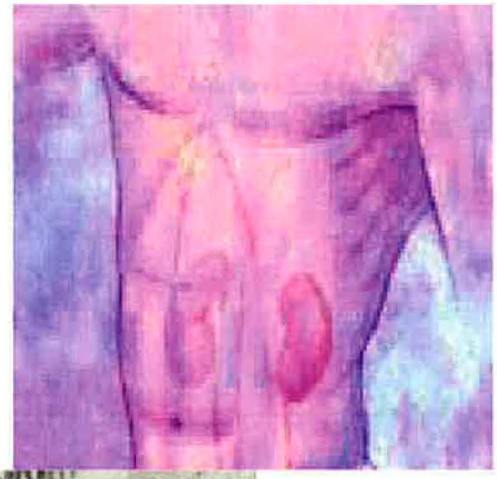
Broken Hearts and Blue Beans:
Depression in Heart and Kidney Disease



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Research Interests:

1. Depression: epidemiology, diagnosis, and treatment in Chronic Kidney Disease and End-Stage Renal Disease
2. Cardiovascular disease, epidemiology and outcomes in Chronic Kidney Disease (*Dallas Heart Study*) and End-Stage Renal Disease
3. Randomized clinical trials in anemia of Chronic Kidney Disease

I. Introduction

It is well established that depressive symptoms are associated with recurrent cardiac events among patients with heart disease and novel cardiac events among patients with no known history of coronary artery disease. Depressive symptoms are very prevalent among patients recovering from an acute myocardial infarction (MI), and at least one in six patients with MI experience major depression (1). Depression is in fact an independent risk factor for post-myocardial infarct mortality (1-7).

Patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) experience excessive rates of cardiovascular death from myocardial infarction and other complications of atherosclerotic heart disease (8). Compared to patients without CKD, those with the disease are 60 percent more likely to develop cardiovascular disease and 70 percent more likely to develop atherosclerotic heart disease (8). Chronic kidney disease is now well recognized as an independent predictor of cardiovascular events, including death. A post-hoc analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT) revealed that below a GFR of 81 ml/min/1.73 m^2, each reduction of the estimated GFR by 10 units significantly increased the hazard ratio for death and nonfatal cardiovascular outcomes by 10% (9). Moreover, epidemiologic data from Kaiser Permanente of Northern California among 1.2 million participants demonstrate that there is a graded increase in death rates, cardiovascular hospitalization and cardiac mortality inversely related to the level of kidney function (10).

Given the excessive rate of cardiovascular death in patients with ESRD, and the correlation of depression with increased cardiovascular events, it becomes imperative to investigate whether treatment of depression improves not only quality of life, but cardiac morbidity and mortality among patients with both CKD and ESRD. Despite the recent large randomized, placebo-controlled SADHART trial that reported both safety and efficacy of sertraline use in patients with acute MI or unstable angina (11), anti-depressant treatment rates among patients with heart and/or kidney disease are very low.

The objective of this presentation is to emphasize the high prevalence of depression in cardiovascular and kidney disease, to review the association of depression with poor cardiovascular outcomes and potential mechanisms for this association, and to review safety and efficacy of anti-depressant use in these populations of patients.

II. Prevalence of Depressive Symptoms and Major Depression

Before discussing prevalence, a distinction needs to be made between depressive symptoms, as assessed by patient self-administered depression scales, such as the Beck Depression Inventory (BDI), and a diagnosis of depressive disorder made by the physician based on the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV) (12-15). Patients with coronary heart and kidney disease may report symptoms of decreased energy, poor appetite and sleep disturbance on self-report depression scales that may not be confirmed as a depressive disorder during a DSM IV-based structured

clinical interview (12, 13). These increased somatic symptoms reported by a chronically ill patient may, therefore, be misclassified as symptoms of a depressive disorder (16). The use of such self-report scales in previous research makes it difficult to accurately estimate the prevalence of major depression, particularly in ESRD patients (12, 13, 17, 18) (Table 1), which in turn complicates the formulation of sample size calculations for designing future treatment studies of depression in this population of patients (12).

Table 1
Depression Prevalence

Symptoms by BDI	
Coronary Heart Disease	31%
Congestive Heart Failure	35%
End-Stage Renal Disease	45%
Diagnosis by DSM IV	
Coronary Heart Disease	16%
Congestive Heart Failure	14%
End-Stage Renal Disease	26%

Prevalence in patients with cardiovascular heart disease

The prevalence of depression is high among patients with coronary heart disease and those with clinical congestive heart failure (CHF) or low ejection fraction (2, 19-22). Prevalence varies in different reports based on how depression was defined (Table 1). The prevalence of depressive symptoms by BDI score ≥10 was 31% measured 5 to 15 days after acute MI; however, the prevalence of depression by the modified version of the National Institute of Mental Health Diagnostic Interview Schedule (DIS, which is a DSM-validated structured psychiatric interview) (23) in the same cohort was 16%; (2, 3). Of 374 patients admitted with New York Heart Association (NYHA) Class II or higher CHF, 35.3% had a BDI score of ≥10, but 13.9% had major depressive disorder diagnosed by DIS (19). An even higher major depression rate of 36.5% was reported in medically ill hospitalized CHF patients older than 60 years (22).

Prevalence in patients with kidney disease

The use of different scales for depression diagnosis also probably explains why point prevalence of depression has been reported to be anywhere from 15 to 60% in ESRD (12, 13, 17, 24-31). The lack of consistency in these reports could also reflect different co-morbidities, populations assessed at different time-points since the introduction of chronic dialysis, and different baseline characteristics of the population sampled (12).

There is a large body of literature using depression self-administrated scales, such as the BDI, as a screening tool for identification of depressive symptoms among patients on chronic dialysis (12, 13, 27-30), but diagnostic data regarding depressive disorder are more limited. For example, using the BDI as the diagnostic tool, depressive symptoms were reported to be present at a striking rate of 45% at time of dialysis initiation (27, 28). In a multi-center study of over 4,000 ESRD patients receiving chronic dialysis in the U.S. and 5 European countries, the phrases "so down in the dumps that nothing cheers you up" and "downhearted and blue" were used as surrogates of depression (31). The point prevalence of depression using these phrases was 19.5% and 21.5%, respectively (31). The prevalence of physician-diagnosed depression abstracted from medical records in the same group of patients was 17.7%. Interestingly enough, however, the agreement between theses phrases and physician diagnosis was low (Kappa index 0.16 and 0.17, respectively) (31), demonstrating that there was a poor diagnostic correlation between use of these phrases and physician-diagnosed depression (Table 2).

Depression indicator	Prevalence of depression, % n/N			Kappa index	
	Europe	United States	Total	"Downhearted and blue"	"So down in the dumps"
Physician-diagnosed by medical record	16.2 (388/2401)	19.0 (543/2855)	17.7 (931/5256)	0.17	0.16
Self-reported "Downhearted and blue"	24.8 (576/2319)	18.5 (475/2562)	21.5 (1051/4881)	—	0.60
Self-reported "So down in the dumps that nothing could cheer you up"	22.6 (525/2324)	16.6 (429/2577)	19.5 (954/4901)	—	—

Table 2 Poor agreement between self-reported and physician-diagnosed depression. Lopes AA, Kidney Int 2002

Two recent studies actually used the physician-administered Structured Clinical Interview for Depression (SCID) as the gold standard for the diagnosis of depression among samples of ESRD patients (12, 32). The SCID is a structured interview that has been validated against the DSM IV for establishing a psychiatric diagnosis of depression (12, 33, 34). One study was done at Duke where 85% of the sample was African American, and the other study was done in Portland, Oregon where the majority of patients were white (12, 32). Point prevalence of depression among patients with ESRD was 26% in both studies. The point prevalence of major depression was 17.3% and 19%, and the rest of patients had dysthymia or minor depression based on SCID (12, 32).

III. Association of Depression with Poor Cardiovascular Outcomes

Depression is associated with cardiovascular events in patients without known coronary disease

Increased mortality was first reported among patients with "involution melancholia" in 1937 (35). Since then, there have been many observational studies in patients without known coronary heart disease that reported an association between depressive affect and increased risk of future nonfatal MI and death (36-44).

In a global study of risk factors for acute MI which included 11,119 cases of first MI and 13,648 controls from 52 countries (the INTERHEART study), depression was more frequent among cases than controls (24.0% vs. 17.6%, OR 1.55, 95% CI 1.42-1.69) (36). In the Baltimore cohort of Epidemiologic Catchment Area Study (a survey of psychiatric disorders in the general population), the odds ratio (OR) for the occurrence of MI associated with a history of major depressive episode was 4.54, 95% CI (1.65-12.44) independent of coronary risk factors (40). The New Haven cohort of the same study that included 3007 subjects ≥55 years old, reported that odds of dying over a 15-month follow-up period was also four times higher for subjects with affective disorders than for those without; there were no suicides (38). Furthermore, depressed affect was related to fatal ischemic heart disease at mean follow-up of 12.4 years in a cohort of 2,832 adults aged 45-77 years without coronary heart disease at baseline participating in the National Health Examination Follow-up Study (39).

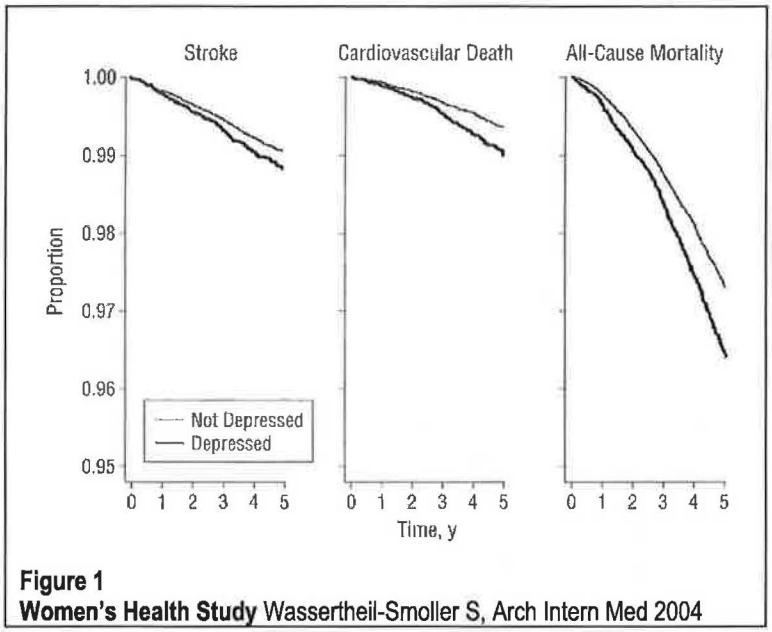

Figure 1
Women's Health Study Wassertheil-Smoller S, Arch Intern Med 2004

Depressive affect was measured in 93,676 healthy post-menopausal women, using the Center for Epidemiological Studies Depression Scale (CESD), who were then followed for a mean of 4.1 years in the Women's Health Initiative Observational Study (37). Depressive affect, as reported by 15.8%, was an independent predictor of cardiovascular death and all-cause mortality after adjustment for age, race, education, income, diabetes, hypertension, smoking, high cholesterol, body max index and physical activity (37) (Figure 1). Among 4,493 participants in the Cardiovascular Health Study without known coronary disease, the adjusted hazard ratio for every 5-unit increase in mean depression score for the development of coronary disease was 1.15 (p=0.006), and for all-cause mortality was 1.16 (p=0.006) (41) (Table 3). The risk of coronary disease increased by 40% and risk of death by 60% for those with the highest cumulative mean depression scores compared with those with the lowest scores (41). Similarly in the Systolic Hypertension in the Elderly Program (SHEP) that included 4,736 persons ≥60 years, there was an increase in depression score prior to MI, stroke or death at 5 years (42, 43).

Table 3 Cardiovascular Health Study: Relationship Between HRs Associated With Every 5-Unit Increase in Cumulative Mean Depression Score and Cardiovascular Events. Ariyo AA, Circ 2000

Incident	No. of Events	Unadjusted HR, 95% CI	*P*	Adjusted HR, 95% CI	*P*
Death	614	1.29 (1.18, 1.41)	0.0001	1.16 (1.04, 1.28)	0.006
CHD	606	1.15 (1.04, 1.26)	0.006	1.15 (1.04, 1.27)	0.006
MI	270	1.12 (0.96, 1.29)	0.141	1.14 (0.98, 1.34)	0.088
Angina without concurrent MI	298	1.18 (1.03, 1.35)	0.018	1.20 (1.05, 1.38)	0.009

Adjusted Cox Proportional Hazards models with the CESD scale as a time-dependent variable indicated a 25% increased risk of death per 5-unit increase in CESD score (RR 1.25, 95% CI 1.15-1.36), and 18% increase in stroke or MI (RR 1.18, 95%CI 1.08-1.30) (43). Finally, in a prospective study of 3,701 subjects aged 70 years, newly depressed men, but not chronically depressed, were about twice as likely to have a cardiovascular event than those that were never depressed (RR 2.07, 95% CI 1.44-2.96) (44).

Depression is associated with mortality in patients with known coronary disease

The association of depressive symptoms and major depression with mortality has been extensively studied in patients with recent MI (2-7, 45-48). In a large prospective cohort

study, 222 patients with acute MI were interviewed between 5 and 15 days following the event and were followed for 6 months (2). The hazard of cardiovascular death was almost 6 times higher in patients with major depression (as diagnosed by DIS interview), HR 5.74, 95% CI (4.61-6.87). This association remained significant after controlling for other predictors of mortality, such as left ventricular dysfunction (Killip class) and previous MI, with adjusted HR 4.29, 95% CI (3.14 - 5.44). The authors also reported an 18-month follow-up of the same cohort (3). In multiple logistic regression analyses, both depression by DIS, OR 3.64, 95% CI (1.32-10.05), and elevated BDI Scores, OR 7.82, 95% CI (2.42-25.26), were related to 18-month cardiac mortality. However, after controlling for other significant predictors of mortality in the data set (previous MI, Killip class, premature ventricular contractions of ≥10 per hour), only the impact of the BDI score remained significant (3). Among 896 post-MI patients who were assessed with the BDI during hospitalization, there was a significant long-term dose-response relationship between depressive symptoms and cardiac mortality (5) (Figure 2). Finally, even low levels of depressive symptoms on BDI (4 to 9) were associated with increased post-MI mortality (4).

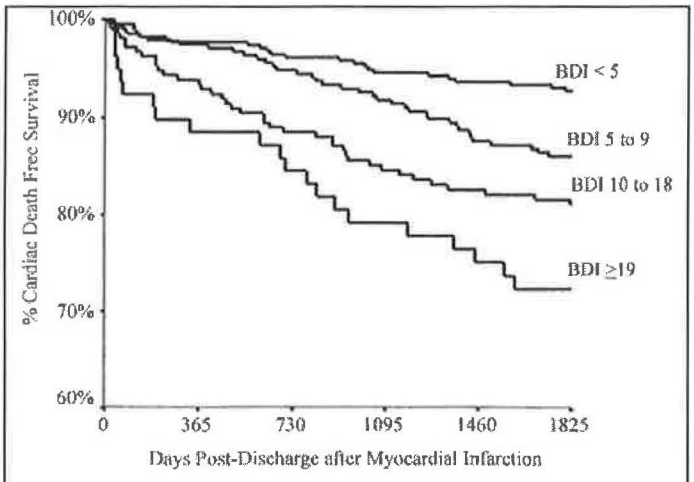

Figure 2 Long-term survival after MI in relation to BDI Scores. Higher scores represent more depressive symptoms. Lesperance F, Circ 2002

Depression is associated with rehospitalization and mortality in patients with CHF

Decreased social support, depressive symptoms by higher BDI scores and depression diagnosis by structured psychiatric interviews have been associated with mortality in patients with CHF (19, 20, 49, 50). In a cohort of over 300 patients who were followed prospectively after hospital admission for CHF, major depression was associated with increased mortality at 1 year (OR 2.23, p=.04) and readmission at 3 months (OR 1.90, p =.04) and at 1 year (OR 3.07, p =.005) (19). Advanced age and higher NYHA class were also associated with higher mortality and readmissions during the 12-month follow-up and might have attenuated the association of major depression with mortality and readmission, but a trend persisted after adjustment (19). The adjusted readmission rate at 1 year was almost 3 times higher and remained statistically significant in patients with major depression vs. those nondepressed or mildly depressed (19).

Depression is associated with cerebrovascular mortality

In a community sample of 6676 initially stroke-free adults, depressive symptoms were assessed by the 18-item Human Population Laboratory Depression Scale (51). During 29 years of follow-up, 169 stroke deaths occurred, and reporting 5 or more depressive

symptoms at baseline was associated with increased risk of stroke mortality, after adjusting for age, sex, and race (HR 1.66, 95% CI 1.16-2.39) (51). The association remained statistically significant after additional adjustments for education, alcohol consumption, smoking, body mass index, hypertension, and diabetes (HR 1.54, 95% CI 1.06-2.22) (51).

Depression is associated with death and hospitalization in patients with ESRD

There is some uncertainty as to whether major depression is an independent predictor of poor outcomes in patients with ESRD (13, 16). Previous studies have been limited by size and the lack of standardized DSM IV-based interviews. Again, most studies that looked at depression affecting outcomes in this population of patients used self-report questionnaires, particularly the BDI, as the diagnostic tool for depression. So there is more evidence for the association of depressive symptoms with poor outcomes than the association of depressive disorder with poor outcomes in this population of patients. While most studies reported an association, other studies revealed no relationship. Devins described a lack of correlation between mortality and depressive symptoms and/or moods in a prospective cohort of 97 ESRD patients that included 34 kidney transplant recipients (52). Christensen was unable to correlate depression based on BDI score with mortality (53). Kimmel reported no effect of baseline score on BDI, but a significant negative effect of time-varying BDI-defined depression on survival (30).

Despite these negative findings, there is sufficient evidence in the literature to suggest that depressive symptoms may be associated with poor outcomes in patients treated with chronic hemodialysis. Soucie and McClellan reported a higher rate of death within 90 days of dialysis initiation for depressed versus non-depressed patients (54). Shulman correlated BDI score with increasing risk of mortality in a stepwise fashion (55). Depression predicted poor outcome in a cohort of home dialysis patients (56, 57). High levels of depressive symptoms based on Minnesota Multiphasic Personality Inventory scoring correlated with death in a cohort of Veterans with ESRD (58).

In a longitudinal prospective study of urban hemodialysis patients living in Washington, D.C., most of whom were African Americans, lower levels of social support, decreased behavioral compliance with the dialysis prescription, and increased negative perception of the effects of illness were independently associated with increased mortality (59). The effects were of the same order of magnitude as medical risk factors. Another study by the same authors prospectively evaluated and followed 57 patients with ESRD, 43 treated with hemodialysis and 14 with continuous ambulatory peritoneal dialysis (60). The BDI as well as the Cognitive Depression Scale (the CDI), a cognitive subset of the BDI, were utilized for the analysis. The mean CDI scores in the group of non-survivors were significantly greater than the scores in the survivors. At two year follow-up, CDI scores were significantly different between groups, and remained significant in a hazards regression. Disease severity, age and duration of dialysis were also significantly related to mortality at two year follow-up (60).

In a prospective cohort study of 295 urban outpatients treated with chronic hemodialysis, patients were assessed every six months for up to two years using BDI (30). Mortality was tracked for a minimum of 20 and a maximum of 60 months. Multivariable analyses controlled for age, medical co-morbidity, albumin concentration, and dialyzer type and site. Although baseline level of depressive symptoms by BDI was not a significant predictor of mortality at 38.6 months, when depression was treated as a time-varying covariate based on periodic follow-up, the level of BDI depressive affect was significantly associated with mortality in both univariate and multivariable analyses (Table 4).

	RR (CI)	*P* value
Baseline Beck Depression	1.09 (0.92, 1.29)	NS
Baseline Cognitive Depression	1.09 (0.91, 1.31)	NS
Time-varying Beck Depression	1.24 (1.05, 1.46)	0.01
Time-varying Cognitive Depression	1.18 (1.00, 1.38)	0.05
Adjusted Time-varying Beck Depression	1.32 (1.13, 1.55)	0.0006
Adjusted Time-varying Cognitive Depression	1.23 (1.05, 1.43)	0.009

Table 4 Depressive affect as a predictor of mortality in ESRD
Kimmel PL, Kidney Int 2000

In a more recent large, multi-center study that included hemodialysis patients from both Europe and the U.S., self-reported depression by two simple questions ("so down in the dumps that nothing cheers you up" and "downhearted and blue") was associated with increased risks of mortality and hospitalization, as was past physician diagnosis of depression ascertained from the medical chart (31) (Figure 3). It should be emphasized that this study was restricted to patients that were enrolled in the Dialysis Outcomes and Practice Patterns Study (DOPPS) and may have been influenced by refusal bias (24, 31).

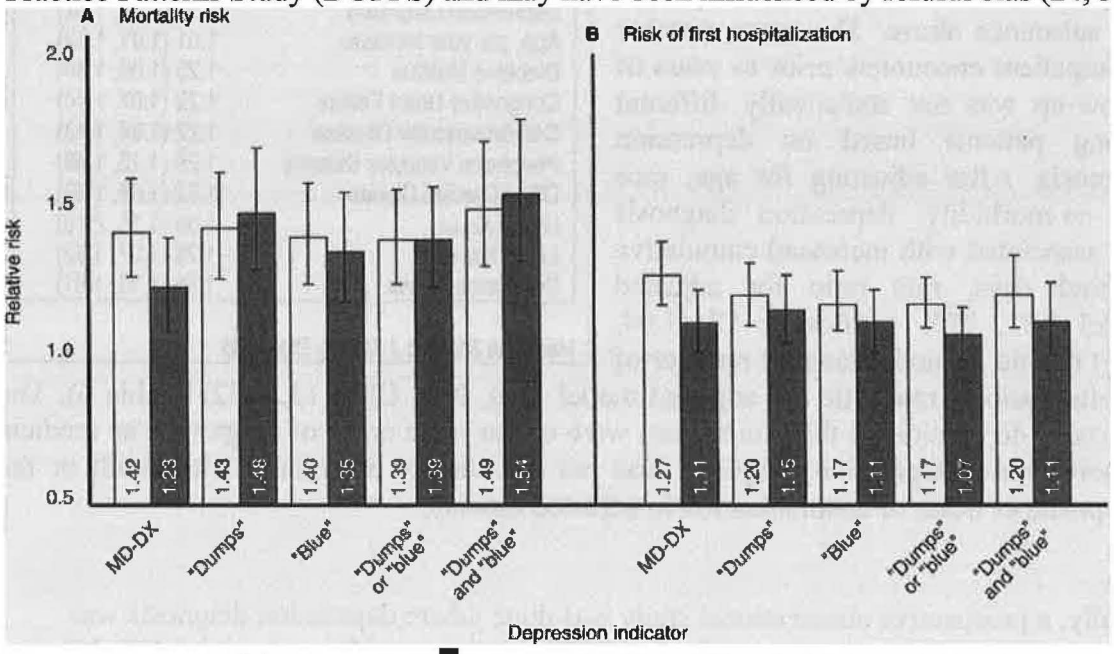

Figure 3 Unadjusted (□) and adjusted (■) relative risks of mortality and first hospitalization for depressed as compared to non-depressed patients. Lopes AA, Kidney Int 2002

Given the limitation of prior studies, a population-based approach was undertaken in a study that utilized centralized Department of Veterans Affairs (VA) databases as sources for identification of patients and physician diagnosis of depression in order to investigate the association of depression with poor patient outcomes (24). Because the VA is the largest healthcare provider in the U.S., these data allowed examination of a large national sample, the entire population of prevalent ESRD patients that receive chronic hemodialysis in the VA system (61). In addition, since these databases capture nearly 100% of all VA hospital episodes (62) and contain information on all ambulatory patient contact with the VA (63, 64), patient co-morbidities and repeated healthcare utilizations could be easily and objectively identified (24). A prevalence cohort of 1,588 male ESRD patients receiving chronic hemodialysis in VA facilities between 9/01/00 and 9/30/00 were identified. Mean age was not statistically different among patients based on depression diagnosis. Patients with a physician diagnosis of depression were more likely to be white, and have hypertension, ischemic heart disease, peripheral vascular disease, liver disease and substance abuse. The mean number of outpatient encounters prior to years of follow-up was not statistically different among patients based on depression diagnosis. After adjusting for age, race and co-morbidity, depression diagnosis was associated with increased cumulative hospital days, rate ratio for adjusted model 1.31, 95% confidence CI (1.04, 1.66) (Table 5), and increased number of hospitalizations, rate ratio for adjusted model 1.30, 95% CI (1.11, 1.52) (Table 6). The effects of depression on these outcomes were of the same order of magnitude as medical comorbidities. Depression diagnosis was not statistically associated with death or the composite of death or hospitalization in adjusted models.

Table 5 Negative Binomial Regression Model for Correlates of Cumulative Hospital Days

	Rate Ratio (95% CI)
Unadjusted Analysis	
Depression Diagnosis	1.41 (1.11, 1.79)
Multivariable Analysis	
Depression Diagnosis	1.31 (1.04, 1.66)
Age, per year increase	1.03 (1.02, 1.04)
Diabetes Mellitus	1.46 (1.22, 1.74)
Hypertension	1.23 (1.02, 1.48)
Peripheral Vascular Disease	1.42 (1.19, 1.70)
HIV Disease	2.27 (1.37, 3.74)
Chronic Lung Disease	1.44 (1.07, 1.94)
Substance Abuse	1.49 (1.16, 1.90)

Hedayati SS, Am J Kidney Dis 2005

Table 6 Negative Binomial Regression Model for Correlates of Number of Hospitalizations

	Rate Ratio (95% CI)
Unadjusted Analysis	
Depression Diagnosis	1.46 (1.24, 1.72)
Multivariable Analysis	
Depression Diagnosis	1.30 (1.11, 1.52)
Age, per year increase	1.01 (1.01, 1.02)
Diabetes Mellitus	1.23 (1.09, 1.39)
Congestive Heart Failure	1.22 (1.07, 1.40)
Cerebrovascular Disease	1.22 (1.04, 1.43)
Peripheral Vascular Disease	1.29 (1.15, 1.46)
Other Cardiac Disease	1.22 (1.08, 1.38)
HIV Disease	1.56 (1.11, 2.18)
Liver Disease	1.28 (1.07, 1.52)
Substance Abuse	1.36 (1.15, 1.61)

Hedayati SS, Am J Kidney Dis 2005

Finally, a prospective observational study was done where depression diagnosis was based on DSM IV-based gold standard of SCID administered by a physician (12, 65).

Ninety-eight patients were approached and enrolled consecutively from three different outpatient dialysis units affiliated with Duke University Medical Center, one of which was the Durham VA Hospital. The patients were followed prospectively for up to a year. Survival analysis was used to investigate the association between depression and time to the first event, which was defined as either death or hospitalization (Figure 4). Models were adjusted for age, gender, race, time on dialysis and number of comorbidities. The cohort had a mean age of 57.2±13.8 and a mean time on dialysis of 4.1±3.8 years. Forty-four percent were female and 14% white. Mean number of comorbid conditions was 3.1±1.8 (65). The prevalence of depression by SCID was 26.5%. Median time to first follow-up was 5.4 months. Twenty-one of 26 depressed patients and 31 of 72 non-depressed patients died or were hospitalized by first follow-up. In the unadjusted model, depression was associated with time to death or hospitalization, with a hazard ratio (HR) 2.11, 95% CI (1.21-3.68) (65) (Figure 4). The association remained significant in adjusted analyses, HR 2.07, 95% CI (1.10-3.90) (65) (Table 7). This is the first report, to our knowledge, of the association of depression diagnosed using a formal structured physician interview with poor outcomes independent of comorbidities in chronic hemodialysis patients. Prospective studies need to be conducted to explore how treatment of depression affects clinical outcomes.

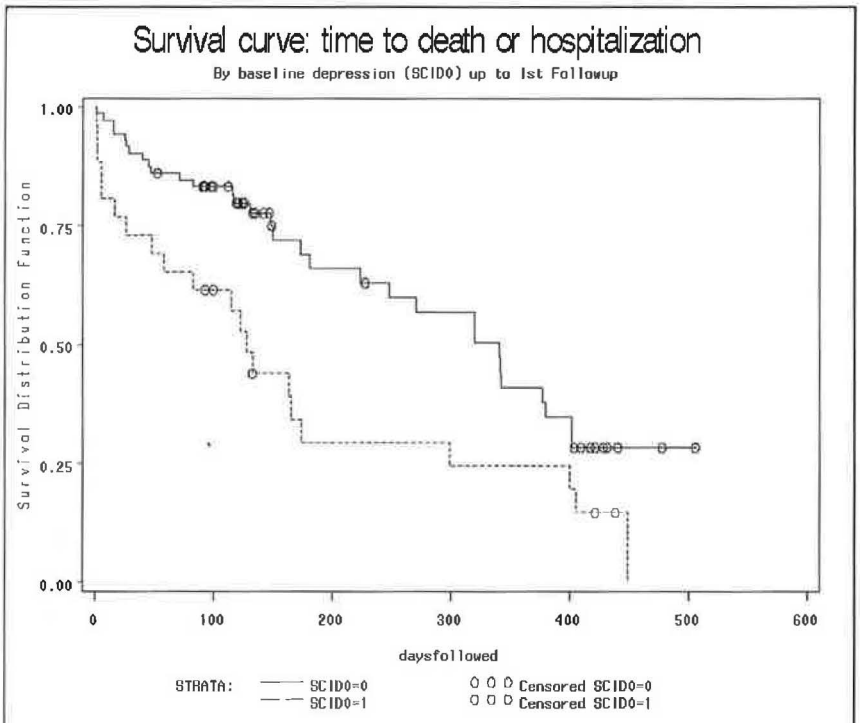

Figure 4 SCID0 indicates no depression and SCID1 indicates depression
Hedayati SS, ASN 38th Annual Meeting, 2005

Covariates	Hazard Ratio
Unadjusted Analysis	
Depression Diagnosis	2.11 (1.21, 3.68)
Multivariable Analysis	
Depression Diagnosis	2.07 (1.10, 3.90)
Age per year increase	0.99 (0.96, 1.01)
White race	1.50 (0.70, 3.22)
Female gender	3.22 (1.65, 6.32)
Years on dialysis	1.03 (0.98, 1.09)
Medical comorbidity	1.34 (1.13, 1.58)

Table 7 Cox Proportional Hazards Model for time to first event
Hedayati SS, ASN 38th Annual Meeting, 2005

Depression is associated with death in patients with CKD and CHF

In an analysis of a prospective cohort of 374 patients admitted with CHF to the Cardiology Service at Duke

University Medical Center, the association between severe CKD, corresponding to creatinine clearance (CrCl) <30 mL/min/72 kg, depression (as diagnosed by the National Institute of Mental Health Diagnostic Interview Schedule, DIS), and 12-month mortality was investigated using logistic regression (16). Patients 18 years or older were eligible for enrollment if they had clinically diagnosed CHF, defined as NYHA classification II or greater, left ventricular ejection fraction of 35% or less, or both. The point prevalence of major depression by DIS was 21.6% if severe CKD was present and 13.0% if absent (16). Both depression by DIS and severe CKD were significant predictors of mortality at 12-month follow-up in adjusted models (16) (Table 8). The inclusion of hematocrit and NYHA class in separate multivariate models did not confound the association of severe CKD and depression with mortality (16).

Table 8 Unadjusted and Multivariate Logistic Model of 12-Month Mortality in Patients Hospitalized with CHF

	Odd Ratio (95% CI)
Unadjusted Analysis	
Severe CKD	4.57 (2.27, 9.21)
Multivariate Analysis	
Severe CKD	3.64 (1.62, 8.13)
Major vs. No Depression	2.07 (0.93, 4.63)
Major vs. Mild Depression	3.13 (1.02, 9.62)
Age, per one year increase	1.03 (0.999, 1.06)

Hedayati SS, Am J Kidney Dis 2004

IV. Risk Factors Associated with Depression

Risk factors associated with depression in patients with recent acute MI included younger age, female sex, and history of diabetes mellitus or cigarette smoking (66). Fewer of the depressed vs. non-depressed were married, and fewer belonged to a racial or ethnic minority group (66). There were a greater proportion of women in the major depression group, and higher NYHA classes were observed in both the mild and major depression groups compared with the no depression group in hospitalized patients with CHF (19).

Severity of chronic kidney disease has also been associated with increased depressive symptoms (16). In the multivariate model, after adjusting for age, race, gender, hematocrit, NYHA class, ischemic origin of CHF, and diabetes mellitus, severe CKD corresponding to creatinine clearance <30 mL/min/72 kg was still associated with depressive symptoms by BDI (OR 2.89, 95% CI 1.39-5.99) (16).

Longer duration of chronic hemodialysis correlated with higher prevalence of physician-diagnosed depression in a large cohort of ESRD patients from both Europe and the U.S. (31). A larger proportion of depressed patients was also female, white, and had lower serum albumin concentrations (27, 31). Those with self-reported depression were younger, less likely to be Black, and more likely to be unemployed and have diabetes mellitus (31).

Most importantly, in ESRD patients, the major risk factor across studies for depression, whether self-reported or physician-diagnosed, is increased number of comorbid

conditions, such as diabetes mellitus, coronary heart disease, cerebrovascular disease, peripheral vascular disease and lung disease (12, 24, 31), as well as lower self-rated quality of life (12, 27). Greater illness burden and comorbidity have been identified as risk factors for chronic major depressive episode and depression in older non-ESRD patients in primary or psychiatric care settings also (67, 68). This correlation of increased comorbidity and disease severity with depression reported in both cardiac and ESRD patients could potentially confound the observed association of depression with poor outcomes (12, 19, 22).

V. Potential Mechanisms

It is unclear whether depression itself has a direct mechanistic role in the development of cardiac events or whether it is merely a surrogate marker for increased comorbidity and cardiovascular disease severity. It is possible that the association of depression with poor cardiac outcomes is confounded by its association with other cardiovascular risk factors such as smoking, hypertension, diabetes or unhealthy lifestyle. However, specific biological and behavioral factors were proposed and investigated as potential mechanisms by which depression may lead to increased cardiovascular events (1, 66, 69-87) (Table 9).

Table 9 Potential mechanisms by which depression may lead to cardiac events

Biological Mechanisms

- Common genetic vulnerability
- Alterations in cardiac autonomic tone
- Enhanced activity of the hypothalamic pituitary-axis
- Increased catecholamine levels
- Increased whole blood serotonin
- Greater platelet activation
- Inflammatory processes
- Lower omega-3 fatty acid levels
- Mental-stress induced ischemia
- Toxicity of tricyclic antidepressants

Behavioral Mechanisms

- Dietary nonadherence
- Lack of exercise
- Medication nonadherence
- Poor social support
- Unhealthy lifestyle

Adapted from Whooley MA, JAMA 2006

Genetic factors: Both depression and coronary heart disease appear heritable in twin studies (72). Scherrer investigated genetic and environmental contributions to the covariation of depressive symptoms and coronary heart disease in a sample of 2,731 male-male twin pairs from the Vietnam-Era Twin (VET) Registry (73). The correlation between genetic influences on depression and on a composite measure of heart disease was 0.42, suggesting that a large proportion of variability in depressive symptoms and coronary disease was attributable to common genetic factors (72, 73).

Alterations in autonomic tone: Low heart rate variability reflects excessive sympathetic or inadequate parasympathetic tone and is a strong independent predictor of death after acute MI (66, 86, 87). Of patients with recent acute MI, those who met DSM IV criteria for depression had significantly lower heart rate variability indices than those without depression (66). After adjustment for potential confounding variables such as age, gender, diabetes mellitus and cigarette smoking, depression remained significantly associated with every index of heart rate variability except for high-frequency power (66). The observation that the post-MI mortality risk associated with depression (by BDI

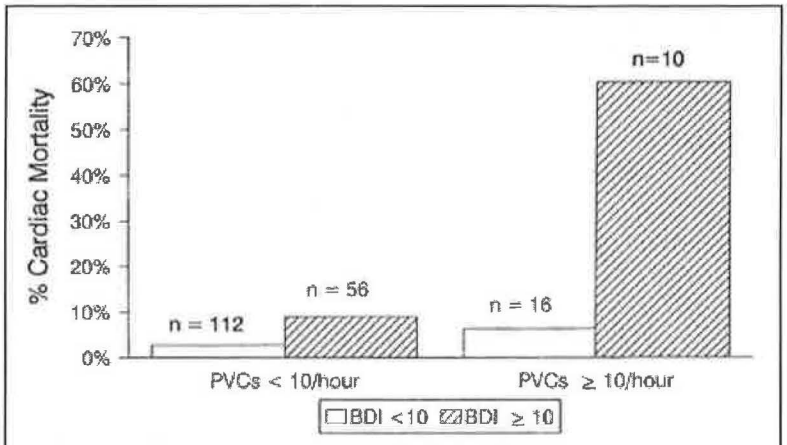

Figure 5 Mortality associated with depression (BDI≥10) was greatest for PVCs≥10. Frasure-Smith, Circ 1995

score ≥10) was greatest among patients with ≥10 premature ventricular contractions per hour further supports the potential mechanistic role of excessive sympathetic tone (3) (Figure 5).

Alteration in endocrine activity: Enhanced activity of the hypothalamic pituitary-axis was also proposed as a mechanism (74). For example, in a cross-sectional study of 693 patients with coronary heart disease, subjects within the highest quartile of 24-hour urinary cortisol had a twofold increase in odds of having depression, compared with those in the lowest quartile. The association remained significant after adjusting for potential confounding variables, with OR 2.4, 95% CI (1.3-4.4) (74). Patient with coronary disease and depressive symptoms also had greater mean norepinephrine excretion levels than those without depressive symptoms in adjusted logistic models (75).

Inflammation: An increase in inflammation, as measured by C-reactive protein plasma levels, and lower omega-3 fatty acid levels was implicated (78, 79). Other investigators have proposed mental-stress induced ischemia and cardiac toxicity of tricyclic anti-depressants as potential mechanisms linking depression with poor cardiovascular outcomes (80, 81).

Platelet activation: Enhanced platelet activation in depressed patients was proposed as one of the mechanisms leading to cardiac death in patients with acute coronary syndrome and depression (88). Although the clinical relevance is not yet clear, there are reports in the literature to suggest that depression is associated with changes in platelet function, and that serotonin-selective reuptake inhibitors (SSRIs) may have anti-platelet activities. Platelets were historically used as peripheral models of central serotonin nerve terminals and, therefore, extensively studied in depression (89, 90). There are reports of increased platelet serotonin receptor 5-HT_{2A} binding density among depressed patients (89, 90). In addition, depressed patients exhibit reduced platelet and brain serotonin transporter (5-HTT) sites as detected by imipramine and paroxetine binding (90, 91). Increased serotonin receptor 5-HT_{2A} binding density, in addition to fewer 5-HTT sites, suggests that patients with depression may be particularly vulnerable to platelet aggregation and vasoconstriction (90). Platelet monoamine oxidase activity was significantly elevated in depressed patients (92, 93). Fluoxetine and norfluoxetine exhibited serotonin-blocking effects in rat platelets (94). Anti-platelet properties of sertraline and its primary metabolite, *N*-desmethylsertraline, were also observed in vitro (95). Treatment with sertraline relative to controls for 8 weeks resulted in a significant reduction in serotonin-

mediated platelet aggregation (96). Observations that fluoxetine may be responsible for inhibition of platelet aggregation induced by ADP, epinephrine, ristocetin, aranchidonic acid and collagen, resulting in mild bleeding and bruising that corrected after withdrawal of the drug (97, 98), were not confirmed by another study that found no difference in platelet aggregation after up to 4 weeks of treatment with fluoxetine or paroxetine (99).

Interestingly enough, retrospective analysis of data from several clinical trials revealed that clinical depression was associated with enhanced activation of platelet and endothelial biomarkers (100). In a pooled study of 281 baseline plasma samples from patients with acute MI (ASSENT-2 study), acute coronary syndrome (PRONTO study) and clinical depression plus recent acute coronary syndrome (SADHART study), patients with acute coronary syndrome and depression exhibited the highest levels of platelet factor 4, β-thromboglobulin, and platelet/endothelial cell adhesion molecule-1 when compared with MI or angina patients without clinical depression (100).

Biomarker and Treatment Group	6 Weeks		Correlation With Drug/Metabolite Level (r)	
	Mean	SD	Sertraline[a]	*N*-Desmethylsertraline[b]
PF4 (IU/ml)				
Sertraline group	26.8	12.8	−0.69	−0.33
Placebo group	38.2	25.9		
β-TG (IU/ml)				
Sertraline group	41.8[e]	13.3	−0.43	−0.29
Placebo group	65.1	34.1		
PECAM-1 (ng/ml)				
Sertraline group	58.6	13.8	−0.82	−0.49
Placebo group	43.8[e]	17.4		
P-selectin (ng/ml)				
Sertraline group	84.0	25.6	−0.82	−0.49
Placebo group	81.6	26.3		
TxB_2 (pg/ml)				
Sertraline group	49.8	23.1	−0.66	−0.59
Placebo group	42.8	25.6		
6-Keto-PGF1α (pg/ml)				
Sertraline group	199.1	103.2	−0.44	−0.014
Placebo group	208.9	112.2		
E-selectin (ng/ml)				
Sertraline group	71.1	21.6	−0.48	−0.28
Placebo group	80.0	17.8		
VCAM-1 (ng/ml)				
Sertraline group	786.3	271.2	0.49	0.66
Placebo group	779.8	308.4		

Table 10 Plasma levels of platelet biomarkers in patients treated with sertraline. **SADHART Study** Serebruany VL, Am J Psychiatry 2005

In order to elucidate whether platelet inhibition by SSRIs may represent an independent mechanism for the benefit of these drugs beyond their effects on treatment of depression in patients with cardiovascular disease, the SADHART study authors investigated whether plasma levels of sertraline and *N*-desmethylsertraline affect the release of platelet and endothelial biomarkers in autologous plasma samples, and whether this effect was dose dependent (88, 101). Biomarkers were measured in 165 plasma samples obtained at baseline and 6 and 16 weeks after treatment assignment from 55 patients (23 in sertraline and 32 in placebo groups). At the time of obtaining blood samples, all patients were being treated with aspirin, and none was receiving clopidogrel or oral anticoagulants. There were no significant differences in plasma biomarker levels between the two treatment groups at baseline (88, 101). Plasma levels of sertraline and *N*-desmethylsertraline showed negative, mostly time-dependent, correlations with predominantly platelet-released markers such as platelet factor 4, β-thromboglobulin, platelet/endothelial cell adhesion molecule-1, P-selectin, and thromboxane B_2 (101) (Table 10, Figure 6).

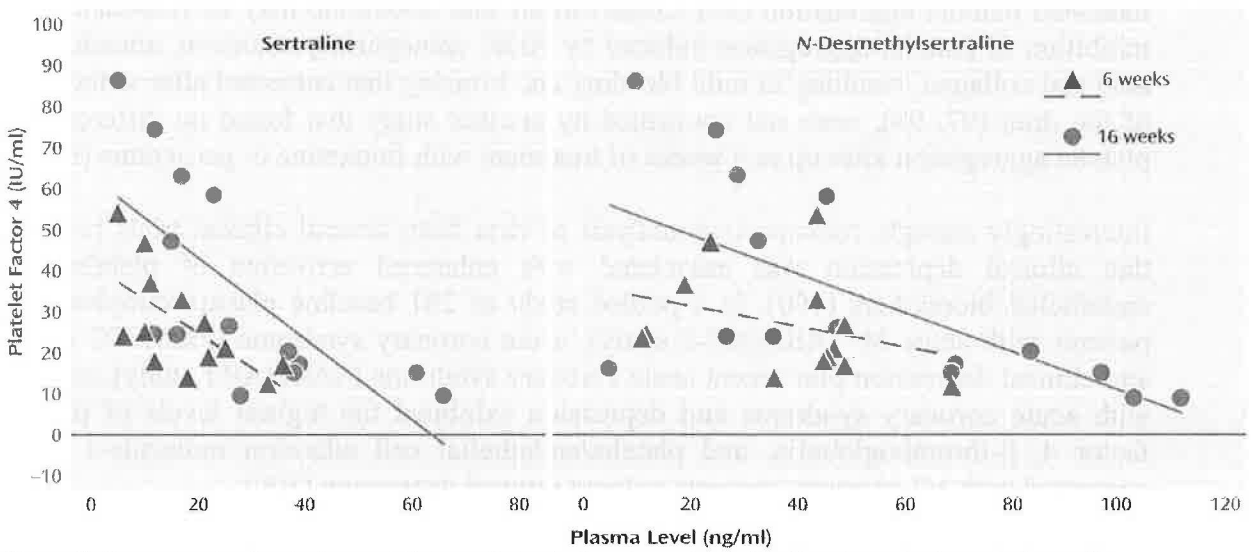

Figure 6 Plasma levels of sertraline and *N*-desmethylsertraline showed negative time-dependent correlations with platelet factor 4. **SADHART Study** Serebruany VL, American J Psychiatry 2005

However, statistically significant differences in mean biomarker levels between the sertraline and placebo groups were only found for plasma levels of β-thromboglobulin and P-selectin at 16 weeks (88, 101), which could be due to lack of enough power to detect a significant difference in the other biomarker levels. The findings that treatment with sertraline in depressed patients after acute coronary syndrome is associated with reductions in platelet activation, despite the co-administration of anti-platelet agents during the trial, may partially explain the trend toward improved cardiovascular outcomes that was observed in SADHART among the sertraline treatment arm (11, 88, 100, 101) .

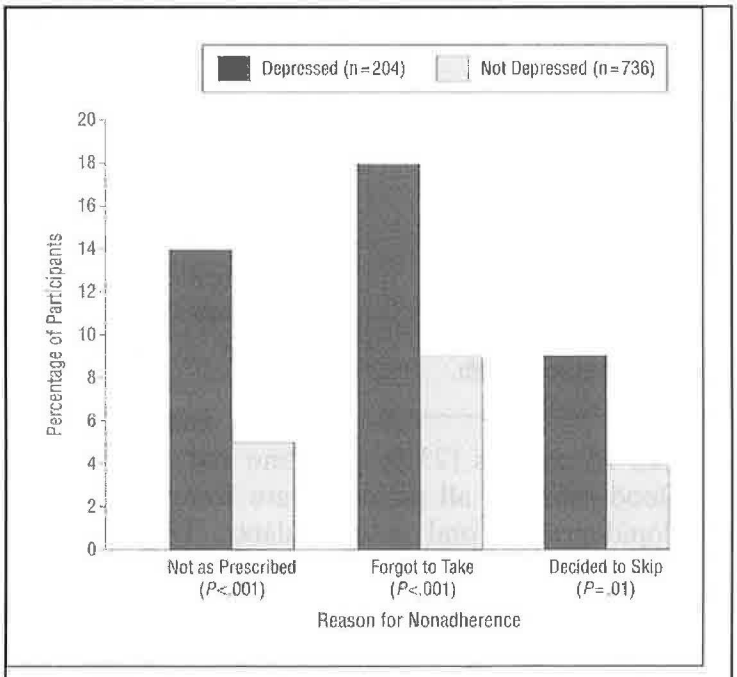

Figure 7 Nonadherence with medications among depressed patients. **Heart and Soul Study** Gehi A, Arch Intern Med 2005

Non-adherence: The different behavioral patterns observed in depressed patients, such as lack of exercise and non-adherence to diet and cardiac medications may increase risk of future coronary events (69, 82-85). Patients with an acute MI and mild to moderate depressive symptoms as measured by BDI score ≥10 or with major depression and/or dysthymia reported lower adherence to a low-fat diet, regular exercise, reducing stress, and increasing social support four months later (82).

Those with major depression and/or dysthymia also reported taking medications as prescribed less often than those without these disorders (82). After adjustment for confounding variables in a cohort of patients with coronary heart disease, those depressed were more likely than those not depressed to report not taking their medications as prescribed, forgetting to take their medications, and deciding to skip their medications, OR (95% CI) were 2.2 (1.2-3.9), 1.6 (1.0-2.7), and 2.1 (1.1-4.0), respectively (102) (Figure 7). In 1612 consecutive subjects referred for evaluation of cardiovascular risk factors, depression was associated with a cluster of unhealthy behaviors including physical inactivity, smoking and poor diet (85). Finally, in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) pilot study, patients with high social support scores, particularly those reflecting perceived support, had lower scores on depression measures at baseline (84).

VI. Treatment

Despite the prevalence of depression and its association with poor outcomes in both patients with cardiac and/or kidney disease, only few of these patients receive adequate diagnosis and therapy (12, 22, 27, 103). A majority of depressed patients with CHF did not receive treatment for their depression with either anti-depressants or psychotherapy, and did not see mental health specialists any more frequently than did the nondepressed (22). Low treatment rates were reported where BDI score $\geq$15 was used to define depression in a cohort of patients initiating hemodialysis (27). Less than half of hemodialysis patients depressed by a DSM IV-validated interview were being treated with anti-depressants, and about half of those were on what could be considered sub-therapeutic doses in patients without renal failure (12). It is recognized that the role of therapy is not only unknown in patients with increased levels of depressive affect in the absence of major depression (104), but also in hemodialysis patients with an established diagnosis of depression (13, 25, 30, 105, 106). Although a large multi-center randomized controlled trial, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, is conducted in primary and psychiatric care settings to investigate the efficacy, safety, and tolerability of augmentation of SSRIs with other anti-depressants (107-109), data in patients with severe kidney and/or heart disease is lacking, since sicker patients are generally excluded from clinical trials of depression (109). There is not enough evidence to clearly suggest that treatment of major depression changes clinical outcomes in ESRD patients (105, 106). Additional research is needed to establish the safety and efficacy of the use of anti-depressants in patients treated with chronic dialysis (12).

There is some evidence for safety and efficacy of anti-depressant medications in post-MI patients (11). Based on this evidence, trial of anti-depressant therapy should be offered to patients with major depression because it may lead both to alleviation of depressive symptoms and improvement in quality of life (69, 110). Treatment of depressed patients with advanced kidney disease, heart failure or acute coronary syndrome may be more challenging due to potential risk of side effects and adverse events associated with anti-depressant medications.

Treatment with anti-depressant medications

The Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) was a randomized, double-blind, placebo-controlled trial conducted in 40 outpatient clinics in the U.S., Europe, Canada and Australia (11). After a 2-week single-blind placebo run-in, 369 patients with major depressive disorder were randomized to receive either placebo or sertraline in flexible doses of 50 to 200 mg per day for 24 weeks. This trial documented no evidence of harm with sertraline therapy in either post-acute MI or unstable angina (11) (Table 11). There was no statistically significant difference between treatment groups in left ventricular ejection fraction, heart rate, blood pressure, PR or QTc interval, QRS duration, or standard deviation of all normal R-R intervals in 24-hr ECG recording (a measure of autonomic balance); nor was there a difference in the number of runs of ventricular tachycardia (11). In addition, a trend toward a reduction in morbidity and mortality was observed among sertraline-treated patients (11). Decreased MI risk with SSRIs was also reported is a case-control study (111). As far as efficacy, the Clinical Global Impression Improvement scale (CGI-I) responder rates were significantly higher for sertraline than for placebo in the total sample (67% vs. 53%; P =.01), in the group with at least 1 prior episode of depression (72% vs. 51%; P =.003), and in the more severe major depression group (78% vs. 45%; P =.001) (11).

	No. of Patients		
End Point	Sertraline	Placebo	RR (95% CI)
Death	2	5	0.39 (0.08-1.39)
Myocardial infarction	5	7	0.70 (0.23-2.16)
Congestive heart failure	5	7	0.70 (0.23-2.16)
Stroke	2	2	0.98 (0.14-6.93)
Angina	26	30	0.85 (0.53-1.36)
Composite end point	32	41	0.77 (0.51-1.16)

Table 11 Relative risk of death and urgent cardiovascular rehospitalizations
SADHART Study Glassman AH, JAMA 2002

Safety of anti-depressant medications

Given the safety of SSRIs reported in SADHART (Table 11) and reports of increased adverse events with the use of tricyclic medications in patients with coronary heart disease, it is advisable that the first choice of therapy would be an SSRI (11, 81, 111-113). Tricyclic antidepressants are associated with cardiovascular side effects including orthostatic hypotension, slowed cardiac conduction, antiarrhythmic activity, and increased heart rate (112). In addition, the relative risk of myocardial infarction was higher in users of tricyclic agents, than in users of SSRIs, when compared with subjects who did not use antidepressants (RR 2.2, 95% CI 1.2-3.8 in users of tricyclic agents vs. 0.8, 95% CI 0.2-3.5 in users of SSRIs) (81). The safety of dual-acting serotonin and noradrenaline reuptake inhibitors in this population of patients is not established (112).

When considering SSRI initiation, it should be noted that although SADHART was a large multi-center randomized trial, it is questionable whether the sample size was too small to identify rare adverse events with use of SSRIs (11). In addition, treatment with sertraline was not initiated until an average of 34 days after acute MI, so safety of use in the immediate post-infarction period less clear (11). Finally, as in all randomized clinical trials, tight exclusion criteria limit generizability of these results to the general population of patients with coronary disease and major depression. For example, patients with significant renal dysfunction and Killip class III or IV CHF were excluded, which are, interestingly, the same groups of patients at higher risk for development of depression. Response to treatment and need for dose escalation, as well as development of side effects and need for dose lowering, should be monitored once medication is initiated.

Anti-depressant medication use in ESRD

There is even less evidence regarding the safety and efficacy of anti-depressant medications in patients with ESRD receiving renal replacement therapy, especially since these patients, as well as patients with advanced kidney disease not yet on dialysis, are generally excluded from anti-depressant treatment trials.

Generally, anti-depressants are highly protein-bound, hepatically metabolized, and not removed significantly by the dialysis procedure (103). Use of fluoxetine in depressed patients on hemodialysis was first reported in 1997 (114). Fourteen patients with major depression were randomized to fluoxetine or placebo for an eight-week period. Subjects as well as investigators were blinded as to treatment. No patients discontinued study medication because of adverse events, all of which were minor. All psychological tests showed improvement in depression at four and eight weeks, although statistical significance could only be demonstrated at four weeks (114). Further, all patients in the intervention arm had serum plasma concentrations of fluoxetine and norfluoxetine less than 250 ng/ml at eight weeks, similar to reported levels in patients with normal renal function (114). Although this study suggests safety and efficacy of fluoxetine use in hemodialysis patients, the sample was very small to perhaps identify rare adverse events and the follow-up was not very long. It also must be considered that should an adverse event occur that requires the discontinuation of medication, the half-life of fluoxetine is long, 24 to 72 hours, and that the half-life of its active metabolite is even longer, seven to nine days.

Unfortunately, while nonrandomized observational studies of anti-depressant therapy in chronic peritoneal dialysis patients reported some improvement in BDI scores with therapy (17.4 +/- 6.6 at the start and 8.4 +/- 3.0 at completion of treatment) (106), not all patients will agree to be evaluated for clinical depression and accept pharmacologic treatment (106, 115). Only three-fourths of depressed patients agreed to therapy and of those, only one-half successfully completed 12 weeks of anti-depressant treatment (106, 115).

Psychosocial therapy

Higher baseline social support was related to improvement in depression symptoms in a prospective cohort of post-MI patients with depression (6). Further, the relationship between depression and cardiac mortality decreased with increased support (6). Although nonrandomized studies reported a decrease in cardiovascular events with psychosocial therapy, randomized trials failed to show a difference in outcomes. In a cohort of 461 men followed over 5 years after MI, taking part in a one-year psychological stress monitoring and intervention (vs. routine medical care) was associated with less risk of re-infarction and cardiac mortality (116). A nonrandomized trial of rehabilitation in patients with coronary heart disease revealed that rehabilitation was associated with a lower rate of death (p=0.009) (117). In the ENRICHD (Enhancing Recovery in Coronary Heart Disease Patients) study, 2,481 patients were enrolled within 28 days after acute MI and randomly allocated to usual medical care or cognitive behavior therapy (CBT), supplemented with an SSRI when indicated (118). Although there was less depression among the CBT arm after 6 months, there was no difference in event-free survival (118).

There is less data regarding psychosocial therapy among depressed patients on dialysis. One hundred and twenty-six ESRD patients were separated into those that participated in a patient support group and those that had not (119). Patients that engaged in group activities survived longer than non-participants (119). This study probably suffers heavily from selection bias, since participants were more likely to be motivated in their own healthcare and more adherent to other medical therapy.

VII. Summary

Major depressive disorder, as well as increased depressive symptoms, is very prevalent in patients with coronary heart disease, those with CHF and those with ESRD treated with dialysis. There is a strong association between depressive affect and cardiovascular morbidity and mortality reported in observational studies. Effects of depression on these outcomes, in fact, were of the same order of magnitude as medical comorbidities. Randomized controlled trials, however, did not reveal a definite decrease in cardiovascular events with anti-depressant medication to confirm causality. Therefore, it can be postulated that the association of depression with cardiovascular mortality is confounded by the strong correlation observed between depression and burden of co-morbid illness. However, many studies suggest potential biological mechanisms by which depression can lead to increased cardiovascular events, the most impressive of which have related to serotonin and platelet activation. Although safety and efficacy of anti-depressant medication was established in patients after acute coronary syndrome in the SADHART study, the rate of depression treatment is low in both coronary heart disease and ESRD patients. More studies are needed to establish safety and efficacy of such therapies in patient on dialysis. Even if treatment of depression does not alter mortality, it may improve quality of life among these patients.

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