0	120.4	118.8	118.5	120.1	114.7	117.1	113.9	112.5	108.2	101.4	96.2	90.9	87.1	84.9
Female	100.4	111.0	112.8	115.2	117.2	118.1	121.0	120.3	123.0	117.9	118.9	115.5	112.3	106.7	100.1	94.1	88.9	83.2	79.9
White	123.4	135.9	139.8	139.2	140.0	142.9	143.8	143.4	144.6	138.3	139.6	136.1	132.9	126.2	117.8	110.4	104.4	98.1	94.9
African American	75.9	81.8	81.9	86.5	88.7	88.1	88.8	89.1	92.1	87.8	90.4	87.9	87.0	85.3	80.8	77.3	72.4	69.6	66.7
Other race	79.4	82.5	79.9	86.9	91.2	102.9	101.8	97.6	103.3	100.5	99.0	93.6	91.2	83.1	78.0	74.1	71.5	69.6	70.9
Diabetes	143.8	151.9	150.6	151.6	151.4	155.6	152.8	150.9	154.3	144.1	145.4	137.3	135.0	128.8	120.2	113.4	107.2	101.5	98.8
Hemodialysis	104.7	114.1	114.9	116.7	118.4	120.3	120.3	120.4	123.0	117.9	120.0	116.7	114.9	109.7	103.1	97.4	92.3	87.5	84.7
Peritoneal dialysis	103.6	112.5	117.4	117.6	117.5	118.2	120.2	116.9	114.1	107.0	104.2	100.4	91.8	89.3	81.2	75.5	69.0	65.0	63.5
Patients with AMI																			
Age: 20-44	6.9	6.3	7.3	6.5	6.4	6.1	5.7	5.7	5.6	5.5	4.5	5.3	4.9	4.5	4.4	3.3	3.3	3.1	2.5
45-64	20.9	21.5	21.0	19.7	18.9	18.9	18.3	17.8	18.5	17.2	16.2	16.0	15.3	12.6	10.9	10.3	9.4	8.3	8.1
65-74	31.9	32.0	30.9	31.6	29.0	27.6	29.2	27.9	27.7	28.2	27.0	25.7	22.9	20.6	17.5	16.2	14.3	13.1	13.0
75+	38.3	39.0	36.9	35.1	36.7	33.9	34.5	34.5	34.9	35.2	34.0	32.9	29.7	25.6	21.5	19.3	18.1	16.3	15.7
Male	24.7	24.6	24.6	23.5	22.4	21.7	22.2	21.8	21.9	21.7	20.8	20.5	18.7	16.6	13.9	13.2	12.0	10.6	10.5
Female	20.2	21.3	20.5	20.5	20.6	19.7	19.8	19.5	20.3	20.0	18.9	18.6	17.4	14.6	12.8	11.3	10.4	9.6	9.0
White	27.6	28.2	28.1	27.3	25.8	25.5	26.0	25.9	25.7	25.3	24.1	23.8	21.9	18.3	16.0	15.2	13.6	11.9	11.7
African American	15.1	15.5	15.1	14.9	15.7	14.2	14.6	14.2	15.0	15.0	14.3	14.3	13.1	11.9	10.4	8.6	8.2	7.8	7.2
Other race	17.9	17.6	17.7	18.6	17.4	19.0	17.9	16.7	19.4	19.4	18.6	15.8	16.0	14.8	10.2	9.4	8.9	9.0	9.4
Diabetes	33.2	32.4	31.8	30.3	28.9	29.1	29.0	28.2	28.3	27.9	25.9	25.3	23.7	20.4	17.3	16.2	14.5	13.1	12.9
Hemodialysis	22.5	22.6	22.4	21.7	21.5	20.8	20.8	20.7	21.3	21.1	20.2	19.7	18.2	15.8	13.5	12.4	11.4	10.2	9.9
Peritoneal dialysis	23.6	26.0	24.6	24.4	22.1	20.9	23.4	22.2	20.4	20.5	18.6	19.8	17.4	15.2	13.0	12.6	10.1	10.1	9.4
Patients with CVA/TIA																			
Age: 20-44	5.8	5.9	5.6	6.0	5.9	5.5	6.1	6.2	5.2	4.9	5.1	5.6	4.9	4.0	4.3	4.2	4.0	3.8	3.4
45-64	10.3	10.3	10.5	10.6	10.8	11.4	11.5	10.6	11.0	10.1	10.4	9.9	8.6	8.3	7.6	7.5	6.6	5.9	5.2
65-74	16.8	17.8	17.1	17.5	16.6	18.1	17.7	17.0	17.3	15.5	15.8	14.5	13.7	11.9	11.4	10.2	8.9	8.3	7.5
75+	22.5	22.7	22.2	22.3	23.6	23.6	22.8	24.1	22.9	21.5	20.1	18.9	17.7	16.9	15.2	13.8	12.9	11.4	9.7
Male	10.7	11.2	10.4	10.7	10.7	11.4	11.4	11.3	10.6	10.6	10.6	9.6	9.6	8.7	8.1	7.8	7.0	6.4	5.8
Female	14.3	14.5	15.1	15.5	15.8	16.2	16.3	16.1	16.7	14.5	14.7	14.5	12.5	11.8	11.0	10.0	9.1	8.1	7.0
White	13.7	13.9	13.8	14.4	14.5	14.5	15.1	14.8	14.7	13.8	14.1	13.0	12.0	11.1	10.3	9.3	8.5	7.7	6.7
African American	10.5	11.4	11.0	11.3	11.7	12.1	11.8	11.9	11.7	10.4	10.4	10.2	9.3	9.1	8.4	8.1	7.2	6.4	5.7
Other race	11.3	11.5	13.0	11.7	9.7	17.7	14.1	13.6	13.7	13.2	12.1	12.7	11.5	8.1	8.3	8.4	7.8	7.3	6.9
Diabetes	18.9	17.9	17.1	18.0	18.0	18.9	18.3	17.6	18.1	16.0	16.1	14.8	13.7	12.8	11.7	10.7	9.7	8.7	7.6
Hemodialysis	12.5	12.8	12.5	13.1	13.2	13.6	14.0	13.8	13.6	12.7	12.8	12.1	11.2	10.3	9.6	9.0	8.1	7.3	6.4
Peritoneal dialysis	12.8	13.1	14.3	13.7	13.8	15.0	13.0	12.9	13.7	11.5	10.8	10.6	9.1	8.1	8.3	6.4	6.5	6.4	5.3
Patients with cardiac arrest																			
Age: 20-44	20.2	23.8	21.4	23.2	26.2	26.2	25.7	24.9	24.1	24.8	25.4	25.8	26.2	25.5	24.5	23.7	22.3	21.0	21.8
45-64	40.0	46.3	45.3	47.4	47.5	50.0	50.6	49.6	51.2	48.4	50.2	49.1	49.4	49.5	46.9	45.7	43.5	42.6	42.2
65-74	66.5	73.3	73.0	76.4	78.6	79.6	80.6	81.1	82.5	77.8	81.9	77.5	78.4	78.0	71.7	68.1	65.0	64.7	64.2
75+	90.3	97.9	103.6	100.9	103.8	112.4	111.2	114.4	118.0	112.4	116.1	113.4	114.3	108.3	104.9	97.0	94.7	90.9	88.5
Male	49.6	55.6	55.1	57.1	59.6	63.3	61.8	63.2	64.7	61.3	65.1	63.7	64.5	63.4	61.1	57.3	55.5	54.7	54.2
Female	46.9	54.0	55.1	57.4	59.0	60.9	64.0	63.7	65.9	63.9	65.8	64.0	65.0	63.7	59.4	57.5	54.5	52.4	51.7
White	56.1	64.0	65.0	65.9	67.8	72.9	72.7	73.7	75.3	71.4	74.9	73.3	74.4	72.4	68.7	64.1	61.7	60.0	59.4
African American	37.0	42.3	42.6	46.9	48.4	48.7	50.2	50.7	52.7	51.6	53.8	52.4	53.6	53.8	50.9	49.9	47.4	46.2	45.2
Other race	39.6	39.2	36.3	38.5	48.9	48.6	54.7	52.8	56.7	53.2	54.9	51.7	51.0	48.3	46.9	45.4	44.3	44.0	44.9
Diabetes	68.1	74.6	73.0	75.1	77.9	81.0	79.5	79.7	82.3	77.3	80.1	75.5	76.7	75.1	71.3	68.4	65.7	63.5	63.6
Hemodialysis	49.3	56.7	56.3	58.5	60.6	63.3	63.8	64.7	66.7	64.0	67.0	65.4	66.7	65.3	62.1	58.9	56.6	55.3	54.6
Peritoneal dialysis	44.4	46.9	49.5	51.8	54.6	57.3	58.5	56.8	56.2	52.2	54.2	51.3	47.7	47.7	42.9	42.7	39.6	37.4	37.6

4.2ii **Unadjusted cardiovascular mortality rates in prevalent dialysis patients**



4.3ii **Unadjusted cause-specific cardiovascular mortality rates in prevalent dialysis patients**



4.4ii **Geographic variations in unadjusted cardiovascular mortality rates in dialysis patients (deaths per 1,000 patient years), by HSA**

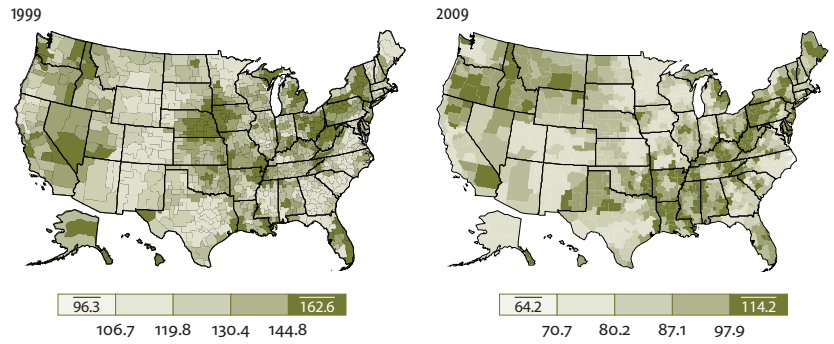


Table 4.a provides a broad snapshot of trends in cardiovascular mortality over two decades. There has been a noteworthy decline in cardiovascular mortality among dialysis patients with diabetes, from 154 deaths per 1,000 patient years in 1999 to 99 in 2009. To meet Healthy People 2020 goals related to cardiovascular mortality, it will be necessary to target this particularly high-risk group of patients. Unadjusted rates of cardiovascular mortality are lower in peritoneal dialysis patients than in those on hemodialysis; it is not clear, however, whether this is due to demographic characteristics of the two populations.

Over the past decade there has been a 50 percent drop in mortality due to AMI in dialysis patients, from 20–21 deaths per 1,000 patient years in 1999 to 9–10 in 2009. The magnitude of this decline is mirrored for stroke; among hemodialysis patients, stroke-related mortality has fallen from 13.6 to 8.4. It has been suggested that stroke may be under-recognized in dialysis patients, so it is possible that the true rates may be higher, but the trend of overall decline is consistent.

Cardiac arrest and arrhythmia continue to be the most frequent cause of cardiovascular mortality in dialysis patients. Unfortunately, the magnitude of the decline in arrhythmic death is considerably less than that seen with other types of cardiovascular disease. As shown in Figure 4.3, there has been an impressive 29 percent decrease in cardiovascular mortality since 2000. Mortality due to cardiac arrest/arrhythmia, in contrast, has fallen only 15 percent, while that due to congestive heart failure has fallen just 9 percent. These data highlight areas to target if the HP2020 goals for reducing cardiovascular mortality in dialysis patients are to be met.

ESRD patients are particularly vulnerable to sudden cardiac death (SCD). Although some triggers for SCD events are ischemic, much of the vulnerability to arrhythmic death in ESRD patients is likely due to a combination of structural heart disease (left ventricular hypertrophy and myocardial fibrosis), compounded by the stress of fluctuating volume and electrolyte status occurring in the setting of conventional thrice-weekly hemodialysis. Although still unproven, it is tempting to think that delivery of frequent longer-duration hemodialysis therapy will be accompanied by a further decline in cardiovascular mortality, including that due to cardiac arrest/arrhythmia.

Maps here illustrate the declining burden of cardiovascular mortality in U.S. dialysis patients. While rates continue to be high in some areas (e.g., Appalachia and portions of the south), the overall rate has fallen from 122 deaths per 1,000 patient years in 1999 to 83 in 2009. There is clearly room for further progress; the last decade, however, has been one of real improvement in cardiovascular outcomes for dialysis patients in the U.S. » **Table 4.a & Figures 4.2–4;** see page 384 for analytical methods.
Period prevalent dialysis patients; unadjusted.

4b ii **Cardiovascular disease & pharmacological interventions (row percent), by diagnosis & modality, 2008**

	N	ACEI/ARB	Beta blocker	Digoxin	Spirono-lactone	Eplerenone	Clopid-ogrel	Warfarin	Cilostazol	Pentoxi-fylline	Dipyrid-amole	Statins	Amio-darone
Congestive heart failure (CHF)													
Hemodialysis	50,962	47.6	64.9	6.7	1.0	0.0	20.0	13.8	1.0	1.0	1.0	38.0	6.1
Peritoneal dialysis	1,701	45.8	64.2	7.2	3.1	0.1	19.1	13.1	0.9	0.9	1.4	42.7	6.7
Transplant	3,330	43.2	75.6	6.4	4.7	0.2	14.6	19.6	0.9	0.8	0.6	53.9	4.7
Acute myocardial infarction (AMI)													
Hemodialysis	4,711	56.8	77.4	6.3	0.9	0.0	48.2	12.4	1.4	1.3	1.3	57.2	6.9
Peritoneal dialysis	190	47.9	78.4	4.2	1.6	0.0	53.7	10.0	0.5	1.1	0.0	61.1	6.8
Transplant	342	52.3	83.3	4.7	2.3	0.0	54.4	14.0	0.6	1.5	1.8	67.0	4.1
Peripheral arterial disease (PAD)													
Hemodialysis	46,908	42.2	57.6	4.2	0.6	0.0	21.5	13.5	2.1	1.5	1.1	38.8	4.7
Peritoneal dialysis	1,521	40.8	55.6	3.5	1.8	0.1	24.4	8.7	3.6	2.2	1.2	46.8	4.3
Transplant	4,723	41.8	65.0	2.4	2.2	0.1	16.9	13.6	2.6	1.5	1.0	54.2	2.1
CVA/TIA													
Hemodialysis	14,320	47.6	62.1	4.4	0.7	0.0	24.9	13.9	1.4	1.1	3.7	42.4	5.0
Peritoneal dialysis	535	47.3	63.9	2.8	1.1	0.0	26.7	12.1	2.2	0.7	3.7	51.8	4.3
Transplant	1,351	42.0	67.7	3.2	2.7	0.1	21.5	17.6	1.3	1.3	4.7	56.6	1.8
AFIB													
Hemodialysis	17,372	38.3	62.6	15.4	0.8	0.0	16.8	41.7	1.2	1.0	0.8	38.1	18.8
Peritoneal dialysis	614	36.5	65.0	13.8	3.4	0.0	19.4	46.7	1.5	1.5	0.5	47.2	19.9
Transplant	2,028	42.9	75.7	14.7	3.3	0.0	9.0	57.2	0.7	0.9	0.7	53.4	12.5
ICDs/CRT-D													
Hemodialysis	687	56.8	77.6	11.6	2.6	0.0	31.0	19.1	1.0	1.6	0.6	46.7	16.6
Peritoneal dialysis	32	62.5	68.8	9.4	3.1	0.0	25.0	6.3	0.0	0.0	0.0	40.6	18.8
Transplant	50	56.0	84.0	20.0	14.0	0.0	16.0	34.0	2.0	2.0	0.0	56.0	14.0
Revascularization: PCI													
Hemodialysis	3,784	57.8	78.6	4.4	0.8	0.1	84.3	9.9	2.0	0.8	0.7	64.1	5.7
Peritoneal dialysis	188	55.3	81.4	4.3	2.7	0.5	84.6	8.0	0.5	0.0	1.1	67.6	4.8
Transplant	351	48.7	77.5	3.7	1.7	0.0	90.0	10.0	1.4	0.9	0.6	71.2	3.1
Revascularization: CABG													
Hemodialysis	673	58.1	82.8	5.3	1.2	0.0	36.0	11.3	0.7	0.6	1.8	70.0	17.8
Peritoneal dialysis	48	60.4	77.1	6.3	0.0	0.0	29.2	10.4	2.1	2.1	0.0	81.3	29.2
Transplant	69	50.7	91.3	7.2	2.9	0.0	44.9	18.8	1.4	0.0	1.4	71.0	15.9

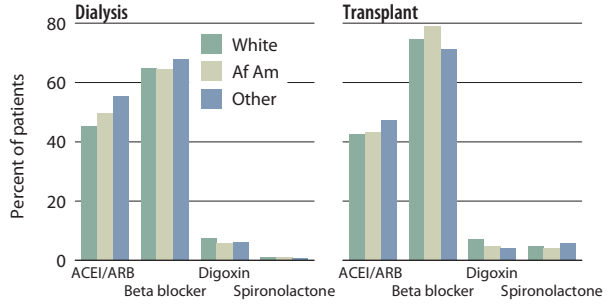
Despite two negative statin trials in dialysis patients (4D and AURORA) there has been no apparent dampening in enthusiasm for the use of these agents. In 2008, statins were used in 57 percent of hemodialysis patients with AMI, and 64 and 70 percent of those undergoing PCI and CABG. Recent publication of results from the SHARP trial (Baigent et al.) might be expected to further increase statin use across the spectrum of CKD.

Only 2–4 percent of patients with PAD receive cilostazol, an approved therapy; 17–24 percent receive clopidogrel, and 39–54 percent statin therapy. As noted in a recent KDIGO Controversies Conference Summary, PAD should be a special cardiovascular target for further improvement in all stages of kidney disease.

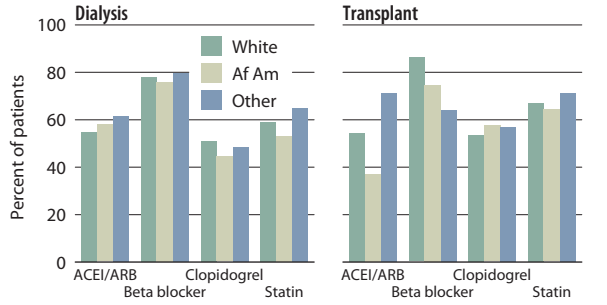
It is noteworthy that beta blockers have been shown to be of benefit only in those with systolic heart failure. Their putative benefits in patients with "diastolic heart failure" are still unproven, and it is likely that some classified as having CHF actually have preserved left ventricular systolic function, and what would be classified as "diastolic heart failure." Nearly 65 percent of dialysis patients with CHF receive a beta blocker, and use is nearly identical in whites and African Americans.

Among 2008 patients with CHF, 37 percent of those on dialysis, and 35 percent of those with a transplant, received an ACEI/ARB and beta blocker concurrently; 65 and 76 percent were on a regimen that included a beta blocker; and 48 and 43 percent received an ACEI/ARB (Figure 4.9). Forty-two percent of dialysis patients treated for AFIB, and 57 percent of AFIB patients with a transplant, received warfarin, while just 19 and 13 percent received amiodarone. Perhaps reflecting the complex pharmacokinetic interactions related to warfarin and amiodarone therapy, only 7–8 percent of patients received concurrent warfarin and amiodarone. Given the relatively frequent use of amiodarone in ESRD patients with atrial fibrillation, further data regarding the efficacy and safety of this agent in this special population would be helpful to clinicians. » Table 4.b & Figures 4.5–10; see page 385 for analytical methods. *January 1 point prevalent ESRD patients with a first cardiovascular diagnosis or procedure between January 1 & November 30, 2008.*

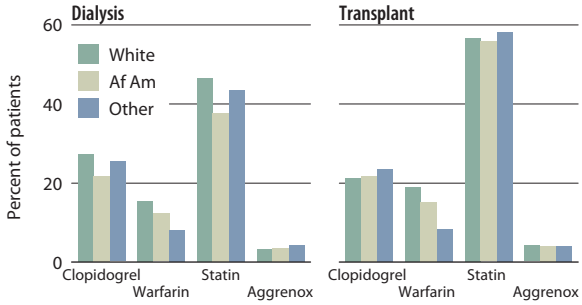
4.5ii Prescription drug therapy in prevalent ESRD patients with CHF, by modality & race, 2008



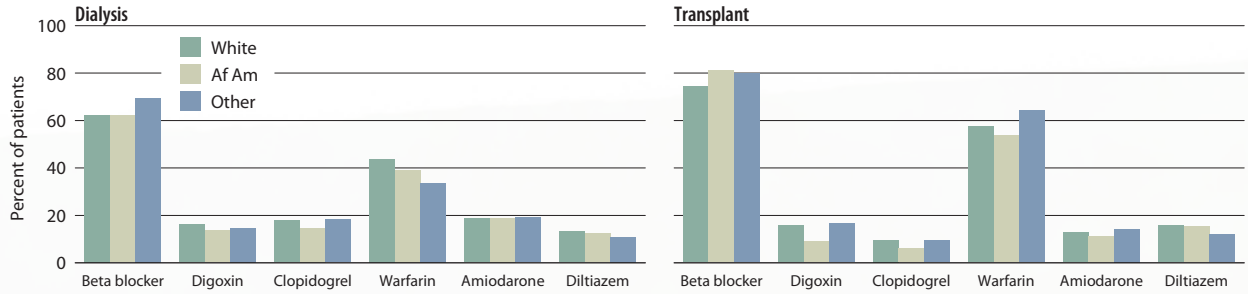
4.6ii Prescription drug therapy in prevalent ESRD patients with AMI, by modality & race, 2008



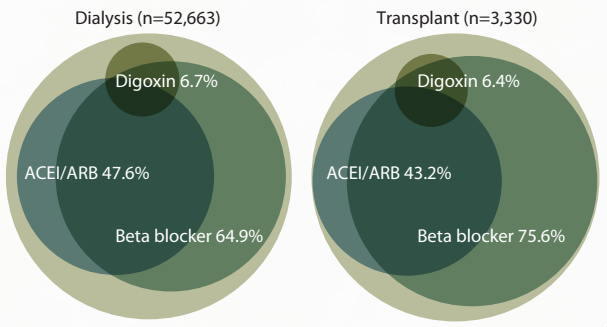
4.7ii Prescription drug therapy in prevalent ESRD patients with CVA/TIA, by modality & race, 2008



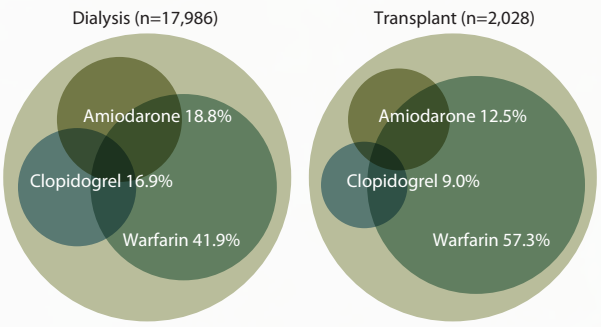
4.8ii Prescription drug therapy in prevalent ESRD patients with atrial fibrillation, by modality & race, 2008



4.9ii Patients treated for CHF, by type of medication & modality, 2008



4.10ii Patients treated for atrial fibrillation, by type of medication & modality, 2008



unadjusted cardiovascular mortality in prevalent patients, 2009

DEATHS PER 1,000 PATIENT YEARS AT RISK

HEMODIALYSIS: ALL CARDIOVASCULAR DISEASE » 1999 123 » 2009 84.7 (TABLE 4.A)

HEMODIALYSIS: AMI » 1999 21.3 » 2009 9.9 (TABLE 4.A)

HEMODIALYSIS: CVA/TIA » 1999 13.6 » 2009 6.4 (TABLE 4.A)

HEMODIALYSIS: CARDIAC ARREST » 1999 66.7 » 2009 54.6 (TABLE 4.A)

DIALYSIS PATIENTS: % DECLINE 2000–2009 » ALL CVD 28.9 » CHF 8.8 » CARDIAC ARREST 15.2 » AMI 52.9 » CVA/TIA 49.2 (FIG 4.3)

cardiovascular disease and pharmacological interventions, by diagnosis and modality, 2008

HEMODIALYSIS: CHF » ACEI/ARB 48% » BETA BLOCKER 65% » DIGOXIN 6.7 (TABLE 4.B)

HEMODIALYSIS: AMI »ACEI/ARB 57% » BETA BLOCKER 77% » STATINS 57% (TABLE 4.B)

HEMODIALYSIS: PAD » CLOPIDOGREL 22% » WARFARIN 13.5 » CILOSTAZOL 2.1 » PENTOXIFYLLINE 1.5 » STATINS 39% (TABLE 4.B)

HEMODIALYSIS: ATRIAL FIBRILLATION » BETA BLOCKER 63% » DIGOXIN 15.4 » WARFARIN 42% » AMIODARONE 18.8 (TABLE 4.B)