Depression Predicts All-Cause Mortality

Epidemiological evaluation from the ACCORD HRQL substudy

MARK D. SULLIVAN, MD, PHD1
PATRICK O’CONNOR, MD, MPH2
PATRICIA FEENEY, MS, MA3
DON HIRE, MS3
DEBRA L. SIMMONS, MD4,5
DEANNA M. MACDONALD, MPH5
CLAYTON B. HALL, MS3
GAELLE M. TROCMÉN, MPH5
AMANDA L. PURCELL, MPH5
DONALD W. WISE, MD6
DONALD R. EMERSON, MD6
LAWRENCE J. FINE, MD, DRPH6,7
K.M. VENKAT NARAYAN, MD9
MOHAMMAD K. ALI, MB, CHB9
WAYNE J. KATON, MD1

OBJECTIVE—Depression affects up to 20–25% of adults with type 2 diabetes and may increase all-cause mortality, but few well-designed studies have examined the effects of depression on the full range of cardiovascular disease outcomes in type 2 diabetes.

RESEARCH DESIGN AND METHODS—A total of 2,053 participants in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Health-Related Quality of Life substudy completed the Patient Health Questionnaire (PHQ)-9 measure of depression symptoms at baseline and 12, 36, and 48 months. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) (95% CI) for the time-varying impact of depression on protocol-defined clinical outcomes with and without adjustment for demographic, trial-related, clinical, and behavioral variables.

RESULTS—In fully adjusted models, depression was not significantly related to the ACCORD primary composite outcome (cardiovascular death, nonfatal heart attack, or stroke) (HR 1.53 [95% CI 0.85–2.73]) or to the ACCORD microvascular composite outcome (0.93 [0.53–1.62]), but all-cause mortality was significantly increased both in those with PHQ-assessed probable major depression (2.24 [1.24–4.06]) and PHQ score of ≥10 (1.84 [1.17–2.89]). The effect of depression on all-cause mortality was not related to previous cardiovascular events or to assignment to intensive or standard glycemia control. Probable major depression (by PHQ-9) had a borderline impact on the ACCORD macrovascular end point (1.42 [0.99–2.04]).

CONCLUSIONS—Depression increases the risk of all-cause mortality and may increase the risk of macrovascular events among adults with type 2 diabetes at high risk for cardiovascular events.

Diabetes Care 35:1708–1715, 2012

Patients with diabetes are approximately twice as likely to meet DSM-IV criteria for major depression than the general medical population, with depressive symptoms affecting up to 20–25% of these patients (1,2). Patients with diabetes and depression have younger age of diabetes onset; poor adherence to diet, exercise, and disease control medications; poorer glycemic control; and an increased risk of macrovascular and microvascular complications (3–5). Six prospective epidemiologic studies have shown that after controlling for sociodemographic factors and clinical severity of illness, comorbid depression in patients with diabetes compared with diabetest alone was associated with a 33–52% increased risk of all-cause mortality (6–11). One recent study of >4,000 patients with diabetes found that probable major depression assessed by Patient Health Questionnaire (PHQ)-9 was associated with a more than twofold risk of non–cancer and non–atherosclerotic associated mortality (6). However, few studies have examined specific effects of depression on macrovascular and microvascular complications. Studies have also not examined the moderating role of preexisting cardiovascular disease (CVD) or intensity of glucose control (9,12).

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial offers a unique opportunity to examine the relationship between depression, mortality, and cardiovascular events in a sample receiving standardized diabetes care. The ACCORD trial also includes rigorous criteria for defining macrovascular and microvascular complications and cause of death. It also allowed us to examine how the effect of depression on mortality and CVD differs between those with and without previous CVD and examine whether any effect of depression on mortality or CVD is modified by randomization to intensive versus standard glucose control. Specific hypotheses from the ACCORD Health-Related Quality of Life (HRQL) substudy examined in this epidemiological analysis are as follows (13). After controlling for baseline factors, depression will be associated with the following: 1) primary composite outcome (death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke); 2) all-cause mortality; 3) composite macrovascular outcome (primary outcome plus any revascularization plus hospitalization for congestive heart failure [CHF]); and 4) composite microvascular outcome (fatal or nonfatal renal failure or retinal photoacoagulation or vitrectomy for diabetic retinopathy). We further hypothesize that these associations will not be affected by preexisting CVD or by randomization to intensive versus standard glucose control. We have previously reported that randomization to intensive glycemic control did not lead to benefits in HRQL in ACCORD but was associated with modest improvement in diabetes treatment satisfaction (14).

RESEARCH DESIGN AND METHODS—The rationale, study design, and entry criteria for the ACCORD...
trial have been described elsewhere and the randomized trial results published (8–10). In brief, this was a multicenter randomized controlled treatment trial testing independent effects of two strategies of control of blood glucose, blood pressure, and lipids on CVD in patients with type 2 diabetes. The glycemia trial randomized 10,251 participants with type 2 diabetes to intensive (goal HbA1c <6%) or standard (goal HbA1c 7.0–7.9%) glucose control. All participants were also randomized within either the blood pressure or the lipid trial arms, resulting in assignment to one of eight treatment cells as follows: 1) intensive glucose/intensive blood pressure, 2) intensive glucose/standard blood pressure, 3) standard glucose/intensive blood pressure, 4) standard glucose/standard blood pressure, 5) intensive glucose/fibrate, 6) intensive glucose/placebo, 7) standard glucose/fibrate, and 8) standard glucose/placebo.

The primary outcome of the ACCORD trial is a composite of death from CVD, nonfatal myocardial infarction, or nonfatal stroke. Secondary outcomes include the following: 1) all-cause mortality, 2) composite macrovascular outcome (major coronary artery disease events, specifically fatal events, nonfatal myocardial infarction, and unstable angina), and 3) composite microvascular outcome (fatal or nonfatal renal failure, retinal photocoagulation, or vitrectomy for diabetic retinopathy). These outcomes are not exclusive of each other.

The goal of the ACCORD HRQL investigation is to assess the overall effect of the ACCORD interventions from the patient's point of view in 2,053 participants randomly sampled from the eight ACCORD treatment groups. Measurements were taken at baseline and at 12, 36, and 48 months. Mean follow-up time was 4.67 ± 1.45 years.

Because of the documented relationship between depression and cardiovascular events and glycemic control (3–7), depressive symptoms were measured in the ACCORD study using the nine-item Patient Health Questionnaire (PHQ-9). The PHQ-9 is the self-report version of the Primary Care Evaluation of Mental Disorders (PRIME-MD), a well-validated psychiatric diagnostic interview for use in primary care settings (9). The PHQ-9 depression measure provides diagnostic and severity information and is used serially to assess responsiveness to depression treatment. Since the PHQ-9 items mirror those of the major depression and minor depression diagnostic criteria in the DSM-IV (15), it is also possible to derive provisional diagnostic categories from PHQ-9 responses. Major depression requires five symptoms scored ≥2, at least one of which is depressed mood or lack of pleasure. A score of 10 on the PHQ-9 has been shown to have 77% sensitivity and 94% specificity to the diagnosis of major depression by structured psychiatric interview (16). In patients with type 2 diabetes, a PHQ-9 score of ≥10 has been associated with higher risk of mortality and dementia, as well as macrovascular and microvascular complications (17). A recent review of the reliability and validity of depression screening tools in patients with diabetes gave the PHQ-9 generally high rates of sensitivity (66–100%) but lower rates of specificity (52–85%) (18). Minor depression is listed as a provisional diagnosis for further study in DSM-IV and requires three to four symptoms scored ≥2, at least one of which is depressed mood or lack of pleasure.

Statistical methods

For each of the four depression measures (PHQ-9 ≥10, probable major depression, probable minor depression, and continuous PHQ-9 score), we ran a series of separate proportional hazards regressions models where the outcome is the time until first occurrence of each event and the predictor of interest is the measure of depression. In each model, depression was a dichotomous, time-varying indicator measured at baseline, year 1, year 3, and year 4. We report rates at which patients met any depression criteria at any time point (“ever depressed”) versus not meeting any depression criteria at any time point (“never depressed”). The first series of models contained the depression measure as well as variables indicating the randomization assignments for the main glycemia trial, with stratification for the blood pressure and lipid trial arms, and primary versus secondary prevention status. As specified in the ACCORD protocol, these models also included adjustments for the following baseline factors: demographics (age, sex, race/ethnicity, BMI, weight, waist circumference, and duration of diabetes), blood pressure (systolic and diastolic), laboratory values (triglycerides, LDL and HDL cholesterol, serum creatinine, Hba1c, and fasting glucose), presence of microvascular complications, and blood pressure and lipid medications. A second series of models contained all of the above adjustments, plus factors known to be related to both depression and mortality in patients with diabetes: education, smoking, alcohol, and living alone. We also divided PHQ-9–assessed depression symptoms into somatic and psychological subsets and assessed whether each was related to all-cause mortality. All models used Cox proportional hazards regression model analyses to obtain hazard ratios (HRs) (95% CI) of the measure of depression. These analyses combined participants from the randomized groups and are thus epidemiologic in nature. There were no adjustments made for postrandomization events or measures. Participants with missing data were omitted from the models, resulting in ~4% loss in the most complex models. Since we conducted 12 statistical tests of hypotheses related to secondary end points and subgroups, there was a 46% chance (i.e., 1 – [1 – 0.05]^12) that at least one of these tests would be statistically significant at an α level of 0.05, assuming independence between tests.

RESULTS—Table 1 compares the demographic and clinical characteristics of ACCORD HRQL substudy participants compared with the full ACCORD sample. As expected, because of randomization, there are no significant differences between the groups.

Table 2 displays the rates at which ACCORD HRQL participants screened positive for depression (PHQ score ≥10) or met criteria for probable major depression or minor depression based on responses to the PHQ. Nearly 20% of participants screened positive for clinically significant depressive symptoms (PHQ-9 ≥10) at baseline, with 8% meeting DSM-IV probable major depression criteria and another 7% meeting DSM-IV probable minor depression criteria. Approximately 31% of participants screened positive for depression at one of the four assessments, with 15% meeting major depression and 18% meeting minor depression criteria at least at one assessment.

Table 3 displays the baseline characteristics of the subjects based on whether they ever met any of the depression criteria. As would be expected from the epidemiology of depression, ever depressed patients were more likely to be younger, female, less educated, cigarette smokers, obese, and have higher Hba1c, higher pulse, lower HDL cholesterol, and higher total cholesterol and triglycerides. They were also more likely to be treated with insulin or sulfonylureas.
Depression predicts all-cause mortality

Table 1—Demographic and clinical characteristics of ACCORD HRQL substudy participants compared with full ACCORD sample

| Baseline characteristics | HRQL substudy | | P |
|--------------------------|---------------|---|---|
| | Yes | No | |
| N | 2,053 | 7,583 | |
| **Demographic** | | | |
| Age (years) | 62.2 ± 6.7 | 62.1 ± 6.8 | 0.5454 |
| Female | 39.6 | 38.4 | 0.3171 |
| Non-Hispanic white | 65.1 | 64.5 | 0.6520 |
| Black | 19.5 | 19.1 | 0.6818 |
| Hispanic | 6.8 | 7.3 | 0.3829 |
| **Education** | | | 0.5130 |
| Highest level of education | | | |
| Less than high school | 13.9 | 14.8 | — |
| High school graduate (or GED) | 26 | 26.7 | — |
| Some college | 33.2 | 33 | — |
| College graduate or more | 26.9 | 25.5 | — |
| **Lifestyle** | | | |
| Living with someone | 80 | 79.7 | 0.7713 |
| Drinking | 22.5 | 24.1 | 0.1358 |
| Cigarette smoker | 13.3 | 14.5 | — |
| Former | 45.6 | 43.7 | — |
| Never | 41.2 | 41.9 | — |
| **Comorbidities** | | | |
| Weight (kg) | 94.1 ± 18.9 | 93.6 ± 18.6 | 0.2735 |
| BMI (kg/m²) | 32.4 ± 5.5 | 32.3 ± 5.5 | 0.2133 |
| Waist circumference (cm) | 107.1 ± 13.9 | 106.8 ± 13.9 | 0.4899 |
| Peripheral neuropathy | 43 | 42.6 | 0.7782 |
| Macrolidemia | 7.3 | 6.3 | 0.1266 |
| Microalbuminuria | 30.1 | 31.4 | 0.2395 |
| Laser photo or vitrectomy | 8.6 | 8.7 | 0.9436 |
| **Diabetes profile** | | | 0.0536 |
| Duration of diabetes (years), median | 10 | 9 | |
| HbA1c (%) | 8.3 ± 1.1 | 8.3 ± 1 | 0.5014 |
| HbA1c (%), median | 8.1 | 8.1 | 0.5712 |
| Fasting plasma glucose (g/dL) | 177.1 ± 57.5 | 174.9 ± 56 | 0.1266 |
| **Other biomarkers** | | | |
| SBP (mmHg) | 136.2 ± 17.1 | 136.2 ± 17.2 | 0.8309 |
| DBP (mmHg) | 74.5 ± 10.9 | 75 ± 10.6 | 0.0837 |
| LDL (mg/dL) | 104.3 ± 34 | 104.3 ± 33.9 | 0.9987 |
| HDL among females (mg/dL) | 47.3 ± 12.6 | 46.9 ± 12.6 | 0.4812 |
| HDL among males (mg/dL) | 38.7 ± 9.7 | 38.7 ± 9.7 | 0.8937 |
| Total cholesterol (mg/dL) | 182.8 ± 41.3 | 182.8 ± 42.1 | 0.9858 |
| Triglycerides (mg/dL), median | 156 | 155 | 0.6812 |
| Potassium (mg/dL) | 4.5 ± 0.4 | 4.5 ± 0.6 | 0.4836 |
| Serum creatinine (mg/dL) | 0.9 ± 0.2 | 0.9 ± 0.2 | 0.2837 |

Medications

- On insulin | 35.9 | 34.8 | 0.3233 |
- On any HTN medications | 85.5 | 85.8 | 0.6968 |
- On any ACE inhibitors | 52 | 52.9 | 0.4560 |
- On β-blockers | 30.3 | 29.8 | 0.6396 |
- On statins | 63.5 | 63.1 | 0.7048 |
- Secondary status | 36.1 | 35.2 | 0.4647 |

Data are means ± SD or percent unless otherwise indicated. DBP, diastolic blood pressure; GED, General Educational Development; HTN, hypertension; SBP, systolic blood pressure.

The primary composite outcome was reached by 2.1% per year (6,000 person-years observed) in the never-depressed group and 1.9% per year (3,239 person-years observed) in the ever-depressed group. All-cause mortality was 1.4% per year in both the never-depressed (6,313 person-years observed) and ever-depressed (3,438 person-years observed) groups. The macrovascular composite outcome was reached by 5.2% per year (5,552 person-years observed) in the never-depressed group and 5.9% per year (2,908 person-years observed) in the ever-depressed group. The macrovascular composite outcome was achieved by 2.6% per year (5,573 person-years observed) in the never-depressed group and 3.2% per year (2,999 person-years observed) in the ever-depressed group. Outcome rates are similar between the ever-versus never-depressed groups, but these results do not account for other clinical differences between these groups.

Table 4 displays the HRs for different measures of PHQ-assessed depression as a time-dependent covariate for time to the ACCORD primary and secondary endpoints. The first set of models was adjusted for the demographic, trial, and clinical variables described as follows. 1) Probable major depression did not significantly increase the risk for the primary composite outcome of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke. The point estimate for major depression is HR 1.53, but the effect is not statistically significant. Neither PHQ score ≥10 nor the PHQ continuous score was significant. 2) Both PHQ score of ≥10 (HR 1.84 [95% CI 1.17–2.89]) and PHQ-assessed probable major depression (2.24 [1.24–4.06]) increased risk for the secondary outcome of all-cause mortality after controlling for age, sex, race/ethnicity, primary/secondary CVD prevention, HbA1c, lipids, blood pressure, BMI, smoking, alcohol consumption, living alone, blood pressure, presence of microvascular complications, CHF, education, duration of diabetes, antidepressant medications, glucose, blood pressure and lipid medications, and assignment to one of eight study intervention arms. The continuous PHQ-9 score was also a significant predictor of all-cause mortality (1.05 [1.01–1.09]). For each point increase on the PHQ-9, all-cause mortality increased by 5%. The increase in absolute risk for all-cause mortality associated with probable major depression at any time point is estimated to be 0.92%.
Probable major depression was associated with borderline significant increased risk for the secondary outcome of macrovascular events, including fatal myocardial infarction, nonfatal myocardial infarction, and unstable angina (1.42 [95% CI 0.99–2.04], P = 0.0552). PHQ score ≥10 was not significantly associated, but the continuous PHQ-9 score was significantly associated with increased risk of macrovascular events (1.02 [1.00–1.04]). 4) Probable major depression (0.93 [0.53–1.62]), PHQ score ≥10 (1.27 [0.90–1.80]), and continuous PHQ score were not associated with increased risk for the secondary outcome of microvascular events.

The models in the second set of Table 4 were adjusted for demographic, trial, clinical, and behavioral variables. The additional adjustment for these potentially confounding or mediating variables slightly attenuated the risk associated with depression. Effects of depression on all-cause mortality remained significant, though the marginal effects of depression on the macrovascular outcome became nonsignificant.

In order to verify that the effects of probable major depression on mortality and the primary outcome were similar in both glycemia arms, we fit a model for each outcome controlling for the randomization factors and including an interaction term between glycemia arm and major depression. We fit the same set of models to see if the effects were the same for participants with prior CVD at baseline. None of the interaction terms of interest in the four models were significant, indicating that effect of probable major depression was consistent across the groups. While some studies of patients post–myocardial infarction have found that only the somatic symptoms of depression (e.g., fatigue, insomnia) are associated with subsequent mortality, we found that both psychological and somatic symptoms of depression as assessed by the PHQ-9 were significantly (and nearly equally) associated with all-cause mortality (19).

**CONCLUSIONS**—This epidemiologic analysis of data from the ACCORD trial revealed that depression, defined as PHQ-assessed probable major depression, PHQ score of ≥10, or continuous PHQ-9 score, was associated with increased risk of all-cause mortality regardless of whether previous CVD was present and regardless of randomization to intensive versus standard glycemia control. Depression marginally increased the risk of the combined macrovascular outcome. Depression was not significantly associated with the primary composite ACCORD outcome or the secondary composite microvascular outcome. In ACCORD, probable major depression was associated with an approximate two-fold risk of all-cause mortality. This is somewhat higher than in previous studies and might be due to the increased capability in ACCORD to control for other clinical variables or due to the fact that study subjects were selected for high risk for cardiovascular events. It is notable that this risk was observed in the context of good glucose control in all groups, since poor adherence and poor glucose control have been proposed to account for the effect of depression on mortality in patients with diabetes (11).

The point prevalence of major depression in primary care patients is between 5 and 10% (20), whereas prevalence rates of major depression in patients with diabetes and coronary heart disease (CHD) have been estimated to be 12–18% (21) and 15–23% (22,23), respectively. The relationship between major depression and diabetes and/or heart disease appears to be bidirectional. A recent meta-analysis of 13 studies found that the pooled relative risk for depressed patients subsequently developing diabetes was 1.60 (95% CI 1.37–1.88) (24). This meta-analysis also found modest evidence that diabetes was a risk factor for subsequent major depression (relative risk 1.15 [1.02–1.30]) (24). Major depression following myocardial infarction is also very common, occurring in up to 25% of patients (22,23). Recent data suggest that approximately one-half of patients who developed major depression post–myocardial infarction had recurrent depressive episodes and that half had their first depressive episode post–myocardial infarction (23).

In the general population, both diabetes and depression increase mortality. They exert a greater than additive effect when both are present. A large prospective study of an aging Hispanic population found that lifetime major depression was associated with a 1.64 (95% CI 1.17–2.28) and diabetes a 1.51 (1.23–1.86) HR for all-cause mortality, respectively, compared with those without history of depression or diabetes (9). When combined, depression and diabetes had an HR of 4.59 (2.12–9.93) of all-cause mortality compared with control subjects without history of diabetes or depression (9). Another study that followed >10,000 participants for 8 years found that subjects with significant depressive symptoms (Center for Epidemiologic Studies Depression Scale ≥16) but no diabetes had a 1.20 (1.03–1.40) increase in all-cause mortality, those with diabetes but no depression had a 1.88 (1.55–2.27) increase, and those with both depression and diabetes had a 2.50 (2.04–3.08) increase in all-cause mortality compared with subjects without depression or diabetes (10).

Recent prospective studies have also examined the association of depression with subsequent development of macrovascular and microvascular complications in patients with diabetes. A 5-year prospective study of >4,000 diabetic patients found that comorbid probable major depression on PHQ-9 was associated with a 24% increased risk of macrovascular complications and a 36% increased risk of microvascular complications (11). ACCORD showed a 42% increase in risk of macrovascular complications, but this was of borderline significance, possibly due to the smaller sample. In ACCORD, there was not a significant effect of depression on microvascular complications. It is possible that some previous studies may have overestimated
### Table 3—Baseline characteristics by depression status

| Baseline characteristics                  | Overall | Ever depressed by any definition | Never depressed by all definitions | P         |
|-------------------------------------------|---------|----------------------------------|------------------------------------|-----------|
| **N**                                     | 2,038   | 712                              | 1,326                              |           |
| **Demographic**                           |         |                                  |                                    |           |
| Age (years)                               | 62.2 ± 6.7 | 61.2 ± 6.8                      | 62.8 ± 6.5                        | <0.0001   |
| Female                                    | 39.5    | 46.2                             | 35.8                               | <0.0001   |
| Non-Hispanic white                        | 65.2    | 64.9                             | 65.3                               | 0.8490    |
| Black                                     | 19.4    | 18.8                             | 19.8                               | 0.6097    |
| % Hispanic                                | 6.7     | 7.7                              | 6.2                                | 0.1854    |
| **Education**                             |         |                                  |                                    |           |
| Highest level of education                |         |                                  |                                    | 0.0031    |
| Less than high school                     | 13.9    | 17.1                             | 12.2                               |           |
| High school graduate (or GED)             | 26.1    | 26.3                             | 26                                 |           |
| Some college                              | 33.2    | 33.4                             | 33                                 |           |
| College graduate or more                  | 26.9    | 23.2                             | 28.9                               |           |
| **Lifestyle**                             |         |                                  |                                    |           |
| Cigarette smoker                          |         |                                  |                                    | 0.0011    |
| Never                                     | 41.1    | 39.3                             | 42                                 |           |
| Former                                    | 45.7    | 43.7                             | 46.8                               |           |
| Current                                   | 13.2    | 17.2                             | 11.2                               |           |
| Living with someone                       | 80.1    | 79.2                             | 80.5                               | 0.4737    |
| Drinking at least 1 alcoholic drink per week | 22.6 | 18.4                             | 24.8                               | 0.0010    |
| **Comorbidities**                         |         |                                  |                                    |           |
| CHD present                               | 36      | 38.2                             | 34.8                               | 0.1319    |
| Heart failure                             | 5.2     | 6.7                              | 4.3                                | 0.0236    |
| Amputation resulting from diabetes        | 2.1     | 2.5                              | 1.7                                | 0.2238    |
| Weight (kg)                               | 94.1 ± 18.9 | 97.1 ± 20.2                      | 92.5 ± 18.1                       | <0.0001   |
| BMI (kg/m²)                               | 32.4 ± 5.5 | 33.7 ± 5.8                       | 31.7 ± 5.2                        | <0.0001   |
| Waist circumference (cm)                  | 107.1 ± 13.9 | 109.6 ± 14.4                     | 105.7 ± 13.4                      | <0.0001   |
| Peripheral neuropathy                     | 42.9    | 43.9                             | 42.4                               | 0.5067    |
| Macroalbuminuria                          | 7.2     | 8.1                              | 6.7                                | 0.2693    |
| Microalbuminuria                          | 30.1    | 30.2                             | 30                                 | 0.9502    |
| Laser photo or vitrectomy                 | 8.7     | 8.1                              | 9                                  | 0.4678    |
| **Diabetes profile**                      |         |                                  |                                    |           |
| Duration of diabetes (years), median      | 10      | 10                               | 10                                 | 0.9449    |
| HbA1c (%)                                 | 8.3 ± 1.1 | 8.4 ± 1.1                        | 8.2 ± 1                           | <0.0001   |
| HbA1c (%), median                         | 8.1     | 8.2                              | 8                                  | <0.0001   |
| Fasting plasma glucose (mg/dL)            | 177 ± 57.5 | 182 ± 61.7                       | 174 ± 55                          | 0.0063    |
| Other biomarkers                          |         |                                  |                                    |           |
| SBP (mmHg)                                | 136.3 ± 17 | 136.3 ± 16.7                     | 136.3 ± 17.2                      | 0.9734    |
| DBP (mmHg)                                | 74.5 ± 10.9 | 75.2 ± 11.2                      | 74.1 ± 10.6                       | 0.0389    |
| Pulse                                     | 72.4 ± 11.8 | 73.6 ± 12                       | 71.8 ± 11.7                       | 0.0010    |
| LDL (mg/dL)                               | 104.3 ± 33.9 | 106.1 ± 35.1                     | 103.3 ± 33.2                      | 0.0842    |
| HDL among females (mg/dL)                 | 47.3 ± 12.6 | 46.1 ± 11.7                      | 48.2 ± 13.1                       | 0.0115    |
| HDL among males (mg/dL)                   | 38.8 ± 9.7  | 37.8 ± 9.8                       | 39.2 ± 9.6                        | 0.0269    |
| Total cholesterol (mg/dL)                 | 182.8 ± 41.2 | 187.4 ± 43                       | 180.3 ± 39.9                      | 0.0003    |
| Triglycerides (mg/dL)                     | 4.8 ± 1.1  | 4.9 ± 1.1                        | 4.7 ± 1                           | <0.0001   |
| Potassium (mg/dL)                         | 156      | 172                              | 147                               | 0.7106    |
| Serum creatinine (mg/dL)                  | 0.9 ± 0.2 | 0.9 ± 0.2                        | 0.9 ± 0.2                         | 0.0025    |
| Estimated GFR                             | 79.8 ± 21 | 77.9 ± 20.1                      | 80.8 ± 21.4                       | 0.5938    |

Continued on p. 1713
the impact of depression on microvascular complications by not establishing whether the depression antedated the microvascular complication or whether the microvascular complication may have contributed to the subsequent onset of depression. One strength of our study is its clear ascertainment of both microvascular complication status and depression status at fixed time intervals during the study period.

Our study adds to the above studies in a number of ways. First, we were able to control for a wide range of baseline clinical characteristics related to cardiovascular risk including age, sex, race/ethnicity, CHD status, HbA1c, lipids, systolic and diastolic blood pressure, BMI, presence of microvascular complications, CHF status, and duration of diabetes. We were also able to control for a number of social and behavioral factors that might confound the depression effect, including smoking, alcohol consumption, living alone, and education. Second, all subjects had reasonably well-controlled glucose, blood pressure, and lipids. Third,

Table 3—Continued

| Baseline characteristics | Overall | Ever depressed by any definition | Never depressed by all definitions | P     |
|-------------------------|---------|---------------------------------|-----------------------------------|-------|
| Medications             |         |                                 |                                   |       |
| Insulin                 | 35.9    | 41.2                            | 33                                | 0.0003|
| Sulfonylureas           | 49.7    | 44.1                            | 52.6                              | 0.0002|
| Metformin               | 59.4    | 59.4                            | 59.4                              | 0.9795|
| TZD                     | 20.3    | 22.3                            | 19.2                              | 0.0972|
| Any antihypertensive medicine | 85.6 | 85.4                            | 85.7                              | 0.8648|
| ACE inhibitors          | 52      | 52.8                            | 51.6                              | 0.976 |
| β-Blockers              | 30.4    | 30.6                            | 30.3                              | 0.8879|
| ARBs                    | 16.6    | 15.2                            | 17.4                              | 0.930 |
| Thiazide diuretic       | 26.6    | 25.4                            | 27.3                              | 0.3604|
| Calcium channel blocker | 18.4    | 17.1                            | 19.2                              | 0.2622|
| α-Blockers              | 2.7     | 2.5                             | 2.8                               | 0.7276|
| Statins                 | 63.5    | 60.5                            | 65.2                              | 0.0386|
| Other lipid-lowering medicine | 10  | 11                              | 9.5                               | 0.2975|
| Aspirin                 | 55.7    | 53.1                            | 57.2                              | 0.0775|

Data are means ± SD or percent unless otherwise indicated. ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; GED, General Educational Development; GFR, glomerular filtration rate; SBP, systolic blood pressure; TZD, thiazolidinedione.

Table 4—Proportional hazard models of depression predicting ACCORD outcomes

| Predictor                                                                 | Model adjusted for demographic, trial, and clinical variables | Model adjusted for demographic, trial, clinical, and behavioral variables |
|--------------------------------------------------------------------------|---------------------------------------------------------------|-------------------------------------------------------------------------|
| Primary composite outcome (cardiovascular mortality, nonfatal MI, or nonfatal stroke) |                                                               |                                                                        |
| Major depression                                                         | 1.53 (0.85–2.73)                                              | 1.47 (0.82–2.64)                                                         | 0.1913 |
| Minor depression                                                         | 1.03 (0.56–1.92)                                              | 0.99 (0.53–1.83)                                                         | 0.9833 |
| PHQ continuous                                                           | 1.01 (0.98–1.05)                                              | 1.01 (0.97–1.04)                                                         | 0.6286 |
| PHQ score ≥10                                                            | 1.13 (0.73–1.75)                                              | 1.07 (0.69–1.66)                                                         | 0.7722 |
| All-cause mortality                                                      |                                                               |                                                                        |
| Major depression                                                         | 2.24 (1.24–4.06)                                              | 2.14 (1.18–3.89)                                                         | 0.0123 |
| Minor depression                                                         | 1.14 (0.59–2.21)                                              | 1.08 (0.56–2.10)                                                         | 0.8143 |
| PHQ continuous                                                           | 1.05 (1.01–1.09)                                              | 1.04 (1.01–1.08)                                                         | 0.0229 |
| PHQ score ≥10                                                            | 1.84 (1.17–2.89)                                              | 1.76 (1.12–2.78)                                                         | 0.0144 |
| Macrovascular composite outcome (major coronary artery disease events, specifically fatal events, nonfatal MI, and unstable angina) |                                                               |                                                                        |
| Major depression                                                         | 1.42 (0.99–2.04)                                              | 1.36 (0.95–1.95)                                                         | 0.0960 |
| Minor depression                                                         | 1.23 (0.85–1.78)                                              | 1.23 (0.85–1.78)                                                         | 0.2762 |
| PHQ continuous                                                           | 1.02 (1.00–1.04)                                              | 1.02 (1.00–1.04)                                                         | 0.0635 |
| PHQ score ≥10                                                            | 1.14 (0.88–1.49)                                              | 1.10 (0.84–1.44)                                                         | 0.4882 |
| Microvascular composite outcome (fatal or nonfatal renal failure, retinal photocoagulation, or vitrectomy for diabetic retinopathy) |                                                               |                                                                        |
| Major depression                                                         | 0.93 (0.53–1.62)                                              | 0.97 (0.56–1.70)                                                         | 0.9229 |
| Minor depression                                                         | 1.14 (0.70–1.85)                                              | 1.14 (0.70–1.86)                                                         | 0.5972 |
| PHQ continuous                                                           | 1.01 (0.98–1.04)                                              | 1.01 (0.99–1.04)                                                         | 0.3168 |
| PHQ score ≥10                                                            | 1.27 (0.90–1.79)                                              | 1.31 (0.93–1.86)                                                         | 0.1273 |

MI, myocardial infarction.
we were able to examine whether the depression effect on cardiovascular events and mortality differed by intensive versus standard use of glucose, blood pressure and lipid medications, clinical center network, and assignment to one of eight study intervention arms. None of these factors interacted significantly with depression status.

Several factors must be considered in interpreting the results of our study. First, study participants may have had less baseline depression and different subsequent depression trajectories based on the requirement to volunteer for the study and to provide informed consent at enrollment. Second, this analysis used a screening instrument (PHQ-9) to detect depression characterized by high sensitivity but low specificity. Up to one-half of patients with diabetes who score ≥10 on the PHQ-9 may not have major depression on structured interview. Patients with only minor depression tend to do as well with placebo as they do with antidepressant treatment. Third, this study does not consider depression treatment in detail, although the use of PHQ-9 scores obtained at four set time points may reflect the adequacy of depression treatment. Fourth, the composite microvascular end point we evaluated was comprised of advanced complications and we did not assess the impact of depression on early onset of microvascular complications, such as on new-onset microalbuminuria. Fifth, while we controlled for severity and duration of cardiometabolic disease, we did not control for all medical comorbidity. ACCORD did exclude patients with significant kidney or liver disease and cancer and those expected to live <3 years.

Despite these limitations, the results of this study highlight the importance of depression detection and effective depression treatment as key elements in quality diabetes care. Patients with diabetes and PHQ-9 scores of ≥10 randomized to collaborative depression and diabetes treatment showed greater improvements in depression, functioning, and quality of life than those randomized to usual care (25). However, no study has shown that depression treatment reduces mortality in patients with diabetes. Moreover, a recent study showed that the older tricyclic antidepressants may increase CVD with long-term use (26). This effect was not found for the more commonly used selective serotonin reuptake inhibitor antidepressants.

The results we report here, in conjunction with data from other studies, support the need for a randomized controlled trial to assess the impact of depression care on mortality in adults with type 2 diabetes.

Acknowledgments—This study was supported by grants N01-HC-95178, N01-HC-95179, N01-HC-95180, N01-HC-95181, N01-HC-95182, N01-HC-95183, N01-HC-95184, IAA-Y1-HC-9035, and IAA-Y1-HC-1010 from the National Heart, Lung, and Blood Institute; by other components of the National Institutes of Health, including the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging, and the National Eye Institute; by the Centers for Disease Control and Prevention; and by General Clinical Research Centers.

The following companies provided study medications, equipment, or supplies: Abbott Laboratories, Amylin Pharmaceutical, AstraZeneca, Bayer HealthCare, Closer Healthcare, GlaxoSmithKline, King Pharmaceuticals, Merck, Novartis, Novo Nordisk, Omron Healthcare, sanofi-aventis, and Schering-Plough. W.J.K. is a board member of Eli Lilly and has received honoraria for lectures to Eli Lilly, Forest, and Pfizer as a speakers’ bureau member. No other potential conflicts of interest relevant to this article were reported.

M.D.S. researched data and drafted the manuscript. P.O. researched data and edited the manuscript. P.F. and D.H. performed statistical analyses. D.L.S., D.W.R., L.J.F., and K.M.V.N. researched data and edited the manuscript. M.K.A. and W.J.K. reviewed and edited the manuscript. M.D.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Parts of this study were presented in abstract form at the 71st Scientific Sessions of the American Diabetes Association, San Diego, California, 24–28 June 2011.

References

1. Eaton WW. Epidemiologic evidence on the comorbidity of depression and diabetes. J Psychosom Res 2002;53:903–906
2. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care 2001;24:1090–1078
3. Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. Diabetes Care 2000;23:934–942
4. Lin EH, Katon W, Von Korff M, et al. Relationship of depression and diabetes self-care, medication adherence, and preventive care. Diabetes Care 2004;27:2154–2160
5. de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. Psychosom Med 2001;63:619–630
6. Lin EH, Heckbert SR, Rutter CM, et al. Depression and increased mortality in diabetes: unexpected causes of death. Ann Fam Med 2007;4:214–221
7. Zhang X, Norris SL, Gregg EW, Cheng VY, Beckles G, Kahn HS. Depressive symptoms and mortality among persons with and without diabetes. Am J Epidemiol 2005;161:652–660
8. Katon WJ, Rutter C, Simon G, et al. The association of comorbid depression with mortality in patients with type 2 diabetes. Diabetes Care 2005;28:2668–2672
9. Black SA, Markides KS, Ray LA. Depression predicts increased incidence of adverse health outcomes in older Mexican Americans with type 2 diabetes. Diabetes Care 2003;26:2822–2828
10. Egede LE, Nietert PJ, Zheng D. Depression and all-cause and coronary heart disease mortality among adults with and without diabetes. Diabetes Care 2005;28:1339–1345
11. Katon W, Fan MY, Unutzer J, Taylor J, Pincus H, Schoenbaum M. Depression and diabetes: a potentially lethal combination. J Gen Intern Med 2008;23:1571–1575
12. Pan A, Lucas M, Sun Q, et al. Increased mortality risk in women with depression and diabetes mellitus. Arch Gen Psychiatry 2011;68:42–50
13. Sullivan MD, Anderson RT, Aron D, et al.; ACCORD Study Group. Health-related quality of life and cost-effectiveness components of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: rationale and design. Am J Cardiol 2007;99(12A):90–102i
14. Anderson RT, Narayan KM, Feeny P, et al.; Action to Control Cardiovascular Risk in Diabetes (ACCORD) Investigators. Effect of intensive glycemic lowering on health-related quality of life in type 2 diabetes: ACCORD trial. Diabetes Care 2011;34:807–812
15. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC, American Psychiatric Association, 2000
16. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16:606–613
17. Katon W. Depression and diabetes: unhealthy bedfellows. Depress Anxiety 2010;27:323–326
18. Roy T, Lloyd CE, Poulter F, Holt RI, Sartorius N. Screening tools used for measuring depression among people with...
Type 1 and Type 2 diabetes: a systematic review. Diabet Med 2012;29:164–175
19. Smolderen KG, Spertus JA, Reid KJ, et al. The association of cognitive and somatic depressive symptoms with depression recognition and outcomes after myocardial infarction. Circ Cardiovasc Qual Outcomes 2009;2:328–337
20. Katon W, Schulberg H. Epidemiology of depression in primary care. Gen Hosp Psychiatry 1992;14:237–247
21. Ali S, Stone MA, Peters JL, Davies MJ, Khunti K. The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. Diabet Med 2006;23:1165–1173
22. Schleifer SJM-HM, Macari-Hinson MM, Coyle DA, et al. The nature and course of depression following myocardial infarction. Arch Intern Med 1989;149: 1785–1789
23. Spijkerman T, de Jonge P, van den Brink RH, et al. Depression following myocardial infarction: first-ever versus ongoing and recurrent episodes. Gen Hosp Psychiatry 2005;27:411–417
24. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. Diabetes Care 2008;31:2383–2390
25. Katon WJ, Lin EH, Von Korff M, et al. Collaborative care for patients with depression and chronic illnesses. N Engl J Med 2010;363:2611–2620
26. Hamer M, David Batty G, Seldenrijk A, Kivimäki M. Antidepressant medication use and future risk of cardiovascular disease: the Scottish Health Survey. Eur Heart J 2011;32:437–442