Association between Multidisciplinary Care and Survival for Elderly Patients with Chronic Kidney Disease

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The effectiveness of multidisciplinary care (MDC) in improving health outcomes for patients with chronic kidney disease (CKD) is uncertain. This study sought to determine the association among MDC, survival, and risk for hospitalization among elderly outpatients with CKD. A total of 6978 patients who were 66 yr and older and had CKD were identified between July 1 and December 31, 2001, and followed to December 31, 2004; 187 (2.7%) were followed in an MDC clinic. Logistic regression was used to determine the propensity score (probability of MDC) for each patient, and MDC and non-MDC patients then were matched 1:1 on the basis of their score. A Cox model was used to determine the association between MDC and risk for death and hospitalization. After adjustment for age, gender, baseline GFR, diabetes, and comorbidity score, there was a 50% reduction in the risk for death for the MDC compared with the non-MDC group (hazard ratio [HR] 0.50; 95% confidence interval [CI] 0.35 to 0.71). There was no difference in the risk for all-cause (HR 0.83; 95% CI 0.64 to 1.06) or cardiovascular-specific hospitalization (HR 0.76; 95% CI 0.54 to 1.06) for the MDC compared with the non-MDC group. In conclusion, it was found that MDC was associated with a significant reduction in the risk for all-cause mortality and, although not statistically significant, a trend toward a reduction in risk for all-cause and cardiovascular-specific hospitalizations. The benefits of MDC and an assessment of their economic impact should be tested in a randomized, controlled trial.

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Chronic kidney disease (CKD) is common and is associated with a poor prognosis, including the development of premature cardiovascular disease and increased mortality (1–5). Given the multiple comorbidities and complexity of care for patients with CKD, it has been proposed that multidisciplinary care (MDC) that is delivered by an interdisciplinary health care team may improve health outcomes in this patient population (6–8).

MDC clinics are being used by the majority of nephrology programs in North America (9), even though their effectiveness in improving morbidity and mortality outcomes for patients with CKD largely is unknown. Although observational studies suggested a survival advantage with MDC (10,11), these studies were limited to patients who initiated dialysis, thereby introducing a potential survival bias. An earlier randomized trial of patients with CKD found no effect of MDC compared with usual care on decline in kidney function, health care utilization, or mortality (12). A more recent randomized trial suggested that MDC was not associated with improvement in vascular structure or function in patients with stages 4 and 5 CKD (13), although a psychoeducational intervention alone did

demonstrate an extension in time to initiation of renal replacement therapy and improved survival (14,15). However, these trials have limitations, including reliance on primary care physicians to implement recommendations (12), inclusion of patients who already are on dialysis (13), and an educational intervention administered without MDC as it currently exists (14,15). In contrast, randomized trials of MDC in other chronic disease conditions have been shown to result in improved morbidity and mortality (16–20). Given the uncertainty with respect to the effectiveness and the resource intensity that is associated with MDC, we sought to determine the association among MDC, survival, and risk for hospitalization among elderly outpatients with CKD, compared with usual care.

Materials and Methods
Data Sources and Identification of Study Population
We identified a cohort of elderly patients with CKD from the Calgary Laboratory Services computerized database (Calgary, AL, Canada). Calgary Laboratory Services provides laboratory testing to the entire Calgary Health Region (catchment population 1.1 million) using a single regional laboratory and standardized methods. To be eligible for inclusion, patients had to be 66 yr or older and have had at least one outpatient serum creatinine measurement during a 6-mo period (July 1, 2001, to December 31, 2001). Laboratory measurements that were associated with a hospital admission were excluded to avoid episodes of acute renal failure. The first outpatient serum creatinine measurement during this period was used to define the index GFR.

The cohort was linked to the Southern Alberta Renal Program com-

puterized database, and all patients followed in the MDC clinic during the 18-mo period from July 1, 2001, to December 31, 2002, were identified (both incident and prevalent MDC patients). The Southern Alberta Renal Program provides care to all patients with ESRD in southern Alberta (including the Calgary Health Region) and maintains a computerized database of all dialysis patients, kidney transplant patients, and patients who have CKD and are followed in the MDC clinic (21). Renal transplant recipients and patients who already were receiving dialysis at study entry were excluded.

The cohort also was linked to provincial administrative data (as described previously) (22,23) to obtain information on prescription drug use in the year before their index GFR. Briefly, all residents of Alberta who are 65 yr and older receive insured health services, including coverage for prescription drugs. For ensuring availability of 1 yr of drug data for all patients, entry into the study was limited to patients who were 66 yr and older. In addition to determining exposure to specific classes of medications (including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β blockers, diuretics, nonsteroidal anti-inflammatory drugs, and cholesterol-lowering drugs), drug data were used to determine the presence of diabetes, as defined by at least one prescription for insulin or an oral hypoglycemic agent in the year before the index GFR, and to derive a measure of comorbidity (24).

Assessment of Kidney Function

An estimate of GFR was obtained from the Modification of Diet in Renal Disease (MDRD) equation, using variables for age, gender, and serum creatinine (25). Preliminary studies have validated this equation in the elderly population (26). Although data on race were not available from the data sources, fewer than 1% of the Alberta population is black (27); therefore, the impact at the population level of eliminating race from the estimate of GFR was expected to be minimal. We limited our study population to individuals with stage 3 or greater CKD (index GFR <60 ml/min per 1.73 m^2).

Multidisciplinary Care Clinics

Patients are referred to the MDC clinic by their primary nephrologist. At the first MDC visit, an education session is held with the patient and his or her family members and is attended by a specialized clinic nurse, registered dietician, and social worker. Patient education includes a discussion of CKD and its progression and complications, fluid and dietary restrictions, monitoring BP, effects of medications, and recommendations regarding exercise and diet. Patients also are provided with a booklet produced by the Kidney Foundation ("Living with Kidney Disease," available at http://www.kidney.ca/files/Kidney/aCompleteManual.pdf). MDC patients undergo blood work every 1 to 3 mo to monitor kidney function and metabolic complications and are seen by their primary nephrologist every 3 to 6 mo. Management in the MDC clinic is focused on medical management and lifestyle modification to delay progression of CKD and target cardiovascular risk factor reduction.

Study Outcome

All-cause mortality, obtained from the Alberta Bureau of Vital Statistics, was the primary outcome. Secondary outcomes included hospitalization (all-cause) and hospitalization for cardiovascular causes (composite of acute myocardial infarction [AMI], congestive heart failure [CHF], cerebrovascular accident [CVA], or transient ischemic attack [TIA], as determined from the Calgary Health Region corporate database. For patients with multiple hospitalizations, only the first hospitalization during the study period was included. Cause-specific hospi-

talizations were based on the following validated codes from the *International Classification of Diseases Ninth and Tenth Revisions*, using the primary discharge diagnosis: AMI (28,29) 410, 411.1, I21, or I22; CHF (30,31) 428 or I50; and CVA/TIA (32) 362.3, 433.x1, 434.x1, 436, 431.x, 430.x, 435.x, H34.1, I63.x, I64.x, I61.x, I60.x, or G45.x.

Statistical Analyses

Characteristics for MDC and non-MDC patients (the remaining patients in the cohort) were compared with χ^2 tests for categorical variables, t test for age, and rank-sum test for the comorbidity score. For the survival analysis, all patients were followed from the date of their index GFR until death or the end of the study (December 31, 2004). Because MDC and non-MDC patients may have different characteristics, we used a propensity score analysis (33) to adjust for differences in the likelihood of being followed in an MDC clinic between the two groups. A propensity score analysis is a method of controlling for confounding in observational studies.

The first step in the propensity score analyses was to calculate an individual's propensity score, which is defined as his or her conditional probability of assignment to the MDC group, given the observed confounders. To obtain this propensity score, we used logistic regression to model the likelihood of MDC as the dependent variable, with independent variables including age, gender, index GFR, diabetes, comorbidity score, and medication use including angiotensin-converting enzyme inhibitor or angiotensin receptor blockers, β blockers, calcium channel blockers, antiarrhythmics, diuretics, cholesterol-lowering agents, and nonsteroidal anti-inflammatory drugs. The predicted probability of the dependent variable (likelihood of MDC) from this model represents the propensity score for each individual and provides an estimate of the probability that an individual was followed at the MDC clinic. The area under the receiver operating characteristic (ROC) curve was calculated to assess the predictive ability of the propensity score model.

MDC and non-MDC patients then were matched using Greedy matching algorithms, on the basis of their propensity score, at a ratio of 1:1. Matching on the propensity score allowed comparison of survival and hospitalization outcomes for individuals with a similar likelihood of being referred and followed in an MDC clinic. One-to-one matching was chosen on the basis of assessment of model fit and a more balanced distribution of patient characteristics and propensity scores after matching. Survival at up to 3.5 yr was calculated for the MDC and non-MDC groups. Kaplan-Meier survival curves were plotted for the two groups, with differences in survival compared using the log rank test.

The association between MDC and survival was characterized further using Cox models and shared frailty modeling techniques, which take into account the matching of patients (34). Covariates that were considered in the model included age, gender, diabetes, baseline GFR, and comorbidity score. We also conducted two sensitivity analyses for the mortality outcome: (1) On a subgroup of patients for whom we had a measure of serum hemoglobin and albumin, to assess their potential confounding effect, and (2) on a subgroup of patients who were in the MDC clinic between July 1, 2001, and December 31, 2001 (the same period that was used to define the non-MDC group), to assess the potential for a survivor bias.

This analysis was repeated using time to all-cause hospitalization, as well as time to hospitalization for a cardiovascular cause, as the outcome. All analyses were conducted using SAS (version 9.1; SAS Institute, Cary, NC) and STATA (version 9.0; STATA Corp., College Station, TX). The conjoint ethics review board at the University of Calgary approved the study.

Results

A total of 6978 patients with CKD were included in the study, 187 (2.7%) of whom were followed in the MDC clinic. Baseline patient characteristics, by MDC status, are shown in Table 1. Compared with non-MDC patients, patients in the MDC clinic were younger and more likely to be male, have a lower GFR, and have increased comorbidity. During the study period, 61 (32.6%) patients in the MDC group died, compared with 1874 (27.6%) in the non-MDC group ($P = 0.13$). Patients in the MDC group also were more likely to initiate dialysis during the study period (43.4 *versus* 1.5%; $P < 0.0001$).

Propensity Score Analysis

The logistic regression model to derive the propensity score, using likelihood of being followed in the MDC clinic as the outcome, had an area under the ROC curve of 0.93, denoting excellent predictive discrimination with respect to the outcome (a value of 1.0 indicates perfect predictive discrimination, whereas a value of 0.5 indicates no ability to discriminate with respect to the outcome). Each MDC patient then was matched at a ratio of 1:1 to a non-MDC patient, on the basis of their propensity score. Baseline characteristics of the MDC and non-MDC group were similar after matching (Table 2). All remaining analyses are based on the 187 MDC patients and the matched 187 non-MDC patients.

All-Cause Mortality

Of the 374 patients in the matched analyses, 61 (32.6%) in the MDC and 77 (41.2%) in the non-MDC group died during the study period. As shown in Figure 1, Kaplan-Meier survival estimates demonstrated a significant increased likelihood of survival for MDC compared with non-MDC patients (log rank

Table 1. Baseline patient characteristics by MDC, before matching[a]

Characteristic	No MDC ($n = 6791$)	MDC ($n = 187$)	P
Age (yr; mean [SD])	78.7 (7.3)	76.0 (6.4)	0.001
Female (%)	61.9	42.8	<0.0001
Baseline eGFR (%)			<0.0001
30 to 60 ml/min per 1.73 m²	88.9	13.4	
<30 ml/min per 1.73 m²	11.1	86.6	
Diabetes (%)	17.5	37.4	<0.0001
Comorbidity score (median)	2791	4167	<0.0001
Medication use in previous year (%)			
ACE-I/ARB	51.6	68.5	0.0002
CCB	31.5	61.0	<0.0001
β blocker	27.4	36.4	0.007
lipid lowering	22.8	43.3	<0.0001
NSAID/COX-2 inhibitors	35.8	22.5	<0.0001

[a]ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker; eGFR, estimated GFR; MDC, multidisciplinary care; NSAID/COX-2, nonsteroidal anti-inflammatory drugs/cyclooxygenase-2.

Table 2. Baseline patient characteristics by MDC, after matching 1:1 on propensity score

| Characteristic	No MDC ($n = 187$)	MDC ($n = 187$)	P
Age (yr; mean [SD])	75.6 (6.1)	76.0 (6.4)	0.46
Female (%)	44.9	42.8	0.68
Baseline eGFR (%)			1.00
30 to 60 ml/min per 1.73 m²	13.4	13.4	
<30 ml/min per 1.73 m²	86.8	86.6	
Diabetes (%)	35.8	37.4	0.75
Comorbidity score (median)	4019	4167	0.32
Medication use in previous year (%)			
ACE-I/ARB	65.8	68.5	0.58
CCB	58.8	61.0	0.67
β blocker	31.0	36.4	0.27
lipid lowering	41.7	43.3	0.75
NSAID/COX-2 inhibitors	21.4	22.5	0.80
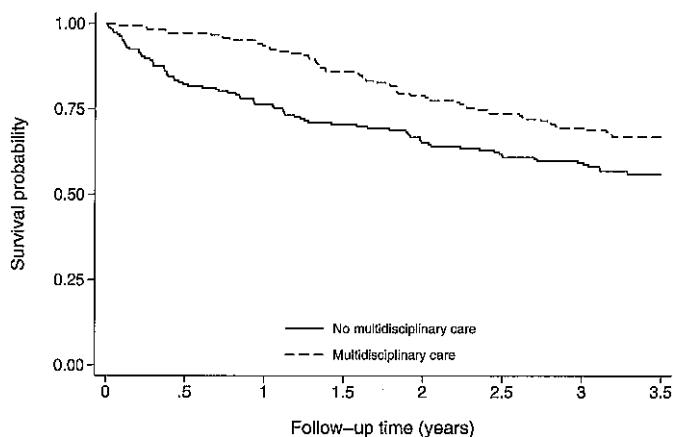
Figure 1. Kaplan-Meier plot of patient survival over time, by multidisciplinary care.

test P = 0.008). In the unadjusted Cox regression analysis, MDC care was associated with a 44% reduction in the risk for death compared with non-MDC care (hazards ratio [HR] 0.56; 95% confidence interval [CI] 0.40 to 0.79). After adjustment for age, gender, baseline GFR, diabetes, and comorbidity score, there was a 50% reduction in the risk for death for the MDC group compared with the non-MDC group (HR 0.50; 95% CI 0.35 to 0.71).

The mortality results were unchanged after adjustment for the potential confounding effects of serum hemoglobin and albumin. In the analyses that were limited to patients who were present in the MDC clinic between July 1 and December 31, 2001 (n = 105), a trend for a mortality benefit was observed (HR 0.69; 95% CI 0.44 to 1.06).

Hospitalizations

A total of 123 (65.8%) patients in the MDC and 131 (70.1%) in the non-MDC group had at least one hospitalization during the study period. There was no difference in the risk for hospitalization for the MDC compared with the non-MDC group (log rank test P = 0.18; Figure 2). In the Cox regression analysis
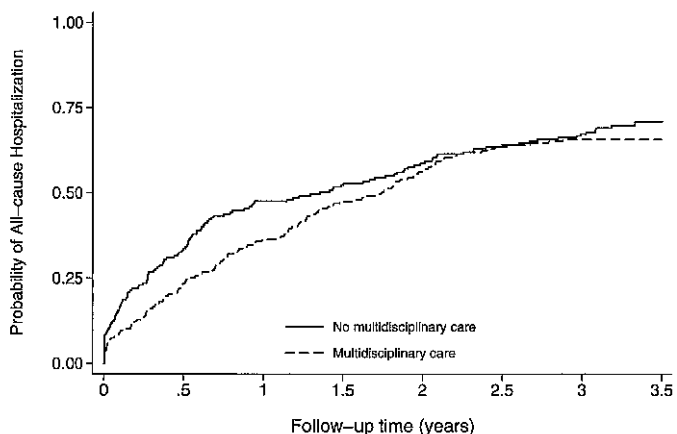
using a frailty model and after adjustment for age, gender, baseline GFR, diabetes, and comorbidity, there was a nonsignificant 17% reduction in the risk for hospitalization for MDC compared with non-MDC care (HR 0.83; 95% CI 0.64 to 1.06).

There was no difference in the risk for hospitalization for the composite outcome of AMI/CHF/CVA/TIA for the MDC compared with the non-MDC group (long rank test P = 0.12; Figure 3). In the Cox regression analysis, adjusting for the variables as listed above, MDC care was associated with a nonsignificant reduction in the risk for hospitalization for this composite outcome (HR 0.76; 95% CI 0.54 to 1.06).

Discussion

The benefits of early referral to nephrology care in reducing adverse outcomes are well documented (35–37); however, the impact of including a multidisciplinary team in the delivery of this care is less well established. Given the complexity of care that is required to treat patients with CKD (38), there are theoretical benefits to a coordinated multidisciplinary approach. This is particularly relevant because current evidence suggests that even timely nephrology care in this patient group may not result in optimal care (39–41). In this community-based study of elderly patients with CKD, we found a significantly lower risk for all-cause mortality for patients who were followed in the MDC clinic, although no significant difference in the risk for all-cause hospitalization and cardiovascular-specific hospitalization was evident.

The majority of previous observational studies that evaluated MDC did suggest a benefit of MDC in improving patient survival, although these studies were limited to patients who initiated dialysis (10,11,42). Given that patients with stage 4 CKD are more than twice as likely to die as to develop ESRD (43), a survival bias may have influenced these results. John *et al.* (44) were some of the few investigators who were able to identify a community-based cohort of patients with CKD. Although a two-fold increase in mortality was reported for pa-
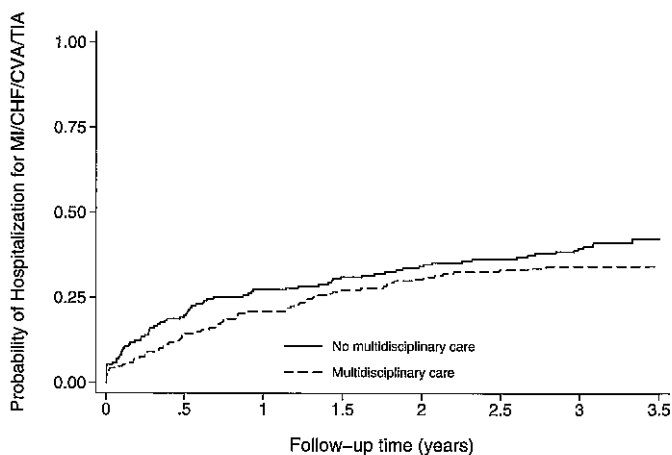

Figure 2. Kaplan-Meier plot of time to first all-cause hospitalization, by multidisciplinary care.

Figure 3. Kaplan-Meier plot of time to first hospitalization for the composite outcome of acute myocardial infarction/congestive heart failure/cerebrovascular accident/transient ischemic attack (AMI/CHF/CVA/TIA), by multidisciplinary care.

tients with no renal care, it is unclear whether renal services included MDC or nephrologists' care alone.

One of the few randomized trials that evaluated MDC in patients with CKD found no effect of MDC compared with usual care on outcomes, including decline in kidney function, health care utilization, and mortality (12). In addition to several other limitations, the investigators relied on primary care physicians to implement recommendations. Lack of adherence to recommendations may have biased the results toward the null. A more recent randomized trial of 200 patients with CKD (13) compared the impact of a physician-supervised, nurse-driven multiple risk factor intervention clinic with conventional care on biochemical and surrogate measures of vascular structure and function. Although the specialized clinic achieved better control of LDL cholesterol, homocysteine, and BP, no difference between the two groups was observed for the outcomes of carotid intima-media thickness or brachial artery reactivity. Although these results suggest limited benefit associated with CKD MDC, it is possible that benefits in atheroma burden or vascular function were not observed because the intervention was too late (approximately 60% of patients were already on dialysis), the study sample was underpowered after dropouts, or one or more specific elements that were chosen for the intervention were, in retrospect, incorrect (e.g., lowering of homocysteine [45,46]). In contrast to the lack of an effect of MDC in randomized trials of patients with CKD, provision of MDC with a focus on multifactorial risk factor interventions has been shown to improve morbidity and mortality outcomes in other chronic disease states, including diabetes (16), congestive heart failure (18–20), and rheumatoid arthritis (17).

There are several possible explanations for the all-cause survival benefits in the MDC group that developed early and persisted beyond 1 yr. Management in the MDC clinic is focused on medical management and lifestyle modification to delay CKD progression and target cardiovascular risk factor reduction. Although not directly measured, it also is plausible that dietary advice and lifestyle modification of hyperkalemia, a common complication of CKD, affected survival. Other interventions that are common in the MDC and also have significant short-term survival benefits include use of statins (47) and smoking cessation (48,49).

Although our study suggests that MDC is associated with a survival benefit, these results should be interpreted within the context of the study's limitations. First, we were unable to determine the specific elements in the MDC clinic that may have affected survival. MDC for the patient with heart failure suggests that three elements are crucial to the success of the program: Specially trained nurses, education of patients and their families, and access to clinicians who are specially trained in the area (18). A noncontemporary, randomized, controlled trial in patients with advanced kidney disease demonstrated an extension in time to initiation of renal replacement therapy and improved survival with a single psychoeducational intervention (14,15). Whether the educational element, independent of the trained nurses or related elements, was important in improving survival in our study is not possible to determine. Second, the use of laboratory data to define the study cohort

limited the study to patients who sought medical care and had at least one outpatient serum creatinine measurement. Because the study sample was based on the elderly, who are more likely to use the health care system and have laboratory testing performed, this is unlikely to bias substantially the study results. Misclassification of CKD also is unlikely, because the majority (86.7%) of patients had stage 4 CKD. Data from a cohort that is identified by laboratory-based case finding also are generalized easily to primary care practice. Third, as with all observational studies, the possibility of residual confounding cannot be excluded. Although we adjusted for comorbidity on the basis of medication use, this may underestimate the true prevalence of these conditions. We also were unable to adjust for other aspects of care, including BP control, medication use, and progression of kidney disease, which may influence the results. However, the use of the propensity score analysis, with matching of MDC and non-MDC patients on the basis of their likelihood of being followed in the MDC clinic, should reduce the potential for such bias. In addition, the results of the logistic regression model to derive the propensity score (with an area under the ROC curve of 0.93) suggest excellent predictive discriminatory ability for the outcome. Fourth, the manner in which the patients were chosen may have introduced a survivor bias. Although this requires a more valid assessment in a randomized, controlled trial, our conservative sensitivity analysis did suggest a persistent benefit of MDC clinics that may have been statistically significant with a larger sample size. Finally, our results are based on the experience within a single center. However, given the similarity of MDC clinics nationally (9), there is no reason to believe that these results could not be generalized to other centers.

Conclusion

We found that compared with usual care, MDC for elderly patients with CKD was associated with improved survival. Although definitive determination of the effectiveness of MDC in improving health outcomes remains to be confirmed from a randomized clinical trial (Canadian Prevention of Renal and Cardiovascular Endpoints Trial [CANPREVENT]) (50), our results suggest that clinicians and decision makers should continue to support MDC to optimize health outcomes for patients with CKD.

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Disclosures

None.

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The issue of how to provide optimal care to patients with CKD is central to nephrology. This article provides data to suggest that multidisciplinary care dramatically reduces mortality in these patients. This reality is reinforced in the accompanying issue of *CJASN* by data presented by Patwardhan *et al.* (pages 277–283) that confirm the additional benefit of having a nephrologist involved in the care of CKD patients relatively early in the course. A *CJASN* editorial by Blantz (pages 193–195) provides excellent perspective on the increasing evidence that supports the long-term benefits of closer cooperation between nephrologists and non-nephrologists *versus* the short-term increased costs of this model.