Diabetes, Depression, and Death

A randomized controlled trial of a depression treatment program for older adults based in primary care (PROSPECT)

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OBJECTIVE — We sought to test our a priori hypothesis that depressed patients with diabetes in practices implementing a depression management program would have a decreased risk of mortality compared with depressed patients with diabetes in usual-care practices.

RESEARCH DESIGN AND METHODS — We used data from the multisite, practice-randomized, controlled Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT), with patient recruitment from May 1999 to August 2001, supplemented with a search of the National Death Index. Twenty primary care practices participated from the greater metropolitan areas of New York City, New York; Philadelphia, Pennsylvania; and Pittsburgh, Pennsylvania. In all, 584 participants identified though a two-stage, age-stratified (aged 60–74 or ≥75 years) depression screening of randomly sampled patients and classified as depressed with complete information on diabetes status are included in these analyses. Of the 584 participants, 123 (21.2%) reported a history of diabetes. A depression care manager worked with primary care physicians to provide algorithm-based care. Vital status was assessed at 5 years.

RESULTS — After a median follow-up of 52.0 months, 110 depressed patients had died. Depressed patients with diabetes in the intervention category were less likely to have died during the 5-year follow-up interval than depressed diabetic patients in usual care after accounting for baseline differences among patients (adjusted hazard ratio 0.49 [95% CI 0.24–0.98]).

CONCLUSIONS — Older depressed primary care patients with diabetes in practices implementing depression care management were less likely to die over the course of a 5-year interval than depressed patients with diabetes in usual-care practices.

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Diabetes and depression are two of the most common problems seen in primary care settings. Epidemiologic data indicate that diabetes and depression are intimately related. Depression is a risk factor for diabetes (1), and risk of depression is increased by a factor of two in patients with diabetes (2). Depression is not only common in patients with diabetes but also contributes to poor adherence to medication and dietary regimens, poor glycemic control, reduced quality of life, and increased health care expenditures (3). Depression has been specifically linked to prognostic variables in diabetes such as micro- and macrovascular complications (4). Evidence from intervention trials shows that treatment of depression in patients with diabetes improves depression (5–7), but findings regarding improvement in glycemic control have been mixed (5,8,9). Although cohort studies document that depression is associated with increased risk of death among individuals with diabetes (10–13), no known intervention study has evaluated whether treatment for depression modifies this increased risk of mortality among older primary care patients with diabetes.

We investigated the relationship between diabetes, depression treatment, and all-cause mortality using data from the multisite, randomized trial, Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT), supplemented with a search of the National Death Index (NDI) Plus. The study intervention was implemented at the practice level and involved a depression care manager working with physicians to provide algorithm-based treatment and ongoing care management. Overall, intervention patients had a more favorable course of depression in both degree and speed of symptom reduction compared with usual-care patients (14). We took the opportunity afforded by PROSPECT to evaluate the effect of diabetes and of depression care management on all-cause mortality for the following reasons. While multiple medical conditions are of interest in this intervention trial, depression associated with diabetes has been shown to increase the risk of death (10–13). Furthermore, the demonstrated morbidity, mortality, and health services implications of diabetes and depression separately (15–17) support both understanding of the enormous public health significance of the co-occurrence of diabetes and depression and the urgency to finding evidence-based solutions to reduce the burden of these conditions. We hypothesized that depressed older adults with diabetes in practices randomized to intervention would be less likely to die over a 5-year follow-up interval compared with depressed older adults with diabetes in usual care.

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Abbreviations: CES-D, Centers for Epidemiologic Studies Depression scale; NDI, National Death Index; PROSPECT, Prevention of Suicide in Primary Care Elderly: Collaborative Trial.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

PROSPECT

PROSPECT compared a primary care–based intervention with usual care in improving the outcomes of depression. All study procedures were implemented with written informed consent, and the study protocols were approved by the institutional review boards of Cornell University (Ithaca, NY), the University of Pittsburgh (Pittsburgh, PA), and the University of Pennsylvania (Philadelphia, PA) schools of medicine. Details of the study design of PROSPECT are available elsewhere (14). In brief, 20 primary care practices from the greater metropolitan areas of New York City, New York, and Philadelphia and Pittsburgh, Pennsylvania, participated in the study from May 1999 to August 2001, with individual patients clinically followed for 2 years. Practices ranged in size (solo to medium sized), setting (sparsely populated, suburban, and urban), population type (including two serving primarily African-American patients), and affiliation (16 community-based and 4 academic practices). Practices were paired by region (urban vs. suburban/sparsely populated), affiliation, size, and population type. Within the 10 pairs, practices were randomly assigned by coin flip to intervention or usual care (described below). A two-stage sampling design was used to recruit patients. First, an age-stratified (aged 60–74 or ≥ 75 years), random sample of patients with an upcoming appointment was obtained. The sampled patients were mailed a letter allowing patients to decline. Second, trained lay interviewers telephoned the patients who did not decline. Patients who gave oral consent were assessed for enrollment using the Centers for Epidemiologic Studies Depression scale (CES-D) (18). All patients with a CES-D score >20 were invited into the study, as were those from a 5% random sample of patients with lower scores. Patients with a CES-D score ≤20 and who were not randomly selected were also recruited if they responded positively to supplemental questions about mood, prior depressive episodes, or treatment. A positive response to the supplemental questions triggered a diagnostic assessment.

The intervention, described in detail elsewhere (14), consisted of trained depression care managers offering guideline-concordant recommendations to the primary care physicians and helping patients with treatment adherence. The care managers monitored psychopathology, treatment adherence, response, and side effects and provided follow-up care at predetermined intervals or when clinically necessary. Patients who refused antidepressants were offered interpersonal psychotherapy by the depression care managers. In the intervention, a first-line antidepressant (citalopram, a selective serotonin reuptake inhibitor) and the interpersonal psychotherapy were provided at no cost. In usual care, physicians were informed of patients' depression diagnoses. Physicians also received informational materials and treatment guidelines for geriatric depression. No specific recommendations were given to these physicians regarding individual patients except for psychiatric emergencies. The types and proportions of treatment received over time by individuals in practices randomized to intervention or usual care have previously been published (14,19).

Measurement strategy

Trained research assistants assigned depression diagnoses to patients using the *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)* diagnoses (20). Severity of depression was assessed using the 24-item Hamilton Depression Rating Scale (21).

Individuals were classified as having a medical comorbidity and as having diabetes by self-report. The questionnaire used was based on the Charlson Comorbidity Index (22). To assess for diabetes, participants were asked, "Have you ever been told you have diabetes or high blood glucose?" For the current analysis, patients were considered to have diabetes if they reported having been told that they had diabetes or high blood glucose.

We used standard questions to obtain information from the respondents on age, level of educational attainment, sex, marital status, and self-reported ethnicity. Smoking status was based on report of smoking within 6 months of interview. The Philadelphia Multidimensional Assessment Instrument assessed instrumental activities of daily living and mobility (23). The Scale for Suicidal Ideation measured presence of suicidal ideation (24). The Mini-Mental State Examination is a short standardized mental status examination that has been widely employed for clinical and research purposes (25).

Ascertainment of vital status

Vital status in this investigation was based on follow-up of participants using the National Center for Health Statistics NDI (26). Because obtaining vital status requires that we provide personally identifiable information to the National Center for Health Statistics for NDI searches, confidentiality safeguards warrant discussion here. We did not transmit any PROSPECT data (e.g., information about depression status, physical disorders, or functional status) with identifying data, nor did we transmit identifying data via e-mail. Upon obtaining vital status data, the University of Pennsylvania Data Core sent the data to the sites for verification. Study sites then sent the data file—stripped of any identifying data—to the University of Pennsylvania Data Core for final production of the study data linked to vital status for analysis. The time frame for the ascertainment of vital status was the period of 5 years from overall commencement of PROSPECT.

Analytic strategy

Our analysis involved sorting patients into four groups according to whether patients self-reported diabetes at baseline and practice assignment (intervention or usual care). We carried out survival analysis adjusting for within-practice clustering (27). The Cox proportional hazards model for clustered data was used to explore the effect of variables on survival. Point estimates and associated 95% CIs are provided for the unadjusted and adjusted hazard ratios (HRs) (as presented in previous studies [14,28]). Survival curves were prepared using the method of Kaplan and Meier (29) to illustrate the mortality of each group defined by patient diabetes status at baseline and to practice randomization assignment to intervention or usual care. We began by exploring potential confounding variables using univariate models with baseline characteristics as predictors of time to death. Our final model included influential covariates identified by their association ($P < 0.10$) with the outcome of interest, time to death. The final model included terms to adjust for baseline differences in age, sex, education, ethnicity, smoking status, number of medical conditions, number of disabilities, and cognition.

We have been guided by published criteria for performing and reporting subgroup analyses (30,31). Evaluating our prespecified study hypothesis required a test for effect modification of intervention

Table 1—*Characteristics of the study sample according to randomization assignment of primary care practice and diabetes status at baseline*

Depressed patients	Intervention	Usual care	No intervention	No usual care	Test of equality across groups (*P*)*
n	70	53	241	220	
Sociodemographic characteristics					
Age (years)	71 ± 8.5	67 ± 6.8	71 ± 7.6	71 ± 8.1	0.0004
Education (years)	12 ± 3.0	12 ± 3.2	13 ± 3.3	13 ± 3.3	0.0006
Women	50 (71)	37 (70)	167 (69)	168 (76)	0.3944
Ethnic minority	23 (33)	27 (51)	58 (24)	69 (31)	0.0802
Married	22 (31)	21 (40)	91 (38)	81 (37)	0.5074
Medical conditions					
Current smoker	9 (13)	3 (6)	26 (11)	12 (5)	0.2472
Medical conditions	5 ± 2.9	5 ± 2.4	2 ± 1.9	2 ± 1.9	<0.0001
Number of disabilities (MAI score)	3 ± 2.3	3 ± 2.2	2 ± 1.9	2 ± 1.8	0.0040
Baseline depression and cognitive status					
Depression severity (HDRS score)	18 ± 5.3	19 ± 5.6	18 ± 6.3	17 ± 5.8	0.1789
Suicidal ideation (SSI score >0)	23 (33)	12 (23)	67 (28)	44 (20)	0.0997
Cognitive function MMSE score)	27 ± 4.2	27 ± 2.6	28 ± 2.4	27 ± 2.5	0.0848

Data are means ± SD or *n* (%), with percentages based on the total number in the corresponding column, unless otherwise indicated. Test of equality across groups based on regression models. Data gathered from PROSPECT. The ranges of scores are 0–30 for the Mini-Mental State Examination (MMSE), with high scores indicating less severe cognitive impairment.; 0–76 for the Hamilton Depression Rating Scale (HDRS), with high scores indicating greater depressive symptoms; and 0–38 for the Scale for Suicidal Ideation (SSI), with high scores indicating greater suicidal ideation. *Univariate logistic or linear regression model with random effects. MAI, Multidimensional Assessment Instrument.

assignment on the risk of death by baseline diabetes status. The formal test for effect modification involved introducing terms representing interaction into the Cox proportional hazards model, in addition to main effects for diabetes status and intervention. Consistent with the literature (32), we set α at 0.10 to denote statistical significance for the interaction term in the Cox proportional hazards model. SAS was used to carry out analyses (version 9.1; SAS Institute, Cary, NC).

RESULTS

Study sample

The CONSORT (Consolidated Standards for Reporting of Trials) flow diagram for PROSPECT has previously been published (14). In brief, the study screened 9,072 older individuals, 1,888 of whom were invited to participate. Of the 1,888 individuals invited to participate, 1,238 (65.8%) agreed to a baseline interview. Our study sample included 599 depressed patients, of whom 396 (66.1%) met *Diagnostic and Statistical Manual of Mental Disorders-IV* criteria for major depression. Fifteen people were excluded due to missing data on baseline diabetes status, leaving a sample size of 584 for this analysis.

Sample characteristics

The mean ± SD age of our study sample was 70.3 ± 7.9 years. The age range was 60–94 years. Women comprised 422 (72.3%) of the participants. The self-identified ethnic groups of the participants consisted of 407 Caucasians (69.7%), 161 African Americans (27.6%), and 16 American Indians, Hispanics, or Asians (2.7%). Of all 584 participants, 123 (21.2%) reported a history of diabetes. Table 1 compares baseline characteristics between patients in the intervention and usual-care practices, stratified by diabetes status. After 5 years, 110 depressed patients had died. Only one documented suicide occurred during the study in a depressed patient with diabetes in an intervention practice. The median length of follow-up in ascertainment of vital status was 52.0 months (range 0.8–67.7).

Mortality risk according to diabetes status

Depressed patients with diabetes in the intervention practices experienced a mortality rate of 68.2/1,000 person-years (95% CI 41.0–106.5), whereas depressed patients with diabetes in usual care experienced a mortality rate of 103.4/1,000 person-years (63.2–159.7). Individuals without diabetes experienced similar mortality rates in the intervention and usual-care practices (36.0/1,000 person-years [95% CI 25.3–49.6] vs. 38.2/1,000 [26.4–53.3], respectively).

Table 2 provides unadjusted and adjusted HR estimates according to diabetes status. In the univariate model, depressed patients with diabetes in the intervention practices were less likely to have died during the 5-year follow-up interval than depressed patients with diabetes in usual care (unadjusted HR 0.66 [95% CI 0.36–1.21]), but the 95% CIs included the null. The final model accounted for baseline imbalances in age, sex, education, ethnicity, smoking status, number of medical conditions, number of disabilities, and cognition among patients. Depressed patients with diabetes in the intervention practices were significantly less likely to have died during the 5-year follow-up in-

Table 2—*Relationship of practice random assignment, patient baseline diabetes status, and mortality during a 5-year follow-up interval*

Intervention and usual-care patients' diabetes status	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*
Diabetes	0.66 (0.36–1.21)	0.49 (0.24–0.98)
No diabetes	0.94 (0.58–1.52)	0.79 (0.42–1.47)

Data gathered from PROSPECT.

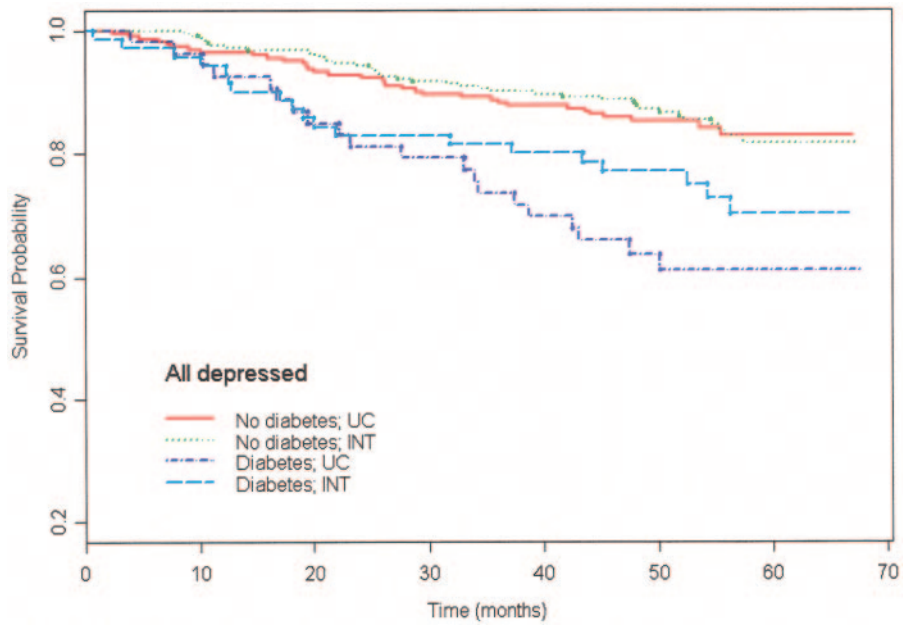

Figure 1—*Survival curves for patients with* (n = *53) and without* (n = *220) diabetes in practices randomized to usual care and patients with* (n = *70) and without* (n = *241) diabetes randomized to intervention practices. Data gathered from PROSPECT.*

terval than depressed patients with diabetes in usual care (adjusted HR 0.49 [0.24–0.98]). In contrast, depressed patients without diabetes in the intervention practices were not at decreased risk compared with those without diabetes in usual care (adjusted HR 0.79 [0.42–1.47]). The interaction of randomization group by diabetes status was statistically significant ($P = 0.04$). We have provided Kaplan-Meier curves according to diabetes status for intervention versus usual care (Fig. 1).

CONCLUSIONS — Depressed older adults with diabetes who were in practices randomized to intervention were less likely to have died at the end of the 5-year follow-up interval than depressed individuals with diabetes in usual care after adjustment for baseline differences. Depressed patients without diabetes in the intervention were not at decreased risk compared with depressed patients without diabetes in usual care. Intervention attenuates the influence of diabetes on mortality risk among older adults with depression. We believe these findings support the integration of depression evaluation and treatment with diabetes management in primary care.

Before discussing our findings, the results must first be considered in the context of potential study limitations. First, we obtained our results from primary care sites in the greater metropolitan areas of New York City, Philadelphia, and Pittsburgh, whose patients may not be representative of other primary care practices in the U.S. However, the participating sites were diverse practices of varying size located in urban, suburban, and sparsely populated areas. Second, diabetes diagnosis was based on self-report alone; however, relying on medical records may also be incomplete because many individuals receive health care from providers in multiple systems. Studies have shown that self-reported data on diabetes as well as other chronic diseases is reliable (33). Third, the question regarding diabetes might have included patients with impaired glucose tolerance who did not have diabetes. However, misclassification of some individuals with impaired glucose tolerance as having diabetes would lead to a conservative bias toward the null (i.e., no intervention effect for patients with diabetes on mortality). Fourth, the mortality reduction among depressed patients with diabetes randomized to intervention may be due to factors other than the specific effects of a depression management program. For example, we only have a limited ability to address whether patients with diabetes in the intervention practices were seen more frequently for reasons other than depression by their physicians; similarly, we do not have information on specific diabetes outcomes such as A1C. Fifth, misclassification of vital status was a potential limitation. However, overall sensitivity of the NDI for ascertainment of vital status has generally been well over 90% in most studies (34).

We selected patients with diabetes as a subgroup from the larger intervention trial (14,35), realizing that we must proceed with caution about the inferences we make. Statisticians are wary of subgroup analyses, but clinicians must make decisions about individual patients (30,36,37). At the same time, large-scale intervention studies carried out in primary care practice are limited, so we need to make the most of the data we have from intervention studies. Guided by published criteria for performing and reporting subgroup analyses (30,31), we have identified a group—older individuals with diabetes—for whom risk of death has been reported to be increased (10–13). In addition, the link between diabetes, depression, and the outcome (mortality) may have common pathophysiologic mechanisms (38,39).

Finally, uncertainty persists about the influence of treatment of depression on outcomes for diabetes and other medical comorbidity (8,9). Consistent with recommendations regarding subgroup analyses, we reported the statistical significance of the interaction between intervention assignment and the condition of interest on the outcome (32,40) and adjusted our estimates for potential imbalances in covariates across treatment groups (41).

Despite some limitations, our study warrants attention because older depressed primary care patients with diabetes in practices implementing depression care management were significantly less likely to die over the course of a 5-year interval than depressed patients with diabetes in usual-care practices. To our knowledge, this is the first study to report on the relationship between diabetes and mortality in a depression intervention trial. A formal test of the interaction between intervention assignment and diabetes on the outcome of interest, all-cause mortality, was significant (32,40). This suggests that individuals with diabetes were more likely to benefit from intervention than individuals without diabetes. Adjustment of the HR for imbalance in the distribution of baseline covariates assessed at baseline can be expected to yield estimates of the hazard closer to the true estimate of the treatment effect (40,41). Because our sample was derived from primary health care, the public health significance of these findings is high.

The combination of clinical evalua-

tion and monitoring, pharmacotherapy, and, in some cases, interpersonal psychotherapy in the PROSPECT intervention appears to be effective in depressed patients with diabetes in reducing all-cause mortality risk. We realize that our study does not examine potential mechanisms underlying the relationship between the PROSPECT intervention and a decreased mortality risk among depressed patients with diabetes. Both physiologic factors, such as increased inflammation (38,39) and poor glucose regulation (3,4), and behavioral processes, such as poor adherence (3), may link depression with increased mortality in patients with diabetes. The potential mediators between treatment assignment and outcomes for patients with diabetes deserve further study.

Our results add to the literature on clinical trial outcomes from treatment of depression in patients with diabetes. Specifically, the collaborative care model for depression, of which PROSPECT is one example, has been found to improve depression care and depression outcomes in patients with diabetes. The IMPACT (Improving Mood-Promoting Access to Collaborative Treatment) trial found that depressed older adults with diabetes in a depression care management intervention had better depression outcomes at 1 year compared with depressed older adults with diabetes in usual care, although A1C levels were unaffected by the intervention (9). The authors point out that because patients had good glycemic control at baseline, power to detect small but clinically important improvements in glycemic control was limited. The Pathways Study randomized 329 patients with diabetes and comorbid major depression or dysthymia to depression care management or usual care and found that although depression outcomes were improved, no differences in A1C levels were observed (8). However, these authors also point out that the patients in the Pathways Study had good glycemic control at baseline.

In summary, our investigation adds new evidence to the literature on depression and diabetes by examining whether the PROSPECT intervention influenced survival among depressed older primary care patients with diabetes. Specifically, these results indicate that a depression care management intervention can significantly reduce all-cause mortality among depressed patients with diabetes. These results should propel the development and dissemination of models of care that better integrate depression management for individuals with diabetes.

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