QUALITY OF CHRONIC KIDNEY DISEASE CARE IN CANADA: ROOM FOR IMPROVEMENT

BRYAN MICHAEL CURTIS

Quality of Chronic Kidney Disease Care in Canada:

Room for Improvement

By

Bryan Michael Curtis MD, FRCPC

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Abstract

Background: Chronic Kidney Disease (CKD) can be associated with many poor outcomes. Studies are required to assess gaps in care and the potential for improvements. Research is needed to determine the optimal process of care for CKD.

Methods: 1) A multi-centre Canadian prospective survey examined patient's clinical status as they initiated dialysis. 2) A case-control study of incident dialysis patients evaluated clinical outcomes of patients previously exposed to formalized multidisciplinary clinic programs versus standard nephrology care. 3) A prospective multicentre Canadian cohort study of patients initially referred to nephrology with measured or estimated glomerular filtration rate less than 50 mL/min/1.73m^2 evaluated patient status at referral, and nephrology intervention at first encounter.

Results: 1) Canadian patients commencing dialysis in 1998-1999 appeared to be doing so in relative concordance with published guidelines with respect to timing of initiation. Despite an increased awareness of kidney disease, a substantial number of patients continued to commence dialysis without previous care by a nephrologist. Of those who were seen by nephrologists, clinical and laboratory parameters are suboptimal according to current guidelines. 2) Despite equal and long exposure to nephrology care prior to dialysis, there appeared to be an association of survival advantage for those patients exposed to formalized clinic care in addition to standard nephrologist follow-up. 3) CKD patients continued to have their first encounter with a nephrologist late in their disease

course. Information on prior evaluation was incompletely transmitted to the nephrologist. There appears to be room for improvement in evaluation and treatment at the first nephrology encounter.

Conclusions: CKD care appears to be sub-optimal. Multidisciplinary clinics may play a role in improving outcomes. Further research is needed to address this care model.

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For my Mother

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Overview

It has been well established that end stage kidney disease (ESKD) is associated with many poor outcomes such as premature death and poor quality of life [1, 2]. As such, there have been significant research achievements made to address these areas for dialysis patients. However, it has become increasingly clear that interventions to improve outcomes should be targeted at an earlier stage of kidney disease—mainly because the numbers of patients are greater at earlier stages, and the belief that intervention is too late once patients reach dialysis [3-6].

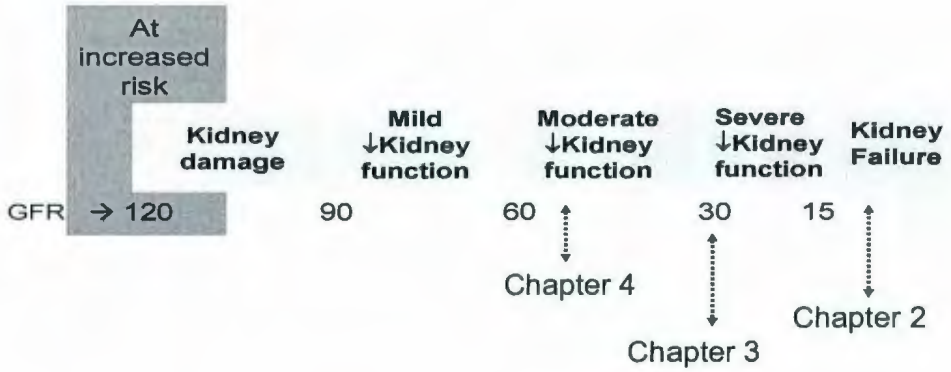
The term Chronic Kidney Disease (CKD) attempts to encompass many disorders pertaining to the kidney. It includes mild disorders, such as kidney stones, to loss of so much kidney function (usually estimated by measuring creatinine in a patient's serum) that dialysis is required to sustain life. Although some patients come to require dialysis because their kidneys fail quickly, most patients reach dialysis via CKD—especially related to diabetes or high blood pressure. However, having CKD does not necessarily indicate an inevitable progression. In fact, these patients also have a significant burden of comorbid disease and are more likely to die from cardiovascular disease before their kidney function deteriorates to the point where they require dialysis [7]. A challenge for health care providers is that CKD is mostly an asymptomatic disease whereby patients present for care at different points along the spectrum of kidney function level. Overall, the goal for better health care must focus on identification of CKD, slowing progression to dialysis and preventing co-morbidity and death.

The first step in improving care using evidence-informed medicine is documenting current practices and outcomes. This allows distinction between what aspects of care are being done well versus where improvement is needed. After problems are identified, hypotheses about how to address care gaps may be generated and subsequently tested. This thesis will focus on areas where CKD care can be further optimized, and highlight the potential role of multidisciplinary clinics.

The first chapter of this thesis will review the published data in relation to the above concerns. Having been written for this thesis, it was subsequently published as a book chapter [8]. This chapter will describe CKD as an important health problem, key goals of care, and the evidence on which these goals are founded. It will also describe the principles of chronic disease management and a model of integrated multidisciplinary team-based care focused on these goals. To complete the chapter, ongoing and future clinical trials are also reviewed.

Further chapters will consist of my work using data from Canadian studies in which I have been involved. This work has also been published [9-11] in peer reviewed journals. My specific roles in Chapter 2 was data interpretation and co-writing the manuscript while my specific roles in Chapters 3 and 4 were collaborating on the design of the study, data collection, data analysis and interpretation and co-writing the manuscript.

For the purposes of this thesis, these subsequent chapters are organized to examine CKD care at different stages along the disease course as follows (GFR denotes Glomerular Filtration Rate, an estimate of kidney function):



Before beginning to address any potential concerns it was important to document the then-current (1998-1999) clinical practice with respect to chronic kidney disease (CKD) care—the main questions were: is there a need for better care of CKD patients in Canada? What aspects of care have room for improvement? The main objective of Chapter 2 was to improve the understanding of the then-current Canadian nephrology practice. It focuses on whether patients are prepared for dialysis when they need to start, what are their metabolic parameters at initiation, and whether patients were referred to nephrologists beforehand. The findings presented in Chapter 2 indicate that patients commencing dialysis in Canada during that period appeared to do so in relative concordance with published guidelines with respect to timing of initiation. However, a

substantial number of patients commenced dialysis without previous care by a nephrologist and of those who were seen by nephrologists, clinical and laboratory parameters were suboptimal according to guidelines at the time. Thus, this survey served as an important baseline for future study and comparisons.

Chapter 3 examines whether multidisciplinary clinics might have a role in care for patients with CKD by evaluating the outcomes of patients exposed to formalized multi-disciplinary clinic (MDC) programs versus standard nephrologist care. The hypothesis is that MDC programs are able to better care for CKD patients prior to dialysis leading to better survival and metabolic parameters. The study findings indicate that despite prolonged exposure to nephrology care prior to dialysis, there appears to be an association of better survival following initiation of dialysis between those exposed to pre-dialysis formalized multidisciplinary clinic care. Thus, the data suggest that knowledge of a patient's status at the time of dialysis start can be important for predicting future clinical outcomes. To address this, the Canadian Care Prior to Dialysis (Can-Care) study was designed [11].

Chapter 4 discusses prospectively collected data on care earlier on in the course of CKD. It uses data from the Can-Care study and describes 1) characteristics of patients at first nephrology encounter for CKD in Canada, 2) the evaluation for cardiac risk factors, cardiac diseases and CKD complications and their management prior to the encounter, 3) changes in management initiated by nephrologists at first encounter, and 4) the availability and use of allied health professional services for CKD care. These data help

to identify opportunities for improvement in CKD care both before and after involvement of nephrologists. The study findings indicate that, in general, Canadian nephrologists tend to encounter CKD patients referred at a late stage in the disease (Stage IV CKD), and information on prior evaluation by other physicians is incompletely transmitted to the nephrologists. In addition, there appears to be room for improvement in the evaluation and treatment by nephrologists at the first nephrology encounter.

A final note—I have decided to leave the previously published papers intact within their respective chapters. This means that the conclusions for each paper remain at the end of each chapter (versus placing them all at the end of the thesis). The final chapter will summarize what has been discussed.

Chapter 1: Review - The Role of the Chronic Kidney Disease Clinic

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1.1 Introduction

The purpose of this chapter is to outline the structure and function of a clinic-based approach for the comprehensive care of patients with chronic kidney disease (CKD) and describe some of the potential utilities of such a clinic. The described structure and function may serve as a template for the future development of such clinics. To ensure a context for such a clinic, the evidence and rationale supporting this concept is reviewed. Unlike the paradigm for care of those with diabetes [12, 13], or more recently for heart failure [14-18], the role of a clinic facilitating the care of patients with CKD has not been as clearly defined. Thus, data to support the concept and implementation are relatively scant, much being drawn from logical arguments as well as from experience with other chronic diseases.

Kidney Disease Is an Important Health Care Concern

The burden of disease and the growing population of patients with end-stage renal disease (ESRD) remain exceedingly high. In the United States a diagnosis of ESRD may impart more lost life years than prostate or colorectal cancer [1]. As of 2001 in the United States, there were over 290,000 patients on dialysis and over 15,000 patients with kidney transplants [2]. Population studies such as the NHANES III cross-sectional survey of 29,000 persons revealed that 3% of people over age 17 had elevated creatinine

[19]. It is estimated that by 2030, the number of patients with ESRD may reach 2.24 million [2]. Furthermore, the direct cost of caring for a patient on dialysis can cost over $50,000 (U.S.) annually [20, 21].

Kidney Disease Is Largely Due to Chronic Disease

In North America CKD is largely due to diabetes and hypertension [2], both relatively easy to identify and treat with evidence-based interventions. The NHANES III survey, for example, showed that an elevated creatinine was more common in people with hypertension [19]. Furthermore, clinical trials and prospective cohort studies have identified risk factors associated with accelerated loss of kidney function. In patients with CKD secondary to diabetic, glomerular and hypertensive/vascular diseases, the strongest predictors of more rapid progression are hypertension, especially systolic [22-30], and the degree and/or persistence of proteinuria [31-34].

Historically, the focus of nephrology delivered CKD care was to coordinate placement of vascular access, to attend to uremic symptoms and complications, and to provide dialysis. However, the focus has changed; not only is it increasingly recognized that the majority of patients with CKD do not progress to ESRD due to varying rates of progression [27, 33] and competing risks for death [7], but also conditions associated with CKD itself, such as anemia and malnutrition, impart significant morbidity. Moreover, there is now a greater appreciation of the epidemiology of the disease, which has led clinicians to understand that the major competing risk for dialysis therapy was death from cardiovascular disease (CVD). Evidence has accumulated regarding the need for more

proactive care and institution of strategies to delay progression. Thus, the focus of CKD care has broadened to include CVD risk reduction, in addition to or concomitant with, reducing the progression kidney decline [35]. As our understanding has grown of the pathophysiology of kidney disease, and CVD within the CKD population, it has become clearer that the treatment and care options are increasingly complex. In addition, it was logical that identification and intervention in the population with earlier stages of CKD would provide the greatest opportunity to reduce morbidity and mortality.

Goals of Therapy

The goals of therapy (figure 1.1) are to (1) delay progression of CKD, (2) delay / treat known CVD comorbidities, (3) manage uremic complications (such as anemia, mineral metabolism, nutrition, blood pressure), (4) ensure dialysis modality choice and timely placement of access for dialysis or assessment for possible transplant, and (5) initiate timely kidney replacement therapy, including preemptive transplantation where feasible. Each of these goals requires education of patients and caregivers, as well as communication between them, and co-management by different caregivers within medicine, including allied health professionals. With the one aim to maintain health, it is essential that the structure of the clinic reflect all goals and the demand for communication and investigation, to ensure success.

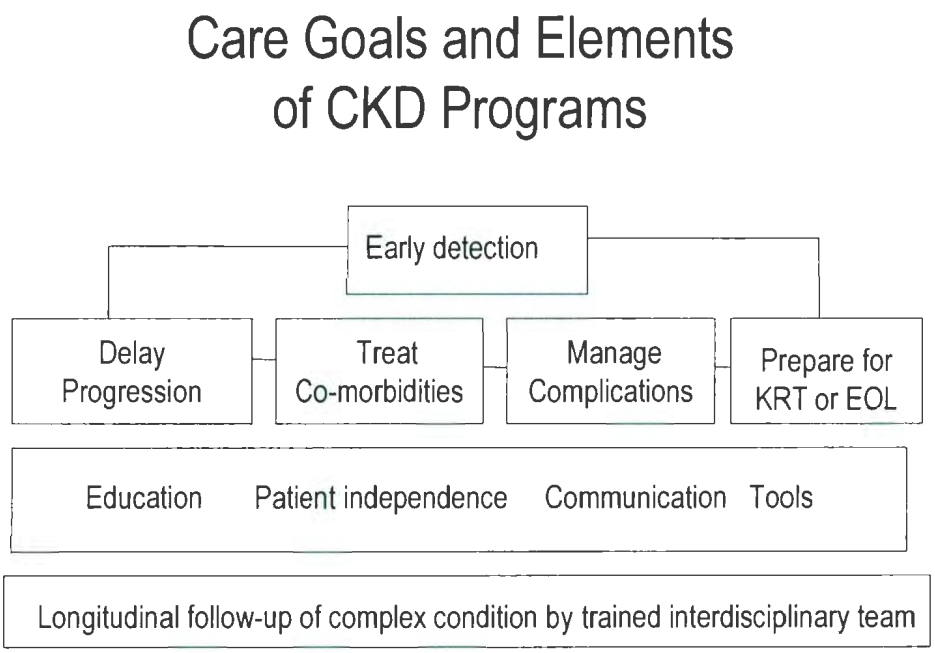

Figure 1.1 Care goals and Elements of CKD Programs. EOL, End of Life. KRT, Kidney Replacement Therapy

Staging and Terminology for CKD and Impact on Need for Coordinated Care

In 2002 the National Kidney Foundation sponsored Kidney Disease Outcomes Quality Initiative (K/DOQI) published guidelines targeting earlier evaluation and intervention in patients with CKD [36]. Using evidence-based review, the cornerstone of the working group was the establishment of five stages of kidney disease (Table 1.1). Importantly, the classification system focused on estimated glomerular filtration rate (GFR) rather then serum creatinine levels alone, because use of serum creatinine alone may lead to overestimation or underestimation of kidney function in those with low (i.e., elderly, women) or high (i.e., muscular males, blacks) muscle mass, respectively. The new

system based the classification not only on severity of kidney function decline, but also on the presence of conditions associated with the kidney disease, such as proteinuria and hypertension. In attempting to clarify the historic terms, which are confusing and sometimes misleading (pre-dialysis, progressive renal disease, progressive renal insufficiency), this new definition and classification system is an important tool, which aids in the understanding of CKD and will help standardize its definition. A universal language or terminology will facilitate knowledge acquisition by the medical community, patients, and public bodies and improve research clarity and applicability.

Staging of Chronic Kidney Disease

Stage	GFR (ml/min/1.73 m^2)	Description
1	> 90	Kidney Damage With Normal or ↑ GFR
2	60 - 89	Kidney Damage With Mild ↓ GFR
3	30 - 59	Moderate ↓ GFR
4	15 - 29	Severe ↓ GFR
5	< 15 or (or dialysis)	Kidney Failure

Table 1.1 Five Stages of Chronic Kidney Disease [36]

The estimates of populations with CKD that were generated from the new classification system, and the NHANES population database, have helped identify the large burden of CKD that potentially exists in the community. The focus on earlier identification will

result in increased referrals for diagnosis, care, and follow-up that will overwhelm current nephrology resources, thus the need to create the appropriately structured care delivery systems described herein and to educate other health care providers in CKD care.

Referral

Late referral to nephrology has been recognized as a problem for many years, because it is associated with increased cost [5, 37-39]. Published recommendations emphasize timely referral to maximize potential gains from involvement of specialized nephrology teams [40]. The appropriate time for referral to a nephrologist is debatable for many reasons, including: (1) other physicians should be capable to manage earlier stages of CKD, (2) estimated high numbers of patients overwhelm current nephrology resources, and (3) many patients with early stages of CKD may not progress. Nonetheless, a minimum recommendation would be for referral at GFR levels of less that 60 mL/min/1.73 m^2 if the primary caregiver cannot identify the cause of the disease or requires help in the management of the disease. All patients with GFR less than 30mL/min/1.73 m^2 should be seen by a nephrology team in order to ensure adequate psychological and clinical preparation for kidney replacement therapy [40, 41], unless the patient is of an age or has a condition that leads them to not consider chronic dialysis. The new CKD staging system focused on GFR estimation should reduce some of the problems of late referral due to misinterpretation of serum creatinine values.

1.2 Overview of CKD Clinic

Philosophic Basis

Clinics for the care of CKD should be based on the fundamental principle of ensuring the delivery of longitudinal, complex care to a large diverse group of individuals. This requires that the structure of the clinic and services offered optimize communication within and between individuals, including the patient and other physicians and medical teams.

Role of Multidisciplinary Clinics

The importance of early referral to nephrologists is not disputed [40], because identification of the myriad of abnormalities and plans for their treatment may be best achieved in consultation with a specialist. However, the ability of nephrologists "alone" to attend to the multiple and complex aspects of care in this patient group is debated [42]. As chapter 2 will show, a multicenter cohort of patients starting dialysis demonstrated that even those patients known to nephrologists for greater than 3 months have suboptimal care. In this study, one third did not have permanent access ready for dialysis initiation, mean hemoglobin was 94 g/L, and mean albumin was below 34 g/L [9]. In another multicenter study of patients with CKD followed by a nephrologist, the majority of patients had blood pressure over recommended targets, and only 50% were taking angiotensin converting enzyme (ACE) inhibitors [43]. While there are undoubtedly patient and compliance factors that explain why patients with CKD under the care of nephrologists do not have optimal care, it is also probable that patients were not provided the appropriate elements of care. It is important to note, however, that it was these

studies and others that contributed to the recognition of the importance of CKD care and lack of attention to it.

Given the multiplicity of goals of CKD care, the complexity of treatment options, and educational needs, it is clear that a team of individuals will be required. Treatment targets, such as blood pressure, may be reached by involving expert nurses, pharmacist, or other members of the team in conjunction with the physician [44]. Thus, a team approach with well-defined roles, responsibilities, and objectives appears to be both logical and practical. Improved patient care and outcomes due to a multidisciplinary team clinic have been demonstrated in disciplines such as diabetology [12, 13, 45], cardiology [14-16, 18, 46], rheumatology [47-49], and oncology [50]. Similarly, compared to standard care by a nephrologist alone, there is evidence of benefit of a multidisciplinary care (MDC) team approach in the care of patients with CKD [51-53]. It appears that outcomes can be improved with protocol-based blood work, clinic visits, and education. This requires involvement of a patient educator, dietitian, social worker, and physician.

There have been few randomized, controlled trials of case management in CKD. The first, published by Harris and associates [54] did not show a benefit to case management in CKD. However, the intervention in that study was limited to written suggestions made to primary care physicians and the assigned clinic patients did not receive any specific treatment for anemia, mineral metabolism, or preparation for dialysis / transplant. Failure to show a benefit in the Harris study may well have been due to the failure of individual

primary care physicians (PCP) to implement the recommendations from the clinic. Given that PCPs are inundated with protocols and guidelines for the management of numerous chronic conditions, it is unrealistic to expect them to be able to fully attend to the many complex issues of advancing CKD.

A more recent Australian randomized control trial [55] compared a physician-supervised, nurse driven multiple risk factor intervention clinic with conventional care. The clinic focused on dyslipidemia, hyperhomocysteinemia, hypertension, anemia and hyperphosphatemia control in patients with stage 4 or 5 CKD. Although the study did not show improvements in the primary outcome measures, atheroma burden (via carotid initmamedia thickness) and endothelial function (via brachial artery reactivity), the intervention group showed significant improvements in serum lipid and blood pressure control.

Structure and Definition of Multidisciplinary Clinics

These definitions help to clarify the various possible variants of a multidisciplinary team. It allows the determination of what type of resources are currently available and may help in the interpretation of clinical studies so that similar types of clinics can be compared. Clinic structures can be categorized as follows with respect to multidisciplinary teams:

Formal Multidisciplinary Team: Nurses, nurse educators, dietitians, social workers, and physicians allied in a formal relationship, who interact with the patient and each other defines a multidisciplinary team. Although it is recognized that there are a number of different configurations due to funding and local health care system issues, for the

purpose of definition, this team is readily identifiable as dedicated (part time or full time) to CKD care, and may or may not have team rounds or meetings to discuss patient care.

Informal Multidisciplinary Resources: Nurses, social workers, dietitians, and physicians associated with the kidney team to whom patients are referred may constitute informal resources. In such a schema, patient access is dependent on individual patient needs, and the group of individuals may or may not interact as a team or be necessarily dedicated to the longitudinal follow-up of patients. Each team member is able to interact with the patient on a regular basis as necessary, but no coordination with other team members is inherent to its structure.

No Multidisciplinary Team: Nurses, social workers, and dietitians may or may not be available to the patient. There is no team structure or function.

1.3 Key Goals of CKD Care

The following section describes the key goals of comprehensive CKD care, citing evidentiary basis as appropriate for the described strategies. This includes diagnosis, education, delay of progression, identification and treatment of co-morbidities associated with CKD and of complications of CKD. As well, the institution of primary prevention strategies, including vaccination programs and the preparation of patients for renal replacement therapy as appropriate, will be discussed. The goals described are comprehensive and complex, thus the need for a protocolized structured delivery system, such as a formal clinic.

Diagnosis

The first goal of the nephrology clinic medical staff should be to attempt to establish or confirm a diagnosis and to determine the rate of progression of kidney disease. The nephrologist should ensure that appropriate tests have been undertaken to establish a diagnosis. Kidney biopsy or imaging may be helpful [40], especially to rule out any potentially treatable or reversible etiologies such as rapidly progressive glomerulonephritis or obstruction. In early visits, reversible causes of kidney disease should be sought, even if a chronic etiology is suspected, especially if there has been a rapid decline in kidney function. In addition to diagnostic tests, review of current medications to ensure the absence of nephrotoxic medications is prudent. Further workup includes a review of family history and a search for systemic disease, including diabetes, vascular disease, connective tissue disorders, infections, and malignancy. Several contributory factors may coexist. The extent of comorbidities, especially the commonly associated vascular diseases [56] should be continually assessed. Although established kidney disease may progress even if the original cause is removed [57], similar interventions that can slow loss of kidney function may prevent cardiovascular complications. Potentially harmful interventions, such as iodinated intravenous contrast dye, must be reviewed with the patient so that educated decisions may be made regarding their use.

Education

Patient education and awareness are an integral component of the clinic. Education is important from a decision-making perspective as well as to alleviate fear and psychological suffering. Educated patients are more likely to take an active part in their care, with better outcomes noted in other chronic diseases [58-60]. Ideally, involvement of family members or other support network individuals should be encouraged. The clinic environment can provide a set of resources as well as sessions related to patient education. Minimal education should include the following, presented at the appropriate stages of CKD:

- Explanation of normal kidney function, blood pressure, and laboratory test results and their significance.
- Explanation of specific disease conditions, symptoms, and complications of CKD.
- Dietary teaching and diabetes education, if appropriate.
- Ensuring that patient understanding of medications is adequate.
- Discussions about vein preservation (blood taking and blood pressure)
- Erythropoietin hormone therapy teaching, including: importance of anemia and its treatment; ensure patient understanding of dose changes; warning of the side effects of iron therapy; self-administration or local administration by PCP or community nurse; and provision of educational materials to PCP.
- Discussion of choices for treating ESRD, including conservative therapy, hemodialysis, peritoneal dialysis, and transplant.

- The education effort can be augmented with pamphlets or video materials. Using the principles of adult learning, regular reinforcement of the key messages should be incorporated into the education program.

Delay of Progression

The cornerstone of CKD care is to delay progression of kidney disease and, thereby reduce complications related to kidney failure. The evidence is relatively consistent in citing that interruption of the renin-angiotensin system (RAS) is a key component to delaying progression. Control of hypertension and reduction of proteinuria are important consequences of RAS interruption and are described more fully later.

Hypertension Treatment

Blood pressure should be based on the average of two or more seated readings on each of two or more office visits [61]. There is substantial evidence to support the optimal and target blood pressure of less than 130/80 mmHg in patients with established kidney disease, as suggested in the guidelines of the Seventh Joint National Committee for Prevention, Detection, Evaluation and Treatment of High Blood Pressure [27, 61-64]. The goals are to reduce the rate of decline of kidney function [65-67] and decrease cardiovascular events and mortality. The recommended target blood pressure for patients with proteinuria greater than 1 g/day is less than 125/75 mmHg [64]. This is based on evidence of slower progression of kidney failure at this level of blood pressure in a large randomized trial, which showed the greatest gain in those with the most proteinuria [27, 28]. Patients with kidney disease often need between three and four different

medications in addition to lifestyle modification in order to achieve this goal [66]. ACE inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, and diuretics are key drug classes for achieving blood pressure control [27, 68-70].

Proteinuria Reduction

Patients with CKD and persistent proteinuria of greater than 3 g/day may progress to requiring dialysis or transplant within 2 years [22, 71, 72]. A number of large, randomized, controlled trials demonstrated the efficacy of ACE inhibitors in slowing progression of kidney disease, reducing proteinuria, and also in regressing left ventricular hypertrophy [73-79]. As some of these trials were placebo-controlled, it is difficult to be sure that the benefit was drug specific and not just due to blood pressure lowering. Nevertheless, follow-up studies suggest that long-term ACE inhibition, as a component of blood pressure therapy, can be associated with stabilization and even improvement of kidney function [79]. Prophylactic use can also be justified in type II diabetes, because ACE inhibition preserved kidney function for over 6 years in normotensive type II diabetics without microalbuminuria [80]. More recently, the use of angiotensin receptor blockers (ARB) have been shown to reduce the time to doubling of serum creatinine, reduction of proteinuria, and time to dialysis [68, 69, 81]. All of these recent studies have been preformed in diabetics. Mann and associates have demonstrated the utility of ACE inhibitor use in patients with established CVD, diabetes plus one risk factor and kidney disease, in a subanalysis of HOPE [82]. More recently, a trial demonstrated that dual blockade of the renin-angiotensin system with both an angiotensin-converting enzyme inhibitor and an angiotensin–II receptor blocker (vs. monotherapy and placebo) may offer

additional renal and cardiovascular protection in type II diabetic patients with diabetic nephropathy [81].

Management of Comorbidity: Secondary Prevention

Cardiovascular Disease

CKD is a risk factor for vascular events and death [83, 84]. Creatinine values as low as 130 to 150 μmol/L confer a threefold risk of death within 8 years [83]. Cardiovascular death is 25 times as common as death due to kidney failure in type II diabetics with microalbuminuria [85]. The prevalence of cardiomyopathy, symptomatic heart failure, and symptomatic ischemic heart disease is very high at dialysis initiation [86]. This suggests that the later stages of CKD are a state of high cardiac risk.

Reversible cardiac risk factors, identified in these earlier stages, persist following entry to dialysis. Left ventricular hypertrophy (LVH) occurs in the CKD population, and its prevalence is inversely related to the level of declining kidney function [87]. Anemia and hypertension are also risk factors for progressive LV growth [87]. In kidney transplant recipients, a model of CKD, hypertension is a risk factor for LV growth, de novo heart failure, and de novo ischemic heart disease [88-90]. In addition, anemia predisposes to de novo heart failure [90] while dyslipidemia and smoking are risk factors for ischemic heart disease [91].

The National Kidney Foundation convened a task force in 1997 to specifically examine the epidemic of CVD in chronic kidney disease [92]. With a focus on decreasing death

rates via strategies for prevention of disease, the task force considered whether strategies learned from the general population are applicable to patients with CKD. Recognized traditional risk factors identified in the general population include diabetes, hypertension, smoking, family history of coronary disease, male gender, older age, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, physical inactivity, menopause, and psychological stress (Table 1.2).

Risk Factors for Cardiovascular Disease

Traditional	Uremic
Diabetes	Hemodynamic overload
Hypertension	Anemia
History of smoking	Malnutrition
Family history of coronary disease	Hypoalbuminemia
Male gender	Inflammation
Older age	Prothrombotic factors
Dyslipidemia	Hyperhomocysteinemia
Proteinuria	Increased oxidative stress
Physical inactivity	Divalent ion abnormalities
Menopause	Vascular calcification
Psychological stress	Hyperparathyroidism

Progression of CKD

Table 1.2 Risk Factors for Cardiovascular Disease: As CKD progresses there is a parallel evolution of risk factors from traditional to those characteristic of chronic uremia.

As CKD progresses, additional risk factors related to chronic uremia also emerge. Excess cardiac risk may also be due to hemodynamic and metabolic perturbations, including fluid overload, anemia, malnutrition, hypoalbuminemia, inflammation,

dyslipidemia, prothrombotic factors, hyperhomocysteinemia, increased oxidative stress, divalent ion abnormalities, vascular calcification, and hyperparathyroidism [93, 94].

Patients with kidney failure therefore require assessment and therapy for vascular disease and associated risk factors. It should be noted that many risk factors for CVD are also associated with the risk of progression of chronic kidney failure [56]. Thus, risk factor reduction strategies used to prevent CVD in the general population can be applied to patients with CKD and may slow the progression of kidney disease as well [56]. It remains unclear whether a raised serum creatinine is a marker for more severe hypertension, diabetes mellitus, and vascular disease, which causes death, or a marker for some intrinsic property of kidney disease, which accelerates CVD. However, some factors thought to induce cardiac risk are more peculiar to kidney disease (anemia, hypoalbuminemia, dyslipidemia), and may be amenable to intervention.

Anemia

It has become increasingly evident that anemia is an important predictor of morbidity and mortality in the dialysis population [6, 95, 96]. It is associated with ischemic heart disease, left ventricular hypertrophy, and impaired quality of life [95-97]. Correction of anemia in CKD improves physical function, energy, cognitive function, and sexual function [95, 98-101].

Treatment of anemia with erythropoietin is effective. Studies are currently underway to determine whether early initiation of therapy among individuals with earlier stages of

CKD is effective in preventing CVD, decreasing progression of kidney disease, or improving QOL [96, 102, 103]. There is evidence to suggest that iron supplementation in early kidney disease is important to maintain erythropoiesis, and that erythropoietin therapy is needed to maintain hemoglobin levels. Specific targets for hemoglobin levels have not yet been determined, though levels between 100 and 125g/L are the current recommended guidelines [11, 95, 104, 105].

Mineral Metabolism

There is evidence to support the efficacy of calcium and/or vitamin D supplementation for treatment of hyperparathyroidism [106-109]. Recommendations regarding target values for patients with earlier stages of CKD have been extrapolated from those for patients with ESRD. An approach that attempts to prevent hyperparathyroidism and its associated long-term complications is suggested. Phosphate reduction using dietary restriction, and inexpensive phosphate binders / calcium supplementation in those who have evidence of elevated intact parathyroid hormone (iPTH), and low normal calcium levels is reasonable. Vitamin D analogues are useful for those in whom PTH remains elevated despite calcium supplementation and phosphate restriction. Physiologic release of hormones is pulsatile and thus, intermittent oral vitamin D therapy is recommended. Unfortunately, evidence for the effectiveness of therapeutic strategies and for specific target levels of each of the variables mentioned above is not available for earlier stages of CKD. Adherence to the principle of prevention, combined with early identification of calcium, phosphate, and PTH abnormalities at early stages of CKD, should lead to minimizing hyperplasia of the parathyroid glands and the attendant metabolic

derangements. Future studies will need to address long-term targets and therapeutic strategies.

Nutrition

Malnutrition is common in patients with later stages of CKD. There is a strong association between decreased albumin and worse nutritional status, and adverse outcomes [98, 110-112]. Even small decreases in albumin are associated with increased mortality. Unfortunately, albumin is a late index of malnutrition and is a negative acute phase reactant. Acidosis is also a contributor to protein breakdown and mineral metabolism aberrations. Thus, assessment of nutritional status generally requires the expertise of a dietitian.

Low protein diets have been extensively studied as a means to slow the progression of kidney disease, with mixed results. Meta-analyses and a large, randomized trial suggest that the impact may be slight [27, 113-115]. Optimal dietary protein intake is not clear [113], and there is a potential for protein malnutrition. Appropriate nutritional counseling to avoid malnutrition, acidosis, and phosphate excess is important. There are extensive guidelines for assessment of nutritional status and dietary management proposed by the National Kidney Foundation [116]. Ensuring adherence to a prescribed diet is difficult and requires frequent, continuous input from dietitians. This becomes especially important as the patient approaches ESRD, since worsening malnutrition may become the principal indication to initiate dialysis.

Management of Comorbidity: Primary Prevention

Primary prevention strategies are also important in the management of patients with CKD and may sometimes be overlooked due to the time-intensive management of conditions associated with uremia. Although it is not clear who should be mainly responsible for these issues (nephrologist versus family physician or other specialist), they will be discussed here because all these professionals can be part of the CKD patient's team, and the nephrologist may be able to input expertise for this specific population. Vaccinations, use of aspirin and lipid lowering agents and other CVD primary prevention strategies, as well as diabetes control, smoking cessation, and lifestyle modification are important. This section briefly touches on these strategies in CKD patients.

Vaccination

Hepatitis B infection remains a concern in dialysis populations, and current recommendations are to vaccinate if appropriate. In addition, there are recommendations to vaccinate patients with CKD against pneumococcal infection and influenza, which are common sources of morbidity in patients with chronic illnesses. Vaccination programs have been less successful among CKD patients compared to the general population, both in terms of implementation and response to vaccine. Reasons for poor response include malnutrition, uremia, and generalized immunosuppressive state of patients with CKD. However, variations in vaccination dose and dosing schedule to increase response rates in dialysis patients have been tried with reasonable success, which could be implemented among patients at all stages of CKD. In general, patients with higher GFR levels are

more likely to respond with seroconversion to hepatitis B and other vaccines [117]. This reinforces the need to identify CKD early and provide comprehensive care.

Aspirin

The use of low dose aspirin should be considered to reduce the risk of subsequent CVD in patients with coronary artery disease or in those who are at high risk of developing coronary disease [92], which include most patients with CKD. Recommendations to use aspirin should take into consideration the individual patient's risk of bleeding or other complications of aspirin. If there are contraindications to aspirin use, the use of other antiplatelet agents could be considered.

Dyslipidemia

There are no trials showing that treating dyslipidemia slows the progression of kidney disease. With respect to preventing cardiovascular disease in this population, post hoc analysis of the Cholesterol and Recurrent Events study [118] and the Anglo-Scandinavian Cardiac Outcomes Trial [119] suggested a benefit in patients mainly with stage 2 and 3 CKD. Regarding lipid targets, the Heart Protection Study suggested benefit in treating patients with coronary disease, other occlusive arterial disease, or diabetes largely irrespective of initial cholesterol concentrations [120]. Until ongoing trials such as the Study of Heart and Renal Protection [121] answer the question of treating lipids specifically in CKD patients, current guidelines recommend an aggressive approach to lipid abnormalities in diabetics and other high-risk patients, which would include those with CKD [63, 122]. Thus, best practice would suggest following the guidelines of the

National Cholesterol Education Program Adult Treatment Panel II for initial classification, treatment initiation, and target cholesterol levels for diet or drug therapy [123].

Diabetic Control

Optimal glycemic control in those patients with diabetes mellitus should be encouraged and facilitated with referral to a diabetes clinic if possible. Tight glucose control in both types I and II diabetes may prevent or stabilize the early stages of microvascular complications, including nephropathy [124, 125]. The impact seems to be sustainable for years [126]. However, diabetic control has not been shown to slow progression of advanced diabetic nephropathy. Furthermore, as kidney function deteriorated, diabetes management will require modification.

Lifestyle Modification

Smoking cessation is recommended for many reasons, including the possibility that it may slow loss of kidney function [127, 128]. Obesity, poor diet, and sedentary lifestyle contribute to diabetes, hypertension, and vascular disease. Current recommendations are thus to achieve and maintain an ideal body mass index and moderate level of physical activity for 30 minutes per day for most days of the week [92].

Rehabilitation

Cost of kidney disease from loss of work and associated loss of QOL is substantial. Strategies to enable patients to remain working or return to work should be in place [53, 129] and may involve referral to work retraining programs or occupational therapist, if available.

1.4 Preparation for Kidney Replacement Therapy

Preparation for kidney replacement therapy should be based on a good basic knowledge of kidney function, ideally a long process that begins well before the imminent need for initiation exists. Modality selection is done collaboratively with the team and the patients, with an attempt to ensure that patients maintain independent care status and choose modalities that foster such independence. The appropriate timing of initiation of dialysis remains unclear, but it is certain that it must be individualized and must be based generally on a combination of low GFR, patient symptoms, and other factors. Close follow-up of patients at the later stages of CKD, with objective assessment of global functioning, permits appropriate timing of dialysis initiation.

Modality Selection and Access Placement

Modality selection is a decision for the informed patient. It is unknown whether peritoneal dialysis or hemodialysis imparts a survival advantage over the other, as neither randomized trials have been done nor is one feasible in the future. Transplantation is a medically and economically superior treatment [130] for kidney replacement therapy and is associated with higher quality of life. At any given time approximately 50% to 60% of

patients receiving dialysis are eligible for transplantation, but estimates are not available for those with earlier stages of CKD. Not all patients are eligible for transplantation, such as those with severe underlying illness. Preemptive transplantation, that is, before the need for dialysis, is generally possible for only those with an available live donor. In the United States, approximately 30% of transplants are from living donors, and a fifth of these are unrelated to the recipient.

It is clear that for some people, contraindications to one of the modalities may exist; for example, extensive prior abdominal surgery may negate the possibility of peritoneal dialysis. Importantly, the patient's desire to undertake chronic dialysis must be closely explored, because there may be some with serious underlying illnesses who choose to not undertake renal replacement therapy.

The option for kidney replacement therapy need to be reviewed with the patient, and access should be planned appropriately, if needed. The reality of how long it takes to decide on modality, get access placed, and let access mature should be stressed to patients, as should the possibility that the first access may not work. A perspective on the relative amount of time required to prepare for each of the options, including transplantation, should be provided. It should also be stressed that the presence of a working access (such as a functioning fistula) does not mean the patient has to start dialysis any earlier. A functioning, albeit unused, access only ensures that additional procedures, such as placement of a temporary catheter, might be avoided.

Lack of preparation for dialysis increases morbidity and cost [131-133]. Cost and morbidity implications of temporary catheter access are extensive. They include the cost of catheters, insertion fees, radiology tests, and costs associated with complications such as infection and thrombosis, as well as the pain, discomfort, and time of the patient.

Planning for kidney replacement therapy should begin at least 6 months in advance of anticipated start. According to published guidelines [134], access should be created at GFR of approximately 20 to 25 mL/min in those who are anticipated to progress and who do not have reasonable chance for a preemptive transplant. Reasons for lack of access at dialysis start may include patient factors such as denial of inevitable dialysis, being too sick to undergo permanent access procedures, or late decision to undertake chronic dialysis. However, this may also reflect the CKD team's inability to predict dialysis start, lack of resources, or poor planning. Late recognition of CKD and late referral to nephrology contribute to the problem. In consultation with the patients and the clinic team, optimal timing around education, decision making, and access creation should be undertaken.

Timely Initiation

When to initiate dialysis is a complex decision that involves the consideration of many variables. There are some easily identified absolute indications for initiation [135], however, debate exists with respect to 'timely" dialysis when these indicators are not so apparent. Indeed, since the 1970's Bonomini has argued for initiation of dialysis before clinically significant markers of uremia appear. His studies suggested a positive

association between residual kidney function at dialysis initiation and clinical outcomes [111, 136-139]. Unfortunately, lead-time bias, patient selection, or referral bias may favor outcomes in the population of patients starting "timely" dialysis. Further complicating the issue is the lack of a tool to define where a patient is on the time-line of CKD, for both planning and comparison of study results. To date, there is no solid evidence regarding how "early" dialysis should be started for optimizing patient outcomes.

Presently, two main indices for initiating dialysis for the treatment of kidney failure following progression of CKD are: (1) low GFR and (2) symptoms or signs of uremia, or evidence of malnutrition [140]. Despite the lack of firm evidence, the National Kidney Foundation guidelines, first published in 1997 and updated in 2000, recommend that patients should begin dialysis when the GFR falls below 10.5 mL/min/1.73m^2 (approximately a Kt/V urea of 2.0), unless edema-free body weight is stable or increased, the normalized protein nitrogen appearance (nPNA) rate is greater then or equal to 0.8 gm/kg/day, and there are no clinical signs or symptoms of uremia. More recently, the Canadian Society of Nephrology has recommended that dialysis should be initiated when the GFR is less than 12 mL/min if evidence of uremia or malnutrition (nPNA < 0.8 g/kg/day, or clinical evidence of malnutrition) exists. Despite these and other guidelines, when to initiate dialysis remains debatable. Overall, the key factor is to avoid commencing dialysis when the patient is so ill that education opportunities and the chances for maintaining independence are impaired.

Hemodialysis

The goal is a non-traumatic start to hemodialysis care, and the CKD clinic staff should ensure the appropriate commencement of dialysis, including ensuring that patients have appropriate vascular access and are oriented to the hemodialysis unit. Schedules should be coordinated with appropriate team members in the hemodialysis unit, family members, and other medical professionals. The CKD clinic should send initial dialysis orders and transfer summaries to the hemodialysis unit.

Peritoneal Dialysis

Patients should be oriented to the peritoneal dialysis unit and staff. The role of the CKD clinic in organizing peritoneal dialysis catheter placement will vary from center to center. However, the timing, placement, and preliminary education should be done in concert with the peritoneal dialysis team. As in hemodialysis, specific orders and transfer summaries should be sent to the peritoneal dialysis unit and the training / initiating schedule coordinated with appropriate team members, family members, and other health professionals.

Transplant

As part of the educational process early in the course of CKD, the concepts of transplantation and living donation should be explored with patients and families. The CKD clinic working closely with the transplant assessment team can help determine eligibility for a transplant. Furthermore, a CKD clinic can facilitate preemptive

transplantation, which is generally only possible if the patient with CKD has an available living donor.

Conservative Care

Not all patients will desire or benefit from kidney replacement therapy; longer-term education, longer follow-up time, and an established relationship with CKD team members will facilitate making this choice. In these cases, the CKD clinic staff may be the first to be aware of the wishes of the patients and families, and other caregivers should be informed of these decisions. Once such a decision is made, end-of-life wishes should be formalized, in particular extent of resuscitation attempts, with appropriate consent and documentation. Resources to ensure appropriate supportive care short of dialysis should be mobilized, because much can be done to maintain a patient who chooses to not undertake chronic dialysis. The patient should have referral for home care and for palliative care when appropriate. Patients may benefit from remaining in the care of the CKD team as plans of care may require revision or the patient may change his mind.

1.5 Clinic Logistics

Services

The CKD clinic would presumably exist within a health care system and society where the common goal is the health of the patients. Comprehensive care delivered in only one location is presumed to be beneficial. The frequency with which any individual patient accesses care is determined by the specific circumstances of the medical system, the other

physicians involved in patient care, additional comorbid conditions, as well as the specific stage of disease. The clinic should provide a wide range of services for patients with kidney disease, and their physicians, with the overall goals of:

1. Ensuring patient and family understanding of kidney disease.
2. Ensuring understanding of health care system / hospital and outpatient systems and services available to kidney patients.
3. Identifying potential issues related to long-term patient management.
4. Facilitating longitudinal and parallel care of patients with CKD.

Key Components of the Clinic

The clinic should ideally be an outpatient facility providing easy access to all facilities and personnel in one location. This permits familiarity with team members and access to ancillary services as needed. If also located in proximity to the hospital or dialysis center, it provides familiarity with the respective hospital services and locations. Non-English patients should have interpreters provided and booked for entire duration of the clinic visit. It helps if interpreters are able to return with specific patients to facilitate continuity. An information package should be available and given out at the first visit, including an introduction to how the clinic works and various educational materials, including goals and expectations. Patients and families should also have an introduction to team members, and explanation of roles of responsibilities. Finally, the clinic should facilitate peer support for patients with CKD.

In addition to ongoing assessment of patient by the team through regular clinic visits, weekly multidisciplinary rounds should be organized to facilitate communication and develop or adjust plan of care. This will allow for comprehensive follow-up by nurses, clerical staff, and others and facilitate:

- Bookings for tests (Ultrasound, CT Scans, etc.) and referrals to other specialists
- Medication changes / tolerance, etc.
- Reminders for appointments/blood work.
- Follow-up of test results.
- Liaison with laboratories and pharmacies.
- Liaison with GP and other consultants, including palliative care team (in hospital or community).
- Patients should receive education about kidney or kidney / pancreas transplant and screening for potential donors and referrals as appropriate.

Individual Roles

In order for any team to function, definition and clarification of roles of the individuals involved are important. Below are listed key roles and responsibilities for each of the key staff deemed important in the delivery of CKD care. The specifics may vary depending on local issues, but the principal roles need to be clearly defined.

Nurse

The CKD nurses function as case managers and facilitate care of patients, directly and through physician and team member liaison. Nursing support should be available 5 days

a week by telephone or in person to triage medical concerns, answer questions, and provide education or emotional support and referral to other team members or community resources. This should allow for ongoing collaboration and reevaluation with the patient, and facilitate changes in care plan with input from team members. A regular review of symptoms, medications, and monitoring of lab work results should occur, again responding to critical values by notifying physician, patient, and dietitian as necessary. The nurse should be able to liaise with family physicians, consultants, and other chronic disease clinics (e.g., diabetes, health heart, heart function clinic).

Nurses should be able to implement protocols such as hepatitis screening and vaccination program or peri-angiogram protocols. Similarly, they should be able to arrange treatment and procedures such as intravenous iron and transfusions or arrange referral for dialysis access and follow-up care. If patients progress to kidney failure, then the nurse should ensure coordination of initiation of dialysis or referral for transplantation and transfer of relevant data to dialysis or transplant facility. Finally, they should coordinate services in remote setting for the convenience of patients.

Dietitian

Patients should receive individualized diet education and counseling regarding CKD, diabetes, and heart disease, from a dietitian knowledgeable about the nutritional abnormalities of CKD. The dietitian should review diet history, habits and nutritional health, and advise patient about food choices and meal ideas. There should be a periodic dietary review, including blood work, to help reach goals and to avoid malnutrition.

Social Worker

Social workers may provide assistance with emotional and practical concerns of patients and their families, and assess emotional needs or potential issues that may arise, such as acceptance of kidney failure and end-of-life issues. The social worker should have a mechanism to liaise with psychiatry as needed. They also advocate on the patient's behalf to ensure maximum allowable benefit from available resources such as home support, financial assistance, employment / retraining, and housing, and may need to assist the patient with insurance issues, including referral to institutional financial counselors.

Pharmacist

If possible, pharmacy services should be available for initial medication review and follow-up. They may advise about medication costs, pill burden, and possible interactions. They may also provide education and support as needed.

Clerical or Administrative Support

Clinics should have a dedicated unit coordinator / clerical support worker. Their main role is to ensure that data and patient charts are maintained accurately. A paper / electronic chart should be established with complete information available and maintained with ongoing follow-up data. This will include data such as laboratory results, medications, and comorbidities. The coordinator is an essential component of the team as the organization of booking and coordinating appointments with other clinics,

consultants, diagnostics, and community resources and follow-up is essential. Additionally, they are integral for information and chart transfer to programs within the kidney programs such as dialysis or transplant clinic. They may also triage patient concerns with the team and have appointment reminders for patients. Finally, they should identify interpreter requests and book interpreters as needed.

CKD Clinic Role in Longitudinal Care: Different Stages of CKD

Given the current estimates of the CKD population (between 10 and 20 million in the United States), it is unlikely that the optimal resources described in this chapter are available to all patients with CKD. It is still debated whether a nephrologist must see all patients will early CKD, as it is not clear who will and will not progress. Although there is consensus that nephrologists and teams need to see the patients at least 6 months, and ideally 12 months, prior to dialysis start for access, there remains skepticism regarding the utility of nephrology input prior to that time.

Although much has been learned about care of patients close to initiating dialysis, it is not known how to optimally care for patients in early CKD (frequency of visits, frequency of blood work, when to initiate "early" drug therapy, etc.). It seems reasonable that a "phased" approach is applicable. As outlined, the focus of the clinic must be adjustable from early disease detection and risk factor modification to preparing for kidney replacement therapy. Key at all phases would be communication and education between patients, medical caregivers, and allied health teams (figure 1.2).

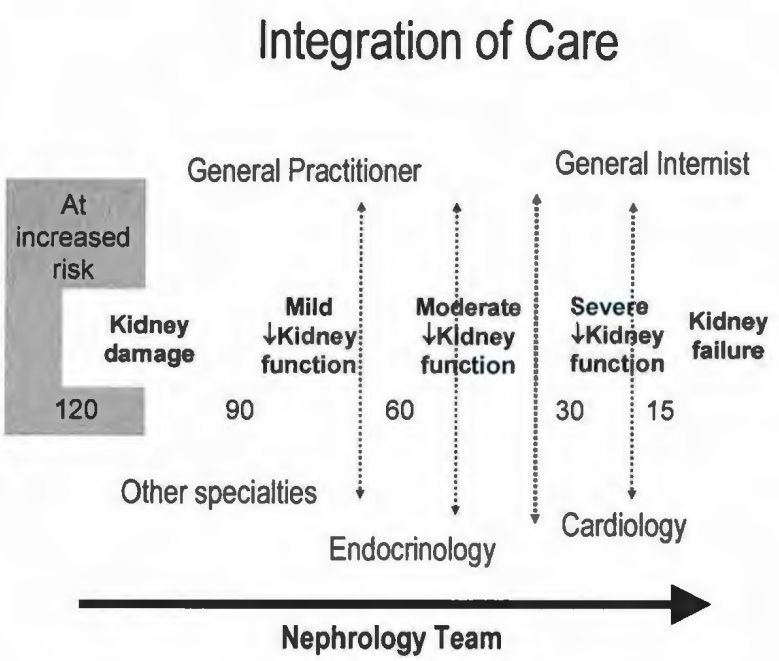

Figure 1.2 Integration of care over the progression of CKD (Longitudinal Care) and between other caregivers (Parallel Care).

One end of the spectrum is an early referral (stage I or II) and a broad plan outlined to another caregiver about goals of treatment of that caregiver to follow. Patients could be familiarized with the clinic and kidney disease at this initial period and then referred back to the clinic if the kidney function deteriorates, for further education and refinement of management plan. Both the patient and the other caregiver are informed that the clinic is available when needed for either informal consultation or formal evaluation. The other end of the spectrum is for the clinic to assume most of the care, if not all, surrounding issues pertaining to kidney disease and other issues such as diabetes management. In between, the clinic could do a formal initial evaluation and then arrange follow-up once

every year or so. To date there are no studies that have systematically evaluated the impact of different methods of care at earlier stages of CKD, though a number of trials are being planned.

CKD Clinic Role in Parallel Care: Integrating with Other Caregivers

An important issue in dealing with individual patients who are obtaining care in parallel locations (i.e., family physicians, diabetic services, and CKD clinic) is communication. The clinic should be viewed as a resource to both patients and parallel caregivers such as family and other physicians, and as such, could integrate care with other caregivers. For example, other caregivers could call to seek advice regarding safety of medications, and the clinic can serve as a facility to follow the patients during acute events (e.g., increased creatinine around diarrhea and temporarily holding the ACE inhibitor). It is vital for such a clinic to communicate information about patient status, medications, plans, and so forth, not only to the patient but to all other caregivers involved (family physicians, diabetes clinic).

When patients are accessing different care systems due to the complex nature of their disease or due to practical issues such as locale, it is not so clear how to determine the responsibility of each of the individual medical practitioners. Should the CKD clinic assume the ACE inhibitor is being managed by the heart failure clinic? Or does the CKD clinic assume the diabetes clinic is managing the blood sugar control or counseling about smoking cessation? At what point in the stage of CKD does the CKD clinic take a more active role? These are not questions that will be answered in clinical trials, so practical

solutions to the issue of responsibility for care implementation will need to be developed. The key issue is the communication between different physician groups and medical teams and customization to individual patient and health care system particulars. There is an accumulating body of literature that suggests involvement of the patient in all implementation plans, and knowledge of and active involvement in therapy targets and test results improve the ability of physicians to implement care strategies [58-60].

Other Benefits of the CKD Clinic and Organized Protocolized Care

The key to the care of patients with chronic disease is acknowledgement of the complexity of the conditions(s) and the need for longitudinal follow-up by a well-trained team. As in oncology, rheumatology, and other areas of medicine, the care of CKD patients requires some adoption of protocols for investigations, therapy, and follow-up (figure 1.3 and Table 1.3). In so doing, we will be able to develop sensible strategies bases on data, and management of selected conditions will be uniformly undertaken. The systematic evaluation and management of patients with chronic diseases has been demonstrated to reduce resource utilization and to enhance patient compliance.

Minimum follow-up / bloodwork intervals as a function of kidney function

Creatinine Clearance (mL/min)	Interval between visits / bloodwork	
	Diabetics	Non-diabetics
31-60	3 months	3 months
15-30	2 months	3 months
10-14	1 month	2 months
<10	1 month	1 month

Table 1.3 Example of a Protocol for Follow-up / Blood Work Intervals. Maximum intervals (or minimum frequency) between visits are given for stable patients. Shorter intervals may be necessary at discretion of physician or specialized nurse in less stable patients or be specified in therapy titration algorithms (e.g. initiation of erythropoietin replacement therapy).

The additional advantages to the clinic models for the care of CKD include the ability to optimize all aspects of care by using individual team member's expertise more appropriately and to optimize follow-up and monitoring of large groups of patients in one area. Furthermore, a clinic-based approach would allow database development and evaluation of outcomes in large cohorts of patients, the ability to enroll patients in clinical

trials, and importantly, the adoption of newer proven therapies may be easier in a clinic setting than in individual physician offices.

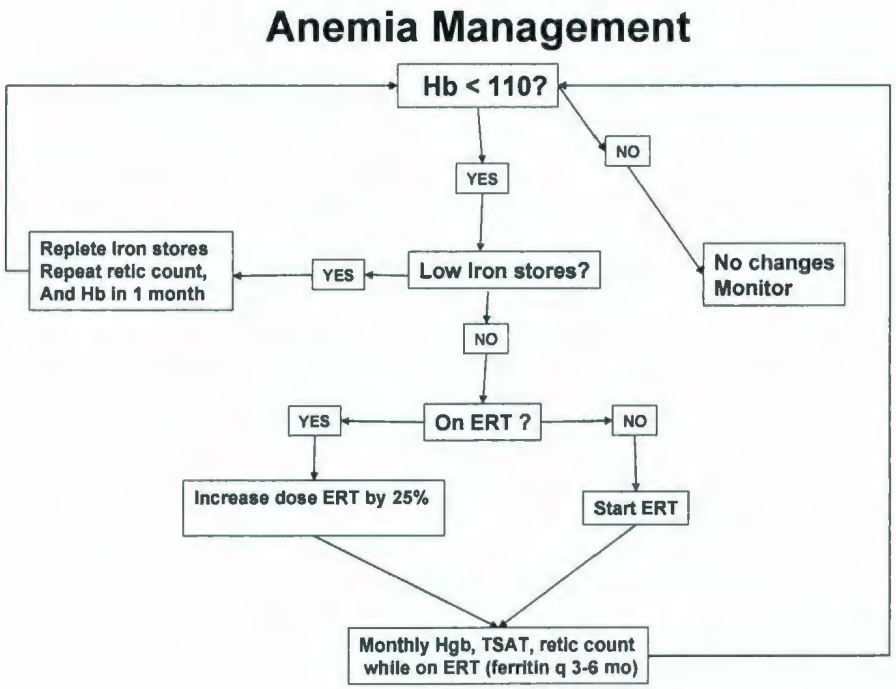

Figure 1.3 An example of a protocol for anemia management that may guide therapy by physician or specialized nurse. It assumes all secondary causes of anemia have been ruled out. ERT, erythropoietin replacement therapy; Hb, hemoglobin; mo, months

.

The clinic structure may also ensure that patients have access to appropriate current information and materials that may not be available in individual physician offices. Also, it will permit coordinator of care plans and execution of those plans within any health system structure.

Barriers to care or implementation of strategies can be identified in a clinic setting. The costs and the number of medications required for CKD is becoming progressively daunting and leads to problems with compliance. Furthermore, the potential ability to emphasize the role of patient and family in self management may be crucial where the interventions require lifestyle modification and / or adherence to complex medical therapies. These problems are more likely to be identified within a clinic setting, where social workers, pharmacists, and other may identify issues not identified by physicians. The importance of an asymptomatic condition can be reinforced in clinic setting where the patient-team interaction is far longer than the usual patient-doctor interaction [51]. Although there may be multiple problems and barriers that interfere with achieving the care goals in any one individual, the presence of an organized team approach is more likely to ensure the identification of those barriers in a timely manner.

1.6 Other Studies

The CAN-CARE (Canadian Care Prior to Dialysis) Study is a prospective multicenter cohort study of incident patients with estimated GFR less than 50 mL/min referred to nephrologists across Canada. Enrollment began November 2000 with a planned follow-up of up to 4 years. The objectives are to describe: (1) the specific care ("elements") these patients receive over time, (2) the prevalence of cardio-renal risk factors at referral and at 12 and 24 months, and (3) the link between specific elements of care and outcomes / quality of life [11]. The Study of Treatment for Renal Insufficiency: Data and Evaluation (STRIDE) registry will study data on prevalent CKD patients in nephrology practices in the United States [141]. The Chronic Renal Insufficiency Cohort (CRIC)

Study will examine risk factors for progression of CKD and CVD among those patients. The main goal is to develop models identifying high-risk subgroups and subsequently, increase application of preventive therapies [142]. The Kidney Early Evaluation Program (KEEP) was implemented to increase awareness to increase awareness of kidney disease among those at highest risk and, subsequently, to improve outcomes through early detection and referral for care. The KEEP 2.0 screening program identified persons with reduced kidney function and suboptimal care. The KEEP 3.0 will continue to identify individuals at high risk for kidney disease and will address educational needs by randomly assigning participants to one of several educational programs [143].

The Can-Prevent trial is a Canada-wide multicenter clinical trial addressing the hypothesis that compared to usual care, a nurse supported by a nephrologist, running a protocol guided, multiple risk factor intervention and disease management clinic for people with moderate chronic kidney disease identified by laboratory based case-finding, will reduce or delay the onset of advanced kidney disease, cardiovascular events, and death. The study will also assess the effect on health care resource use, costs and quality of life. Interventions applied will include lowering blood pressure to target, maximal use of renin-angiotensin system interruption, treatment of dyslipidemia, prophylactic aspirin when indicated, treatment of renal anemia, disordered calcium / phosphate and parathyroid metabolism, use of β-blockers in heart failure and post myocardial infarction, control of diabetes, and smoking cessation. This trial is currently at an advanced stage of a pilot study that includes 500 cases randomized at five sites, with an average 2 year

follow-up scheduled to be complete by May 2008. No data have been published from this trial to date.

1.7 Conclusion

Kidney disease involves the complex physical, mental, and social aspects of health mandating an understanding and rational utilization of available resources. Opportunities exist to improve early identification and follow-up of patients with CKD and to ensure better outcomes overall, regardless of whether patients ultimately require dialysis.

In order to focus on these complex aspects of care, the inclusion of medical, nursing, dietary, social work, and pharmacy staff in a coordinated system, with protocolized goals and systematic approaches to longitudinal follow-up is required. It is hoped that the information supplied herein will help develop templates and delivery of care models for further evaluation, so that, ultimately, the outcomes of patients with CKD at all stages of disease are improved.

Chapter 2: Canadian Survey of Clinical Status at Dialysis Initiation 1998-99: A Multicentre Prospective Survey.

Previously published as: Curtis B, Barrett BJ, Jindal K, Djurdjev O, Levin A for the Canadian Renal Disease Alliance: Clinical Nephrology 58(4):282-8, 2002.

2.1 Introduction

An understanding of current nephrological practice is essential for both the measurement of future success and the planning of care for patients with kidney disease. A number of recent publications recommend both earlier patient referral to a nephrologist [131-133, 140, 144] and an earlier initiation of dialysis [111, 135] with the intent that these interventions will lead to improved long-term outcomes of patients receiving kidney replacement therapy [145-147]. It is hoped, and indeed cohort studies suggest, that the specific intervention of care by a nephrologist improves quality of life and life expectancy.

The timing of initiation of kidney replacement therapy should reflect a patient's estimated residual kidney function and/or symptoms. Key-measured elements at initiation, such as serum albumin and hemoglobin, have been shown to affect subsequent patient outcomes [42, 110, 112, 147-149]. Similarly, lack of preparation for dialysis increases morbidity and cost [131-133].

This cross-sectional survey of a convenience sample of dialysis units across Canada describes the status of patients commencing dialysis before the impact of recent guidelines. In describing current practice, we will be able to more rigorously define

objectives for future studies, and this information will serve as a baseline for initiatives in changing current care and attitudes.

2.2 Patients and methods

This Canadian multicentre cross-sectional study examined patients starting dialysis between October 1998 and December 1999. A letter was sent to Canadian community and university affiliated nephrology programs involved in existing collaborations requesting participation in the study. All centres that desired to participate in the study were included. Specifically, the centers were St. John's, Halifax, Montreal (2 centres), Quebec City, Toronto (2), Hamilton, Kingston, Winnipeg (2), Saskatoon, Vancouver (2) and Penticton. Centers ranged in size from 40 to over 500 prevalent patients and were predominately located in urban environments and affiliated with university-based teaching hospitals. These 15 centers represent almost two-thirds of current dialyzing centers in Canada. Each center selected a 1-month patient entry period according to their convenience. Within that 1-month period, consecutive patients starting dialysis in that center were entered. Patients with acute renal failure and with failing kidney transplants were excluded. Acute renal failure was defined as a new onset of potentially reversible cause of kidney failure requiring dialysis. Patients with acute "chronic kidney failure" were included in the data collection study. No attempts were made to modify any aspect of practice or therapy.

Data collection and measurements

Data were collected on incident dialysis date and concurrent demographic variables (age, gender, diabetes), clinical variables (pre-dialysis weight, presence of symptoms), and laboratory measurements (pre-dialysis serum creatinine, albumin, hemoglobin, 24-hour urine urea and creatinine clearance). Standard laboratory measurements were used, specific to each institution. Specifically, albumin was measured using either the bromcresol green assay or bromcresol purple method. Results of bromcresol purple were adjusted for comparison purposes as per Clase et al [150]. Clinical symptoms were obtained using a checklist as close to dialysis initiation as possible and in some cases, collected retrospectively within a few weeks of starting dialysis. Each of the following was noted to be present or absent from the patient's perspective: nausea, vomiting, anorexia, cramps, itching, restless legs, fatigue and cognitive impairment. Severity of these symptoms was not quantified for simplicity of data collection purposes.

Residual kidney function was calculated as creatinine clearance, estimated using the Cockcroft-Gault formula [151] and as glomerular filtration rate, using the "four-variable" (abbreviated) Modification of Diet in Renal Disease (MDRD) study equation (figure 2.1) [152]. Dialysis-specific information (modality, access) was recorded, as was whether a nephrologist had followed the patient for more than 3 months. Permanent access was defined as the presence of an AV fistula or graft, irrespective of maturity, a peritoneal dialysis (PD) catheter or a tunneled catheter that was planned to be used as long-term access.

Figure 2.1: Abbreviated MDRD Study Equation estimating glomerular filtration rate

Estimated Glomerular Filtration Rate (ml/min/1.73 m^2)

$= 186 \times (S_{Cr} / 88.4)^{-1.154} \times (Age)^{-0.203} \times 0.742$ (if female) $\times 1.212$ (if African-American)

Abbreviations and units: S_{Cr} , Serum creatinine in μmol/L; Age, in years; Weight, in kg

The following variables were analyzed at dialysis initiation: residual kidney function, presence or absence of permanent access, hemoglobin, serum albumin and presence or absence of symptoms.

Data management and statistical analysis

All data were collected at each site by nephrologists or in-training nephrology fellows and forwarded directly to a central data entry location (St. Paul's Hospital, Vancouver, Canada). Descriptive analyses are presented as mean ± standard deviation or median with 25^{th} and 75^{th} percentiles, when appropriate. Continuous variables were compared using the Student's t-test or Wilcoxon rank sum test for comparisons between 2 groups and the ANOVA and Kruskal-Wallis test for comparisons of more than 2 groups depending on the distribution. Categorical variables were compared using the χ^2 test. A p value of less than 0.05 for 2-sided tests is considered significant.

2.3 Results

Demographics, laboratory data and dialysis access

Data on 251 patients with end-stage kidney disease were collected; of these, 238 had sufficient data to be included in the analysis. At dialysis initiation, the mean estimated creatinine clearance was 10.9 ml/min using the Cockcroft-Gault formula, mean serum albumin was 32.7 g/L and mean hemoglobin was 92.6g/L. Only 41 patients had estimates of glomerular filtration rate measured by 24-hour urine collections for creatinine (and 9 patients for urea). In those 41 patients, the measured creatinine clearance was 8.6 mL/min; correlation between 24-hour measured and calculated using Cockcroft-Gault formula creatinine clearance was moderate ($r = 0.45$) and similar to those between 24-hour measured and MDRD formula ($r = 0.51$). The correlation of MDRD with serum creatinine is higher than that of Cockcroft-Gault formula (-0.91 vs. -0.51), and the MDRD formula on average yielded a 2 – 3 mL/min lower estimate of residual kidney function than the Cockcroft-Gault formula (mean difference 2.9, range – 5.3 to 19.5).

67% of patients commenced hemodialysis (vs. peritoneal dialysis) and of these 40% had permanent access. All patients starting peritoneal dialysis had permanent access in place at the time of this initiation, though not all patients with PD catheters commenced PD as their initial dialysis.

Exposure to nephrology care

As demonstrated in Table 2.1, two thirds of patients (65%) in the sample were known to a nephrologist for more than 3 months prior to commencing dialysis. There was a significant difference in age (58 years vs. 63 years, $p = 0.028$) and in albumin levels (33.7 g/L vs. 30.6 g/L, $p = 0.0004$) in those seen by nephrologists for more, versus less, than 3 months. While there was no statistical difference in hemoglobin and residual kidney function between these groups, there was a trend toward lower values in those not seen by nephrologists.

A greater percentage of patients had permanent access if a nephrologist had followed them for 3 months or more ($p = 0.001$). However, even if permanent access had been in place, 14 patients commenced dialysis through a temporary line.

Table 2.1 Summary Demographics and Status at dialysis initiation in those patients known and not known to a nephrologist for greater than 3 months

	CORR Data† (1999)	All patients (n=238)	Known (n=154)	Not Known (n=84)	p‡
Age (years)	61	59 ± 17	58 ± 17	63 ± 16	0.028
Female (%)	41	43.7	43.5	44.1	0.94
Diabetes Mellitus (%)	31.3	38.1	39.2	36.1	0.64
Serum Creatinine (μmol/L)	--	656 (521-804)	634 (532-785)	697 (496-896)	0.18
CrCl (ml/min)	--	10.9 ± 4.9	11.3 ± 4.9	10.1 ± 4.7	0.057
MDRD (ml/min)	--	8.0 ± 3.4	8.1 ± 3.1	7.7 ± 3.9	0.40
Symptoms	--	3 (2-5)	3 (2-5)	3.5 (2-5)	0.33
Albumin (g/L)	--	32.7 ± 6.3	33.7 ± 6.2	30.6 ± 6.0	0.0004
Hemoglobin (g/L)	--	92.6 ± 18.1	94.3 ± 17.6	89.5 ± 18.6	0.051
Initial Modality (%*HD)	78	66.7	67.5	65.1	0.70
Permanent Access (%)	79**	52.5	65.6	28.6	0.001
Temporary Line (%)	20**	53.2	41.2	75.0	0.001

† See text for details, ‡ denotes comparison of Known vs. Not Known,

*HD – Hemodialysis, ** Represents prevalent data

Clinical Symptoms

Frequency of symptoms reported by these patients is given in Figure 2.2. The most common symptoms were fatigue, anorexia and nausea, reported by more than 50% of subjects. The number of symptoms reported at dialysis initiation are reported in Table 2.2: nearly 90% of patients had at least 1 symptom. Those with the lowest calculated MDRD glomerular filtration rate had the least number of symptoms. Low albumin was associated with the greatest number of symptoms. None of the other laboratory values correlated with symptom type or number.

Figure 2.2: Symptoms at Dialysis Initiation

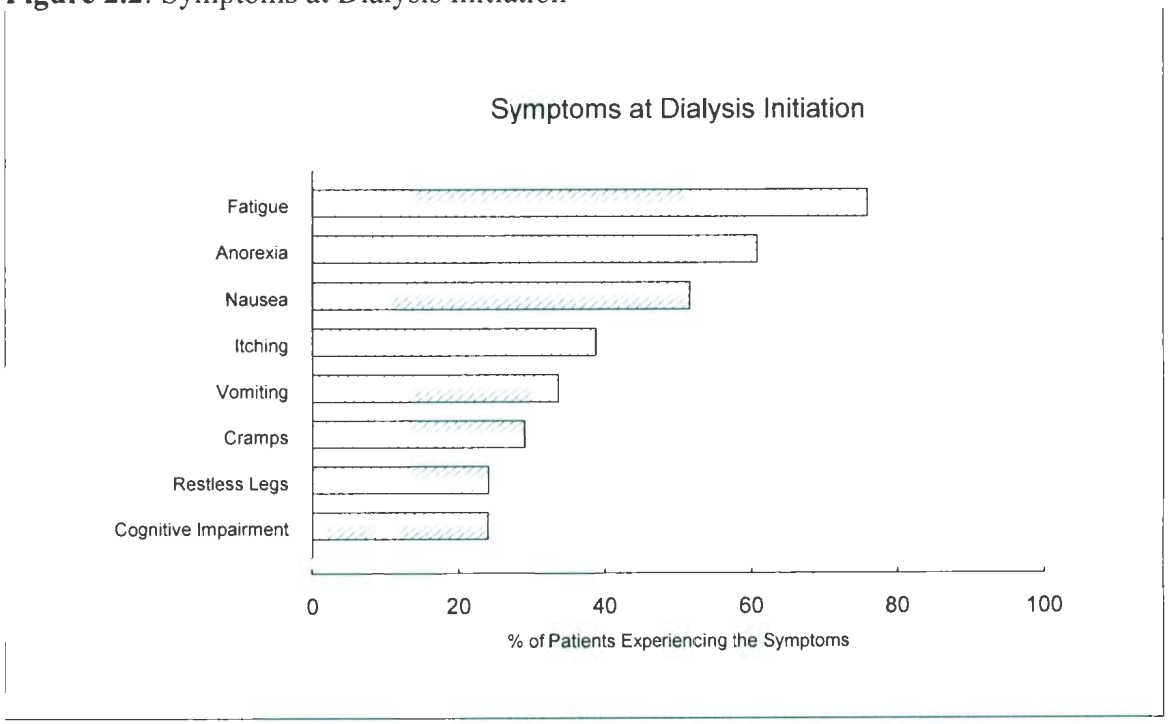

Table 2.2 Symptoms at dialysis start

	No symptoms	1 – 2 symptoms	3 – 4 symptoms	5 – 8 symptoms	p
Total (%)	11.5	27.8	29.5	31.2	
Age (years)	56±21	57±17	60±17	62±15	0.26
Female (%)	40.7	41.5	46.4	45.2	0.58
Diabetes Mellitus (%)	26.9	31.3	46.4	42.5	0.07
CrCl (mL/min)	10.7±4.4	10.2±4.0	11.1±5.6	11.4±5.3	0.54
MDRD (mL/min)	8.0±3.1	6.9±2.6	8.5±3.7	8.4±3.8	0.03
Hemoglobin (g/L)	97.8±18.3	89.4±16.5	94.9±18.6	92.0±18.9	0.16
Albumin (g/L)	35.2±6.5	33.7±5.1	32.8±6.7	30.9±6.2	0.0084

Age and Diabetes

Table 2.3 shows the data divided according to 4 age cohorts. Older patients started dialysis with lower estimated creatinine clearance than younger patients. However, if the MDRD formula is used, the kidney function estimates are similar. Despite lower creatinine clearances, hemoglobin values were higher in the older age groups. A comparison of diabetics and non-diabetics is shown in Table 2.4. Diabetics started

dialysis with a higher calculated creatinine clearance and are more likely to do so with a temporary access.

Table 2.3 Age group differences in status at dialysis start

	19 - 44	45 - 64	65 – 74	75 +	p
Total (%)	22.4	31.5	26.5	20.6	--
Female (%)	45.1	50.1	33.3	44.9	0.23
Diabetes Mellitus (%)	30.0	48.0	39.7	29.2	0.102
Serum Creatinine (μmol/L)	710 (581-914)	658 (517-840)	666 (510-798)	623 (486-685)	0.012
CrCl (mL/min)	12.9 ± 5.8	11.9 ± 5.0	10.0 ± 3.7	8.5 ± 3.5	0.0001
MDRD (mL/min)	7.7 ± 3.5	7.8 ± 3.4	7.9 ± 3.3	8.5 ± 3.5	0.58
Hemoglobin (g/L)	89.3 ± 25.3	89.6 ± 14.7	95.0 ± 17.0	97.4 ± 13.8	0.042
Albumin (g/L)	33.3 ± 7.2	32.2 ± 6.2	32.3 ± 5.7	33.0 ± 6.4	0.79
Modality (% HD)	50.9	73.3	63.1	73.5	0.043
Permanent Access (%)	64.7	48.0	54.0	44.9	0.18
Temporary Line (%)	39.2	61.3	50.8	58.3	0.084

Table 2.4 Comparison of diabetics and non-diabetics patients

	Diabetics	Non-diabetics	p
Age (years)	60 ± 15	59 ± 18	0.89
Female (%)	48.9	40.4	0.20
Serum Creatinine (μmol/L)	631 (502-773)	666 (540-843)	0.062
CrCl (mL/min)	12.2 ± 5.8	10.1 ± 4.0	0.0011
MDRD (mL/min)	8.4 ± 3.7	7.7 ± 3.2	0.18
Hemoglobin (g/L)	91.9 ± 18.3	93.0 ± 17.9	0.68
Albumin (g/L)	31.7 ± 6.0	33.2 ± 6.5	0.097
Modality (% HD)	70.0	64.8	0.41
Permanent Access (%)	45.6	56.2	0.11
Temporary Line (%)	64.0	47.3	0.012

2.4 Discussion

We have described the characteristics of end-stage kidney disease patients initiating dialysis across Canada. Previous studies have addressed similar issues but have involved only single centers or multiple centers involving multiple health care systems [42, 145, 153, 154]. Our study is unique in that it surveyed multiple centers within a single health care system across 7 provinces. Furthermore, this study was conducted in the current era during which both the Dialysis Outcomes and Quality Initiative and Canadian Society of Nephrology guidelines concerning dialysis initiation were being developed and published. This provides us with baseline data from which to evaluate the impact of guideline implementation in the future.

We, like others, identify that substantial numbers of patients are not seen by nephrologists before the initiation of dialysis. Similar to other studies, lack of nephrology care is associated with lower serum albumin, hemoglobin and lack of vascular access. These factors have been shown in numerous publications to be associated with an increase in morbidity and mortality [42, 110, 112, 131-133, 147-149]. The cost and morbidity implications of temporary catheter access are extensive. They include the cost of catheters themselves, insertion fees, radiology tests and costs associated with complications such as infection and thrombosis.

Of note, however, patients known to nephrologists also start with temporary access to a significant degree (41%). While this is almost half the rate as compared to those who were not known (75%), it is still of concern. It may be that the conventional cut-off of 3

months, used in previous studies, and based on the premise that this allows time to establish permanent access is inappropriate. Current guidelines for access creation suggest that GFR<25mL/min or 6 months in advance of dialysis initiation is needed for adequate vascular access maturation and the insertion of PD catheters between 2 and 3 weeks prior to use (depending on techniques used). Thus, the fact that even those known to nephrologists did not all commence dialysis with permanent access may be a function of poorly defined cut-offs for late referral. Unfortunately, we did not collect specific information of data of first contact with a nephrologist, and thus, are unable to review other possible time point cut-offs. This study was unable to capture reasons for "late" referral, but does serve to document that late referral continues to exist in the Canadian health care system.

The utility of various formulas for estimating kidney function was not a major focus of this study. However, we did observe the "performance" of the MDRD formula relative to the Cockcroft-Gault formula and the 24-hour urine collection. This provided interesting results. While the estimated creatinine clearance showed no relation to the number of symptoms, the MDRD formula showed a lower symptom frequency with lower glomerular filtration rate, suggesting that patients with less severe symptoms started dialysis later. Conversely, while values for creatinine clearance varied in different age cohorts and diabetics vs. non-diabetics, the MDRD values were similar, suggesting significant differences in the performance of these formulas in these populations. It is well-known that at lower levels of kidney function, the Cockcroft-Gault formula overestimates glomerular filtration rate: this is borne out by the data in this study, if

MDRD and 24-hour values are viewed as relative "gold standards". Recent recommendations suggest the use of any formula versus serum creatinine alone improves estimates of kidney function [36].

This study is the first dialysis initiation study to review symptoms in relation to the timing of dialysis start in Canada. We note that the majority of patients commence dialysis with at least 3 symptoms, and those are most commonly, fatigue, anorexia and nausea. Those with low albumin had a greater number of symptoms and yet a higher MDRD glomerular filtration rate suggesting the non-specific nature of the symptoms and possible correlation with factors other than residual kidney function.

The strength of this study is that it surveys current practice during a time of increasing attention to the quality of dialysis care, including initiation practices. Although the centers included were largely academic, 80% of current dialyzing centers in Canada are affiliated with university-bases teaching hospitals. Limited available data on both incident and prevalent patients from the Canadian Organ Replacement Registry (CORR) demonstrate similarity with respect to demographics as shown in Table 2.1 [155]. No other incident data exist for comparison between this cohort and the Canadian dialysis population. It is the first study in Canada which attempts to determine presence of symptoms at dialysis initiation, as well as laboratory and clinical values. Weaknesses include: lack of clear documentation as to decision processes prior to dialysis initiation (both patient and physician), lack of documentation as to reasons for late referral and the arbitrary selection of 3 months of nephrology exposure as being an "acceptable" time

prior to dialysis initiation to ensure improved outcomes. The latter is based on current convention in the literature, but will need to be revisited in future studies if patients continue to initiate dialysis as described in this survey. Furthermore, the uremic symptoms we were interested in were limited to those easily captured and did not include other comorbid features such as cardiovascular disease or sexual dysfunction. These additional factors would be included in future studies.

This survey of dialysis initiation practices in Canada during 1998-1999, demonstrates that Canadian patients are commencing dialysis in a similar condition to that of patients in other western countries [132, 145, 153, 154]. Unfortunately, the presence of low hemoglobin, hypoalbuminemia, symptoms and lack of permanent access continue to be prevalent, irrespective of whether patients have or have not been seen by nephrologists prior to dialysis initiation. Although this survey was not designed to properly evaluate the question of sub-optimal nephrological care there is certainly an apparent "advantage" to nephrology referral at least 3 months prior to initiation of dialysis. This is true with respect to status at initiation (trend toward higher hemoglobin, higher albumin and the presence of an access) relative to not being known to a nephrologist for at least 3 months, but from the data presented there is variability in patient conditions at dialysis start irrespective.

Of key interest is that of patients referred late to nephrologists, a substantial proportion belongs to an identifiable high-risk group (diabetics). Given the exposure of these patients to a medical system, it is clear that we need to continue rigorous public and

medical education strategies to identify reasons for late referrals. In this way, we may substantially reduce the prevalence of late referrals and improve patient outcomes [40].

The importance of this study is that it serves as a baseline from which to evaluate the impact of focused educational strategies, early referral and improved management of patients prior to dialysis care. If we are to improve timeliness of referral and patient outcomes it is important to identify those barriers that continue to interfere with optimizing the management of patients with kidney disease.

Chapter 3: The Short and Long Term Impact of Multi-Disciplinary Clinics in Addition to Standard Nephrology Care on Patient Outcomes.

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3.1 Introduction

Mortality and morbidity of kidney failure patients remains high despite the many advances in dialysis treatment [1, 155-157]. Indeed, kidney failure is a culmination of a complex set of processes with widespread pathophysiological consequences. It is well recognized that much of the disease burden is well established prior to the initiation of dialysis therapy [43, 158]. Opportunity thus exists for proactive intervention to modify disease progression and risk factors associated with poor outcomes.

Although it is believed that a nephrology team is important in the management of patients with kidney disease [51, 53, 140, 156, 159], there is no uniform definition of such a team, nor a description of implementation practices. Given that multi-disciplinary teams impact on health care resources, it is imperative to evaluate their effectiveness in comparison to current clinical practice. The impact of a multi-disciplinary team clinic has been studied in other disciplines such as diabetology [12, 13, 45], cardiology [14-16, 18, 46], rheumatology [47, 48], and oncology [50] and shown to benefit patient care and outcomes.

There is substantial evidence that late referral leads to poor outcomes for patients with kidney disease and that early referral is of benefit [131-133, 144]. The unique purpose of

this study was to examine patient outcomes as a function of two different clinical care model exposures, both over a prolonged period of pre-dialysis time: that is, we sought to examine the question of the effect of different care when late referral is not an issue. We compare two cohorts of patients who commenced dialysis in two countries. All patients had been exposed to conventional nephrologist care or nephrologist and multi-disciplinary team care for an extended period of time. We evaluated the impact of care prior to dialysis on survival and other objective parameters shown to influence long-term outcomes [42, 148]. This study extends previous observations [51] into the current era, and internationally, in order to improve the generalizability of the findings.

3.2 Patients and Methods

This study of incident dialysis patients examines those patients initiating dialysis in two tertiary care institutions: St. Paul's Hospital (SPH), University of British Columbia, Vancouver, Canada and Instituti Ospitalieri di Cremona, Italy. In the Canadian cohort, patients commencing chronic dialysis at SPH during calendar years 1997 and 1998 were considered for inclusion. In the Italian cohort, all patients commencing dialysis in Cremona from 1 January 1999 until 30 June 2002 were considered. The total cohort of dialysis patients during the time periods was 352, but only adult patients (over the age of 18 years) and those followed by nephrologists for more than 3 months were eligible for inclusion for this analysis, given the specific questions being addressed. The 3 month convention attempts to remove patients with 'late referral' based on duration of time needed for education, modality selection and access creation in a non-urgent manner. All

patients gave informed consent and local ethics boards of each respective institution approved the study.

Patients were categorized according to prior exposure to a multi-disciplinary clinic-based education and follow-up program and compared with a concurrent cohort who received standard nephrologist care in the same centres. Details of the MDC are described below. Patients were excluded if they had a failed kidney transplant or had been on dialysis previously for any reason.

In both countries, the dialysis centres are accessed by patients who are from the same referral group practice and referral base of nephrologists. All nephrologists in each centre had the same opportunity to access facilities and personnel of the multi-disciplinary clinic for their patients. The reasons for non-referral or non-attendance at the clinic were not obtained. Care after dialysis initiation was standardized and managed according to unit practices.

Details of the multi-disciplinary clinic have been described in more detail elsewhere [51]. Briefly, the formal programs in both Canada and Italy have a standardized philosophy including educational programs as well as regular, protocolized clinic and laboratory follow-up of patients with chronic kidney disease. The frequency of both visits and laboratory tests is predetermined based on the level of kidney function with reminder systems to facilitate follow-up. Regularly scheduled blood work and clinical examinations and pre-specified educational topics are reviewed with each patient.

In the Canadian centre, the complete formalized multi-disciplinary clinic team consists of a nurse educator, physician, social worker, nutritionist, and pharmacist, though exposure to each individual is varied depending on level of glomerular filtration rate (GFR). In the Italian centre the team consists of program-dedicated nephrologists and multi-disciplinary nurses responsible for implementation of recommended diagnostic and intervention strategies, information, education and support. The formal team accesses the nutritionist, psychologist, and social worker when necessary.

In both countries the average duration of exposure of the patient to the team is approximately 1.5 hour per visit (range 1-2.5 h). The average number of visits per patient-year depends on the protocol, determined by level of kidney function. For the purposes of this analysis, it is estimated at five visits per year (including a specialized education visit for treatment modality selection at 2 h), thus total exposure to the clinic team is approximately 8 h (4 x 1.5 + 2 h) per patient-year. The average duration of visits to the nephrology office is estimated to be 0.5 h based on office booking schedules. For the purposes of comparison, the number of visits to nephrologist offices is estimated to be the same number: 5 (4 x 0.5 + the same 2 h specialized education session). Thus, patients attending nephrology offices had 'exposure' for ~ 4 h per patient-year. Note that the timing of the 2 h educational session was left to the discretion of the nephrologist for the standard nephrology care patients; however, the same staff from the multi-disciplinary clinic performed it. Thus all patients were exposed to the identical information session.

In Italy, patients in the formal program participate in three 2 h educational dialysis orientation meetings over 3 months, culminating in additional 6 h of education exposure. Those patients who do not attend the program received orientation to dialysis by the physician in charge and the program team; the timing of this is again at the discretion of the nephrologist, and occurs closer to dialysis start than those attending the formal program.

Date collection and measurements

Data were collected on all patients at the time of dialysis initiation, by research assistants. Baseline data included demographic, diabetic status, etiology of kidney failure, date of first nephrology referral and dialysis modality. Serial laboratory data were collected on all patients at the time of dialysis initiation and at follow-up intervals of 6 and 12 months. Patient status (on dialysis, deceased, transplanted, discontinued treatment, or moved) was also obtained at the end of the study period for each cohort.

Statistical analysis

Descriptive analyses are presented as mean ± standard deviation. Continuous variables were compared using the Student's *t*-test or Wilcoxon rank-sum test depending on distribution. Categorical variables were compared using the chi-squared test. Multiple linear regression was used to investigate independent predictors of short-term outcomes (differences in laboratory data at dialysis initiation) adjusting for age, sex, race, diabetes, etiology of kidney failure, estimated kidney function at dialysis initiation, country and attendance of multi-disciplinary clinic (MDC). Survival on dialysis was examined using

the Kaplan-Meier method and survival by clinic attendance was compared using the log-rank test. Patients were censored at transplant, moving away, and end of study period. Cox proportional hazards modeling was used to examine hazard ratios for death as outcome. Multivariate modeling explored the impact of MDC on survival adjusting for variables found previously to impact on survival: age, gender, race, diabetes, duration of follow-up prior to dialysis and country. A p-value of < 0.05 for two-sided tests was considered significant.

3.3 Results

The total eligible cohort of 288 patients consisted of 152 patients in the Canadian cohort and 136 patients in the Italian cohort. During the time period of interest, 352 people started dialysis, of which 64 (18%) were referred to nephrologists <3 months prior to dialysis start. These study cohort populations are similar in demographics to those described in national registries from both Canada and Italy [9, 155, 160]. The only cohort difference between the two countries was racial distribution. All data were thus combined with country and race factored into analyses.

Table 3.1 demonstrates the demographic and initial laboratory data at dialysis initiation for the 288 eligible patients: note that all patients had an average of 42 months of nephrology care prior to dialysis. Comparisons between those patients seen in the MDC ($n = 132$) vs. standard nephrology care ($n = 156$) are presented. Age and race are statistically significantly different between the two groups, with those exposed to the MDC being younger (64 vs. 60 years) and of different racial composition (more East

Indian and less Asians). Analysis of the age distributions confirms similar ranges in both groups.

Patients in both groups commenced dialysis at mean levels of kidney function that were low (below 9 mL/min/1.73m²). The estimated GFR using the 'four variable' (abbreviated) Modification of Diet in Renal Disease (MDRD) study equation [152], was statistically significantly different between the two groups: those attending the MDC started dialysis with mean GFR values of 8.4 mL/min/1.73m², vs. those receiving standard nephrology care alone, who had a mean GFR of 7.0 mL/min/1.73m² (a mean difference between the groups of 1.4, 95% CI: 0.6-2.2 mL/min/1.73m²). In both cohorts, ~60% commenced hemodialysis, and 40% commenced peritoneal dialysis therapy. Home-based hemodialysis therapy was not an option at the time of study.

Short-term outcomes: differences in laboratory outcomes at dialysis initiation.

Table 3.2 describes the laboratory data at dialysis initiation as a function of MDC exposure or standard nephrology care. There were significant differences with respect to hemoglobin (102 vs. 90 g/L, $p<0.0001$), albumin (37.0 vs. 34.8 g/L, $p=0.002$) and calcium (2.29 vs. 2.16 mmol/L, $p<0.0001$) levels in those patients followed in the multi-disciplinary clinic vs. those followed by nephrologist alone. The difference in hemoglobin levels persists during the first year, while the values for calcium and albumin become similar over the course of dialysis. Note that phosphate levels were not different.

Table 3.1. Demographics at Dialysis Initiation. All patients known to Nephrologist for > 3 Months

	Entire Cohort	**Standard Nephrologist Office Care**	**Nephrologist and Multi-Disciplinary Clinic**	p†
N (%)	288	156	132	
Clinic Duration (months)	41 ± 34	43 ± 34	40 ± 33	0.4
Age (years)	62 ± 16	64 ± 16	60 ± 17	0.02
Female (%)	39.9	43.6	35.6	0.2
Diabetes (%)	33.7	33.3	34.1	0.9
Race (%)				0.001
Caucasian	72.1	66.4	78.9	
Asian	17.1	25.0	7.8	
East Indian	6.4	3.3	10.2	
Other	2.5	2.6	2.3	
Etiology of Kidney Failure (%)				0.5
Diabetes	22.3	20.5	24.4	
Hypertension	20.2	21.2	19.1	
GN* / Autoimmune	24.7	23.1	26.7	
Cystic Disease	7.3	5.8	9.2	
Chronic Kidney Disease**	13.6	16.0	10.7	
Other	11.8	13.5	9.9	
Dialysis Modality§ (% HD)	60.4	61.5	59.1	0.7

† denotes comparison between Nephrologist and Multi-Disciplinary Clinic vs. Standard Nephrologist Office Care; *GN – Glomerulonephritis; **Not otherwise specified;
§Percentage of those starting Dialysis, HD – Hemodialysis (versus peritoneal dialysis)

Table 3.2 Laboratory data (mean ± standard deviation) at dialysis start, 6 and 12 months post dialysis

	Standard Nephrologist Office Care	Nephrologist and Multi-disciplinary Clinic	p
Kidney Function at Dialysis start			
Creatinine (μmol/L)	707 ± 188	650 ± 225	0.03
GFR‡ (mL/min/m^2)	7.0 ± 2.6	8.4 ± 3.8	0.001
Hemoglobin (g/L)			
Dialysis start	90 ± 14	102 ± 18	<0.0001
6 months	108 ± 15	116 ± 16	<0.0001
12 months	110 ± 17	120 ± 16	<0.0001
Albumin (g/L)			
Dialysis start	34.8 ± 5.3	37.0 ± 5.4	0.002
6 months	36.5 ± 4.5	37.0 ± 4.7	0.4
12 months	36.9 ± 4.6	37.0 ± 4.2	0.9
Calcium (mmol/L)			
Dialysis start	2.16 ± 0.27	2.29 ± 0.21	<0.0001
6 months	2.33 ± 0.24	2.32 ± 0.22	0.9
12 months	2.28 ± 0.21	2.29 ± 0.17	0.6
Phosphate (mmol/L)			
Dialysis start	1.73 ± 0.55	1.73 ± 0.54	0.9
6 months	1.56 ± 0.51	1.61 ± 0.43	0.4
12 months	1.61 ± 0.47	1.59 ± 0.44	0.8

‡GFR estimated by abbreviated MDRD formula

In a multivariate model, MDC was independently associated with higher hemoglobin (β=12.5 ± 1.9, p<0.001), calcium (β = 0.14 ± 0.03, p< 0.0001) and albumin (β = 2.2 ± 0.7, p=0.002) at dialysis initiation after adjusting for age, sex, calculated GFR at dialysis start, race, diabetes, etiology of kidney failure, and country of treatment.

Long term outcomes: survival analysis

Patients were followed for a median of 14 months after dialysis start. There were differences in important clinical outcomes after dialysis initiation. In the standard nephrology group 12 patients had been transplanted, one had transferred and 46 had died; in those followed by the MDC, seven had been transplanted, two had transferred, and 13 had died. Figure 3.1 demonstrates the difference in survival after dialysis initiation, between patients who attended the MDC vs. those who received standard care, using Kaplan-Meier analysis. Note the statistically significant survival advantage of those attending the MDC over those patients in the standard nephrology cohort (p = 0.01).

Multivariate modeling revealed only age and MDC to be significant predictors of survival (Figure 3.2). Age per 5 years (hazards ratio = 1.36, 95% confidence interval 1.21—1.54) and standard nephrology clinic vs. MDC attendance (hazards ratio = 2.17, 95% confidence interval 1.11—4.28) were statistically significant independent predictors of death.

Figure 3.1 Kaplan-Meier survival after starting chronic dialysis therapy. Comparison is made between patients seen prior to dialysis initiation in The Multidisciplinary Clinic (MDC) versus standard nephrology care

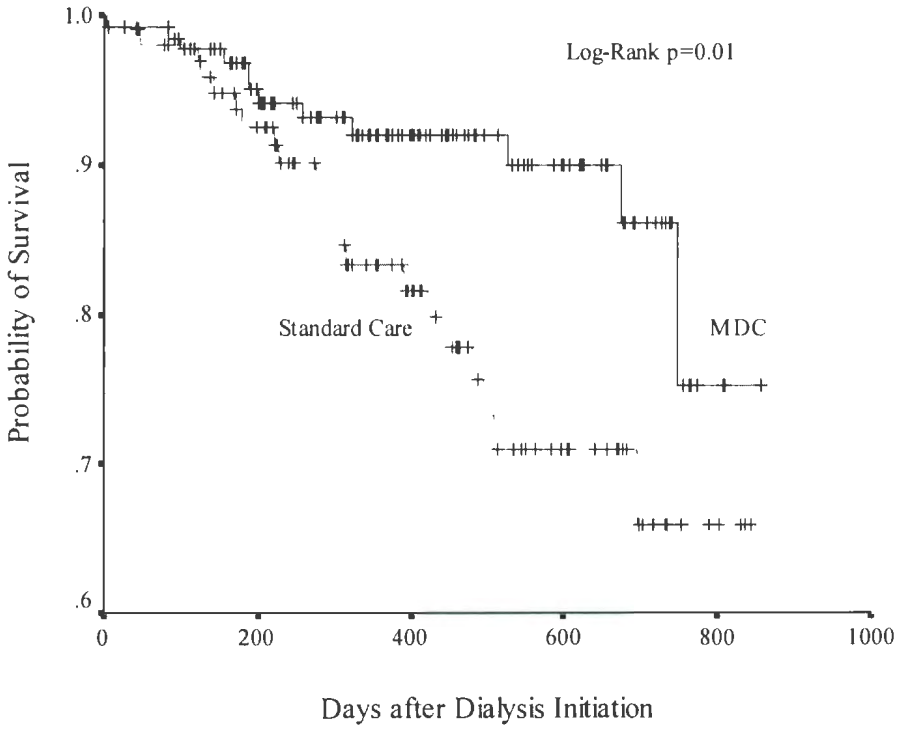
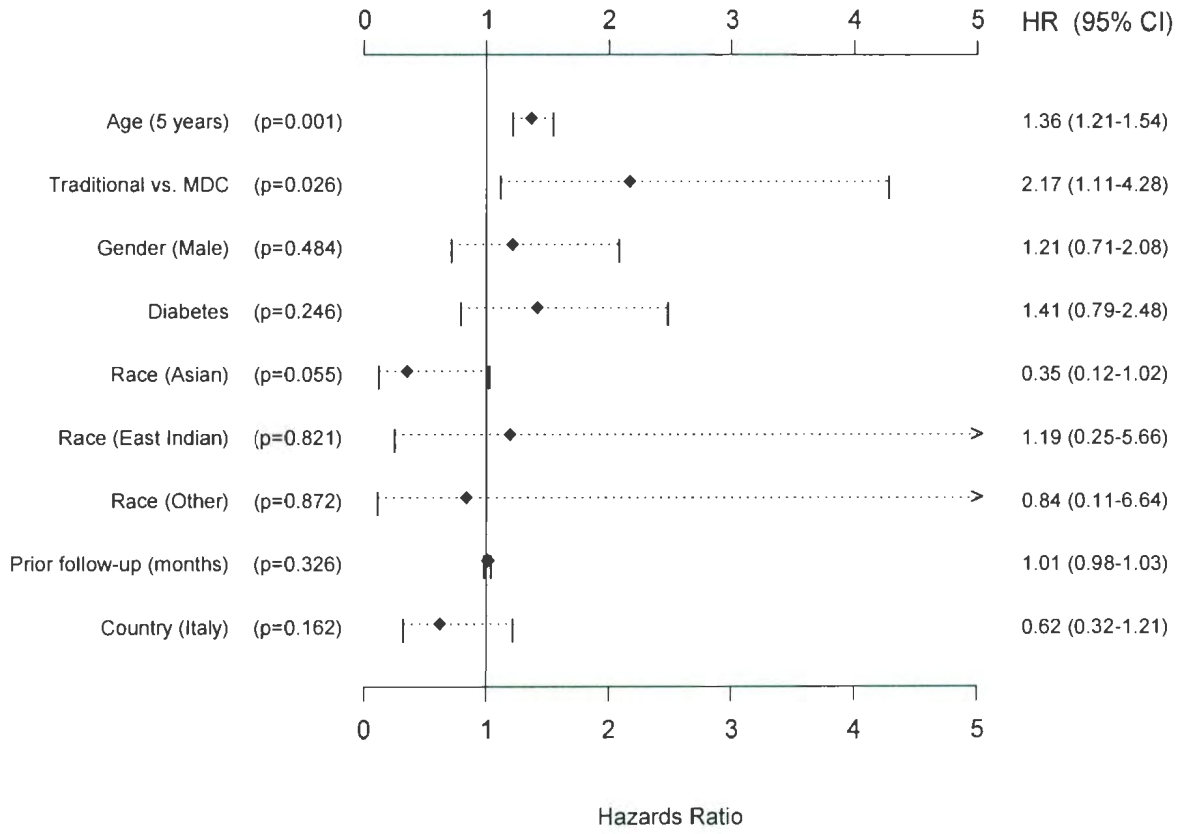


Figure 3.2 Risk of death according to multivariate Cox-Proportional hazards modeling. Comparator for race is Caucasian.



3.4 Discussion

This two country observational study is the first to demonstrate an association between an exposure to formal MDC-based care and survival benefit of patients starting dialysis. Despite similar long exposure times to expert care, those patients exposed to the formalized clinic had higher levels of serum hemoglobin, albumin, and calcium at dialysis start than those followed by standard nephrology care. These measures may be viewed as markers of exposure to care (e.g. nutrition counseling) and have been shown in numerous publications to be associated with a decrease in morbidity and mortality [42, 148]. In fact this analysis demonstrates that MDC care impacts on these parameters independent of GFR: that is, the findings of better laboratory parameters are not explained by higher GFR in that cohort receiving MDC care.

The survival advantage of the multi-disciplinary clinic cohort persists despite adjusting in the Cox proportional hazards model for baseline variables known to impact survival: e.g. age, gender, race and diabetes. There were two major differences in the demographics of the cohorts: age and race. The statistically significant 4 year difference in age is of questionable clinical importance. Racial differences are less easy to interpret and may represent patient preference for care patterns, cultural attitudes or a combination of both. As this study seeks to describe the outcomes of exposure to a specific treatment, this finding does not change the conclusions, but does raise further questions for exploration. Of note Asian / Oriental race is usually associated with better outcomes and East Indian and Caucasian with worse outcomes. Thus, the racial distribution differences would serve to bias the analysis against the formalized clinic cohort. While there was a

statistical difference between the two groups with respect to GFR at dialysis start, the clinical importance of 1.4 mL/min/1.73m² at levels below 9 mL/min/1.73m² is not clear, but unlikely to account for all the findings. Importantly, we did not adjust for hemoglobin and albumin in the survival analysis, as these variables were themselves impacted directly by our treatment of interest: MDC exposure. Therefore, statistically we could not adjust for a phenomenon that occurred as a consequence of the treatment of interest, at a time point after the exposure. Thus, while it is well known that lower values of hemoglobin and albumin at dialysis start impact on long-term outcomes, our analysis demonstrates one mechanism by which these values may be modifiable in a cohort known to nephrologists for a prolonged period of time. Furthermore, we did not adjust for factors which would have been in evidence after dialysis start (such as adequacy of dialysis, severity of illness measures) as our analysis was confined to those factors which would exist prior to dialysis initiation. While it is clear that survival is impacted by adequacy of dialysis and other factors, these factors would not be known to clinicians at the time of initiation, and thus would not be available to inform clinicians as to prognosis: this analysis clearly describes the importance of status at dialysis initiation.

The data from the two countries are not concurrent; this is due to the late implementation of the formal program in Italy, which was modeled after the Vancouver program. Nonetheless, the similarity of the programs, as one was based on the other, despite the different time periods, allows us to combine the data. Importantly, the results demonstrate that even in a more current era, with increasing awareness of the importance of care prior to dialysis, differences in outcomes are maintained.

This study is not a randomized control trial (RCT), thus the nature of the cohort design does not allow us to rule out a referral or case mix bias affecting our results. However, it is important to stress that all patients had equal opportunities to be referred to the clinic, given that the group of university affiliated physicians belonged to the same practice group in the same geographical area, and used the same hospital and educational resources. While attitudinal differences between physicians may exist, the knowledge of the importance of hemoglobin, albumin and other parameters is probably identical. The analysis confirms similar time of follow-up and similar patient cohorts, apart from age and ethnicity. We are unable to know with certainty if there are other unmeasured variables impacting on these results such as blood pressure control or aspects of patients' attitudes. The possibility of selection bias of course remains a weakness of this study, and for this reason we advocate the need for a RCT in order to definitively answer the questions posed herein.

There has been only one RCT in patients with kidney disease, published by Harris et al [54], which did not demonstrate a benefit to case management in chronic kidney disease. The intervention in that study was very different to our study as it was limited to written suggestions made to primary care physicians and the assigned clinic patients did not receive any specific treatment or preparation for kidney replacement therapy. This is in contrast to our study in which treatments were implemented directly by clinical staff. Thus, failure to show a benefit in the Harris study may well have been due to the failure of individual primary care physicians to implement the recommendations from the clinic.

There are numerous examples of benefit of the MDC in chronic illnesses, which do demonstrate benefit in patient outcomes [12, 13, 16, 18, 45-48, 50]. The current analysis specifically compares sophisticated clinic programs, which include protocolized objectives of care, specific treatment regimens and education to solitary nephrology care. Given the difficulties in conducting randomized control trials of care delivery systems, this study is of value. Indeed, a recent review by Powe [161] describes the need for carefully conducted studies such as this where exposure time, methods and outcomes are carefully tracked, as an alternative to the RCT. We believe the current analysis demonstrates the value of this approach, but does not obviate the need for randomized control trials, as mentioned above.

The reasons for improved laboratory and clinical outcomes despite similar length of time exposed to nephrology expertise are not clear but are probably multi-factorial as the finding argues for the potential added value of a team managing the complex set of factors within individual patients with chronic kidney disease (CKD). We are not able to determine which individual aspects of the programs are responsible for the findings. It is likely that variables or combinations of variables, such as attitudes and compliance that are difficult to measure may contribute. As we do not have reliable data regarding initial GFR at time of initial referral in all patients, it is possible that slower progression of those exposed to MDC care may account for the findings. This would require additional confirmation with extended studies. Certainly the duration of individual patient exposure per interaction of at least 2 times longer (8 vs. 4 h), despite similar total patient exposure in months, could be important. We hypothesize that a number of qualitative, not just

quantitative, differences in exposure contributed to the outcomes. Importantly, the actual time spent with the patients may overtly reinforce the importance of the condition to the patients, thereby influencing patient compliance and thus outcomes.

We chose to focus on only those persons who had been exposed to nephrologists for > 3 months prior to dialysis start. This 3 month cut-off is a construct derived from the literature; importantly for this analysis, it serves to eliminate those patients truly referred late. Current guidelines suggest that up to 6 months in advance of dialysis initiation may be needed for adequate vascular access maturation and optimization of care [40, 162]. Nonetheless, even using this 3 month cut-off, the exposure to nephrologists in both groups of interest (formal clinic and nephrology alone) still averaged 42 months: well over 3 years of clinical care. This study then describes the outcomes of patients followed for substantial periods of time. The finding that patients chose hemodialysis 60% of the time irrespective of care model is interesting. It is noted that 60% is well below the national average in both countries (Canada 72%, Italy 89%; and in both regions ~ 70%) thus indicating the higher propensity for these patients to choose home-based peritoneal dialysis as their treatment of choice. This corroborates other studies of early vs. late referral which demonstrate that those referred early are more likely to choose independent-based care than those who are referred later [133].

There is increasing recognition of the importance of CKD [5, 86] and a growing number of CKD patients. It is imperative to develop evidence-based strategies that maximize outcomes. The importance of early referral to nephrologists is not disputed and has been

well described by many authors to date [131-133, 144]. Early referral is essential to identify the myriad of abnormalities, and plans for their treatment are best achieved in consultation with specialist care. However, it may be that the ability of individual nephrologists to attend to the multiple and complex aspects of care in this patient group, in the absence of formal clinic teams, is limited. Publications using United States [42, 163] and Canadian data [164] demonstrate that even the care of patients with CKD who are known to nephrologists continues to be suboptimal. Out study corroborates these findings.

In summary, this study suggests that even after appropriate and timely referral to a nephrologist, there is additional value of a multi-disciplinary team in optimizing both short, and long-term patient outcomes [5, 12]. Uniquely, we extend observations of previous studies and demonstrate a potential survival advantage of formal MDCs. The value of each of the components of the clinic program (i.e. personnel, protocol driven laboratory / visit schedule and treatment plans) is not known. Research needs to be undertaken to prospectively follow patients from entry into the nephrology / MDC care to confirm these findings and determine whether other objectives of the clinic, such as delaying progression, are met.

Chapter 4: Evaluation and treatment of CKD patients before and at their first Nephrologist Encounter in Canada

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4.1 Introduction

The burden of illness in dialysis patients remains unacceptably high [1, 165, 166]. Many of the co-morbid conditions impacting on long-term morbidity and mortality are present in earlier stages of chronic kidney disease (CKD) and are modifiable by education, nutritional counselling, and drug therapies [4, 167, 168]. The goals of care for patients with CKD thus include delay of progression of kidney disease and evaluation and treatment of comorbid conditions and complications.

Although our understanding of the epidemiological characteristics of risk factors for adverse outcomes in dialysis patients has improved, we do not have a good understanding of those in patients with CKD not yet on dialysis therapy. Specific factors linked to adverse patient outcomes include anemia, hypertension, malnutrition, academia, and abnormal mineral and bone metabolism. Data from both the United States and Canada showed that even in patients followed up by nephrologists, many of these factors were evident at dialysis therapy initiation [9, 10, 169-171]. However, it is not known whether this was caused by a lack of optimal CKD care.

Although some studies described care models for chronic disease [12, 17], and multidisciplinary care in patients with CKD [8, 10, 168, 171-173], no formal definition or evaluation of the structure and elements of nephrology care was developed. In addition, it is not clear which elements of care are essential to achieve optimal outcomes.

The main objectives of this study are to describe: 1) characteristics of patients at their first nephrology encounter in Canada; 2) evaluation for cardiac risk factors, cardiac diseases, and CKD complications and their management before the encounter; 3) changes in management initiated by nephrologists at the first encounter; and 4) the availability and use of allied health professional services for CKD care. This exploration will enable the identification of strategies to improve CKD care from both physician and system perspectives.

4.2 Methods

This study is part of the Canadian Care Prior to Dialysis (Can-Care) Study, a larger peer-reviewed study partly funded by the Kidney Foundation of Canada in conjunction with both Baxter Canada and Ortho Biotech Canada. It is a Canadian prospective multi-centre observational cohort study designed to enroll consecutive patients with glomerular filtration rate (GFR) < 50 mL/min/1.73m^2 (< 0.83 mL/s/1.73 m^2; measured or estimated by any means) at their first encounter with a nephrologist. The 4-variable (isotope dilution mass spectrometry) Modification of Diet in Renal Disease (MDRD) Study equation [152] was used to estimate GFR. This study was conducted before creatinine standardization or calibration in Canada.

Patients were enrolled between November 2000 and March 2004. At the time of study initiation, Canadian recommendations were to refer patients to a nephrologist if: 1) serum creatinine greater than 3.4 mg/dL (>300 μmol/L), 2) creatinine clearance less than 30 mL/min (< 0.50 mL/s), or 3) serum creatinine is increasing rapidly [40]. The Canadian health care system provides universal coverage, and specialist referral does not generate direct cost to patients or disincentives to the referring provider. However, documentation accompanying referral requests may vary from "please see this patient with possible abnormal kidney function" to very detailed letters with complete workup documented. Subsequent to referral, nephrologists decide to either discharge the patient back to care of the referring physician (usually with recommendations and suggestions for later referral if needed) or continue co-management with the referring physician

The aim of the overall Can-Care study is to evaluate the hypothesis that exposure of patients with CKD to specific elements of care leads to the achievement of target values for factors linked to morbidity and mortality in dialysis patients. The objectives of the Can-Care study are as follows: 1) to describe the elements of care to which patients with CKD are exposed. The major elements include timing, frequency, extent and / or use of protocol for a) laboratory measurement, b) clinical evaluation (weight, blood pressure, and medication review), c) nutritional counseling, d) educational programs, and e) interaction with a multidisciplinary team; 2) to describe the prevalence of laboratory abnormalities and hypertension at the time of referral and yearly (up to 4 years); 3) to explore the link between elements of care and outcomes (including quality of life).

The participating centres included both community-based practices (Kamloops, BC; Penticton, BC) and urban university settings (Vancouver, BC; Saskatoon, SK; Winnipeg, MB [2 sites]; Toronto, ON [2 sites]; London, ON; Montreal, QC; Quebec City, QC; Halifax, NS; St. John's, NL). Patients with acute kidney failure were excluded, as were patients with CKD believed likely to require dialysis therapy within 3 months of referral (e.g. "acutely recognized" CKD). No attempt to direct practice, alter therapy, or modify follow-up patterns was made as a consequence of enrolment. Research ethics board approval was obtained at participating centres, and individual patient consent was obtained.

Data Collection

Trained research nurses collected all data. Prior to study initiation, a centralized training meeting was held with the nurses to explain the purpose of the study and data collection methods. Standardized data collection forms were developed with input from the nurses. All data were entered centrally. After patient enrolment, data were evaluated for potential errors and missing values with subsequent prompting of the study centres for clarification. After the first year after study initiation, members of the steering committee formally liaised with each research nurse and local principal investigator by conference call. This allowed for potential data collection problems to be remedied further.

The research nurses screened consecutive nephrology referrals, including both hospital and office based. Data collection forms were used to obtain data available both 1) before

the patient was seen by a nephrologist and 2) after nephrology assessment. Although the attending nephrologists were not directly involved in the data collection process, data sources included all those that the nephrologist would have access to: referral letter, outpatient / inpatient / emergency room department charts, computer records (laboratory and radiology data, prior consult / discharge letters, and so on) and patient interviews. Assessments done in the nephrologists' office or at a patient's bedside (eg routine urinalysis by using dipstick) would be available to the research nurse if documented in the consult letter or chart. The research nurse did not have access to data verbally communicated from referring physician to nephrologist that was not otherwise documented. Thus, missing data about prior investigations could be caused by those 1) not done; 2) done, but not available to the nephrologist; or 3) done and available to nephrologist through verbal communication, but not documented.

Data collection included patient demographics, referral patterns (referring physician, time from referral to being seen, travel time and distance to nephrologist, and so on) as well as clinical, laboratory, and medication information. Treatment strategies, such as cardio-renal risk-factor assessment and modification and anemia and mineral metabolism management before and during the first nephrology visit, were examined. The following definitions were used for data collection: coronary artery disease documented by history of same or intervention (angioplasty); left ventricular hypertrophy documented by echocardiogram; myocardial infarction documented by history and/or cardiac evaluations; cerebro-vascular accident documented by history and/or radiological documentation; peripheral vascular disease documented by history / physical examination

(e.g. claudication / pedal pulses) and/or documentation of investigation (e.g. angiogram); any non-specific bone disease documented by history, physical examination, laboratory results (including abnormal parathyroid hormone), and/or documentation of investigation (e.g. X-Ray, bone mineral density); bone pain by history; fracture documentation of spontaneous, non-traumatic fractures or fractures from any trauma.

Availability of and use of additional services, including evaluation and treatment by allied health personnel, educational programs, and nutritional counselling, were documented at first encounter by using questionnaires. Educational programs were defined as those specifically targeting CKD issues (including what kidneys do, what CKD means, what dialysis means, lifestyle modification etc). They involved the patient and family (if requested) meeting with the educator, usually a specialized nurse, and may have also included a set of ancillary learning materials, such as books and video. Nutritional counselling included that which targeted CKD issues (low potassium and phosphate levels) and relevant co-morbid disease (salt restriction for hypertension / congestive heart failure, low fat diet etc). Because counselling could be provided by renal dieticians and may include other members of the team (nephrologist or nurse educator), data were collected for both types of encounters. Furthermore, resources were considered formal (versus informal) if they were part of a follow-up according to protocol with predetermined therapeutic goals specific to CKD. Finally, options for various team structures available at the participating centers were categorized as follows [8]:

Care delivered by a coordinated team dedicated to CKD: Nephrologists and allied health professionals (nurses, nurse educators, dieticians, social workers, and pharmacists) interact with the patient and each other as a formal multidisciplinary team. Although there were a number of different configurations because of funding and local health care system issues, for the purpose of this definition, a team was readily identifiable as dedicated (part or full time) to CKD care. Generally, there would be team rounds or meetings. Average duration of exposure of the patient to the team was approximately 1.5 hours for the encounter. Additional details of the multi-disciplinary clinics also were described elsewhere [8, 10, 51].

Dedicated CKD care delivered outside of a coordinated team: The patient receives care by a professional or professionals from a CKD team dependent on the patient's need but without coordination or input by the entire team.

Ad hoc CKD care: Allied health personnel(s) not affiliated or coordinated as a CKD team provide care to the patient when requested by the nephrologist on an "as needed" basis.

Resource exposure was defined as first contact with an allied health care professional and / or nephrologist. Although all patients in this study were assessed by a nephrologist, it was possible that upon receiving a consult or referral, the nephrologist had the patient assessed by an allied health care professional or the CKD care team before seeing the patient him/herself.

Analysis

Descriptive analyses are presented as mean ± standard deviation or median [with inter-quartile range] depending on distribution. Because of variation in assays and reporting, some laboratory data are shown only as having been ordered or not (ie. specific values for results of parathyroid hormone and urinalysis are not given). Multiple linear regression was used to investigate independent predictors of wait-times. Variables for this model included demographics, referral source (inpatient, emergency department etc), referring physician specialty, patient distance and travel time, blood pressure, laboratory (creatinine, hemoglobin, albumin, urine studies) and co-morbidity (diabetes, hypertension, etc) data.

4.3 Results

Patient Characteristics at first encounter

Four-hundred eighty-two incident CKD patients were enrolled from 13 Canadian centres. We report here only the data from the initial encounter. Follow up data will be analyzed and reported when available. No major differences in patient characteristics were apparent between sites; however, statistical comparisons were limited because of low numbers enrolled at individual centers.

Table 4.1 lists demographic and clinical data at referral. Mean age of the cohort was 69.7 years, with just more than 40% women and a majority of white patients. Two-thirds of the patients were retired, reflecting their age. Importantly, blood pressure was not

optimally controlled and patients were overweight. Of interest, more than 2% of patients were already enrolled in ongoing clinical trials before referral.

Table 4.1 Demographic and Clinical Data for Patients with CKD at the Time of First Referral to Nephrologists

N	482
Age (years)	69.7 ± 12.4
Gender (% Female)	42
Race: (%)	
White	90
Aboriginal	3
Asian	2
Filipino	2
East Indian	2
Black	0.4
Latin American	0.4
Employment Status (%)	
Retired	68
Work > 35 hrs / week	10
Work < 35 hrs / week	3.5
Disability	7
Unemployed	4
Homemaker	6.5
Other	2

Blood Pressure (mm Hg)	147 ± 25 / 76 ± 13
Proteinuria > 0.5 g/day* (%)	13
Weight (pounds)	172 ± 37
Body Mass Index (metric)	29 ± 6
Current Smoker (%)	16
Patient in a Clinical Trial Before Referral (%)	2.3

*Information on proteinuria status was documented before referral for only 64 patients (i.e. 8 of these has proteinuria > 0.5 g). Continuous Data expressed as Mean ± Standard Deviation

Characteristics of Referral

How the CKD patients were referred to Nephrologists and the plans for follow-up after the encounter is shown in Table 4.2. The majority of patients were referred by Family Physicians. Over 90% of patients were referred as outpatients and seen in the Nephrologists' office or clinic. Patients' self-reported median distance from home to nephrologist was 9 miles (15 km) with 75% of patients within 40 miles (65 km)—travel times to nephrologist are concordant with these data. The median wait time from initial referral to first nephrologist visit was 43 days. Independent significant predictors of shorter wait-times ($P < 0.05$) were lower estimated GFR and inpatient referral. The estimated GFR did not change much over this waiting time. Patients were referred with a median estimated GFR of 29 mL/min with 59% of patients referred at CKD Stage IV or V. Nephrologists planned to follow almost this entire cohort of patients in co-management with the referring physician.

Table 4.2 Referral of CKD Patients to Nephrologists in Canada

Referring physician (%)	
Family Physician	80
Internal Medicine	5
Cardiologist	5
Endocrinologist	4
Emergency Physician	1
Other	5
Location where referral or consultation originated (%)	
Outpatient / office / clinic	92
Inpatient	6
Emergency department	2
Physical examination documented by referring physician (%)	39
Location of first nephrology encounter (%)	
Nephrology office / clinic	95
Hospital inpatient	4
Emergency department	1
Distance from patient to nephrologist (miles)	9 [4, 40]
One-way travel time to see nephrologist (min)	25 [15, 60]
Wait-time from referral to being seen (days)	43 [19, 74]

GFR* when referred (mL/min/1.73 m^2)	29 ± 12
	27 [22, 36]
GFR* when seen by Nephrologist (mL/min/1.73 m^2)	29 ± 11
	27 [21, 35]
Median Change in GFR* from referral to nephrologist visit	- 0.3 [-4, 3]
CKD Stage at Encounter (%)	
II	1.5
III	39.5
IV	52
V	7
Plan for follow-up after encounter (%)	
Nephrology office / clinic	92
Family physician	7
Other	1

Continuous data are shown as mean ± standard deviation or median [25^{th} –75^{th} percentile]
*Estimated by Abbreviated MDRD Study equation [152]

Burden of Illness at Referral

Tables 4.3 and 4.4 list the burden of cardiac risk factors, cardiac disease and CKD complications already present at the encounter. Almost half the cohort had diabetes, 80% had hypertension and more than half had a smoking history. Of note, 31% of patients had established coronary artery disease and about 20% of patients had peripheral vascular disease, a previous myocardial infarction, and / or an episode of congestive heart failure. The reported symptoms of patients with cardiac disease listed in Table 4.4 describe this in more detail. One-fifth of patients had established non-specific bone disease or pain.

Table 4.3 Prevalence of Cardiac Disease, Cardiac Risk Factors and CKD Complications at First Nephrology Encounter

Any history of smoking (%)	58
Diabetes mellitus (%)	43
Type II (% of those with diabetes)	87
Hypertension (%)	80
Cardiovascular Disease Co-Morbidities	
Coronary artery disease (%)	31
Prior myocardial infarction (%)	20
Prior coronary artery bypass grafting (%)	9
Prior cardiac angioplasty (%)	7
Congestive heart failure (%)	19
Documented left ventricular hypertrophy (%)	7
Prior cerebro-vascular accident (%)	9
Peripheral vascular disease (%)	18
Mineral Metabolism	
Any non-specific bone disease (%)	15
Bone pain (%)	19
Prior fracture in last 10 years (%)	4

Table 4.4 Reported Symptoms At First Nephrology Encounter for Patients With Cardiac Disease

Heart failure - New York Heart Association classification (%)	
I	42
II	41
III	14
IV	3
Angina – Canadian Cardiovascular Society classification (%)	
I	59
II	24
III	10
IV	4
V	3

Management Before the Encounter

Table 4.5 shows laboratory data ordered by the referring physician and available for assessment by nephrologist at the time of referral. Data are shown as both numbers of tests available, as ordered by referring physician, and test result if available. Of interest, at the time of referral serum creatinine values were available for only 84% of patients, and hemoglobin values for 51%. Results of tests for albumin, lipids, iron, and mineral metabolism (serum calcium, phosphate and parathyroid hormone) were available for less

than a third of patients at the time of encounter. Of results that were available, mean hemoglobin level was 12.1 g/dL (121 g/L), and albumin level was 3.6 g/dL (36 g/L). For patients with an available hemoglobin result and with latest results less than < 12 g/dL, results of iron studies were available for less than 20% of patients. As listed in Table 4.6, before the encounter, less than half of patients were being treated with ace inhibitor / angiotensin receptor blocker, and only 30% were being treated with acetylsalicylic acid or lipid medication. Furthermore, 11% of patients were administered non-steroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-II (COX-II) inhibitors. Specific interventions for proteinuria, previous myocardial infarction, dyslipidemia, and anemia are also listed. We were unable to examine data for mineral metabolism intervention (serum calcium, phosphate, and parathyroid hormone abnormalities and pharmaceutical intervention with phosphate binders or vitamin D analogs) because: a) so few patients had results for these tests available b) even fewer had results that were out of range (e.g. 6 patients had serum phosphate >1.8 mmol/L) and c) different parathyroid hormone assays made comparison impossible.

Management at First Encounter

Percentages of laboratory tests available to or subsequently ordered by the nephrologist are also shown in Table 4.5. Nephrologists had available or obtained the following further investigations in >70% of patients: hemoglobin, albumin, and calcium/phosphate. However, at first assessment nephrologists did not order laboratory testing of parathyroid hormone in 83% of patients, lipid profiles in > 50%, nor iron studies (of those with anemia) in 57%. Interestingly, urine studies (routine or 24 hour urinalysis) were not

ordered in 30%. Medication profiles after the encounter are also listed in Table 4.6. Data show that medical therapies after first nephrologist encounter were similar to those before (including NSAID and COX-II inhibitor use). Data about medications for proteinuria, previous myocardial infarction, dyslipidemia and anemia are based on information available to the nephrologist at the encounter. Use of iron, erythropoietin and calcium supplementation and / or phosphate binders increased at the first nephrology encounter, and 38% of patients with systolic blood pressure > 130 mmHg at referral had blood pressure medications added and/or doses increased (data not shown in table).

Table 4.5 Laboratory Evaluation

	Tests with results available at first Nephrology Encounter		**Tests Ordered by Nephrologist**		**Tests with Results Available to Nephrologist after first patient encounter**
	N (%)	Result†	N (%)	Result†	N (%)
Serum Creatinine (g/dL)	405 (84)	2.4±0.9	381 (79)	2.4±1.0	466 (97)
Serum Urea (mg/dL)	261 (54)	42±17	344 (71)	45±25	412 (85)
Hemoglobin (g/dL)	248 (51)	12.1±1.8	326 (68)	12.1±1.9	404 (84)
Serum Albumin (g/dL)	113 (23)	3.6±0.6	317 (66)	3.7±0.5	368 (76)
Serum Bicarbonate (mEq/L)	79 (16)	26±4	243 (50)	26±4	265 (55)
Serum Transferrin-Sat (%)	27 (6)	23±8	167 (35)	20±9	185 (38)
Serum Ferritin (ng/mL)	45 (9)	52±35	134 (28)	53±52	166 (34)
If Hemoglobin < 12 g/dL	127 (26)		212 (44)		
Serum Transferrin-Sat (%)	12 (9)	22±10	13 (6)	22±7	53 (42)

Serum Ferritin (ng/mL)	23 (18)	50±24	25 (12)	54±34	54 (43)
Serum Calcium (mg/dL)	110 (23)	9.2±0.6	318 (66)	9.3±1.5	365 (76)
Serum Phosphate (mg/dL)	87 (18)	4.0±1.1	301 (62)	3.9±0.9	344 (71)
Serum Parathyroid Hormone*	14 (3)	--	73 (15)	--	82 (17)
Serum Cholesterol (mg/dL)	131 (27)	205±54	106 (22)	197±50	205 (43)
Serum LDL (mg/dL)	114 (24)	120±46	80 (17)	104±35	172 (36)
Serum HDL (mg/dL)	121 (25)	50±35	83 (17)	46±23	181 (38)
Serum Triglyceride (mg/dL)	122 (25)	213±115	88 (18)	221±177	187 (39)
Any Urine Assessment	207 (43)	--	258 (54)	--	337 (70)
Any Routine Urinalysis	120 (25)	--	190 (39)	--	254 (53)
Any 24 Hour Urine Study	135 (28)	--	122 (25)	--	222 (46)

[†]Data are shown as Mean ± Standard Deviation, *Serum Parathyroid Hormone obtained using different assays in various centres; LDL / HDL – Low / High Density Lipoprotein

Table 4.6 Patient Medication Profile Before and After first Encounter By Nephrologist

	% Taking Medication	
	Before Encounter	After Encounter
Ace Inhibitor	36	40
Angiotensin Receptor Blocker	12	10
Ace Inhibitor or Angiotensin Receptor Blocker	46	46
If Proteinuria > 0.5 g/day*		
Ace Inhibitor or Angiotensin Receptor Blocker	55	53
Acetylsalicylic Acid	30	37
Beta Blocker	32	30
If Prior Myocardial Infarction*		
Acetylsalicylic Acid	41	58
Beta Blocker	48	48
Calcium Channel Blocker	31	35
Non-Dihydropyridine		14
Dihydropyridine		22
Alpha Blocker	6	4
Nitrate	14	15
Diuretic	46	46

Any Lipid Medication	30	32
If LDL > 97 mg/dL (2.5 mmol/L)*	38	40
If LDL > 135 mg/dL (3.5 mmol/L)*	49	52
Statin		27
Fibrate		6
Other		2
Iron Supplementation	6	14
If Hemoglobin < 12 g/dL (120 g/L)*	10	23
If Hemoglobin < 11 g/dL (110 g/L)*	16	27
If Hemoglobin < 10 g/dL (100 g/L)*	22	41
Erythropoietin	0	4
If Hemoglobin < 12 g/dL (120 g/L)*	0	8
If Hemoglobin < 11 g/dL (110 g/L)*	0	13
If Hemoglobin < 10 g/dL (100 g/L)*	0	19
Calcium Supplementation / Phosphate Binder	6	18
Calcium Supplementation	5	16
Phosphate Binder	0.6	4
Vitamin D Supplementation	3	4
Vitamin B Supplementation	5	7
Folate Supplementation	2	4
NSAID or COX II Inhibitor†	11	11
NSAID	7	7

COX II Inhibitor	5	5

*Data on disease or lab tests for proteinuria, myocardial infarction, dyslipidemia, anemia were those available to the Nephrologist before the encounter
†NSAID: Non-steroidal anti-inflammatory; COX-II: cyclooxygenase-II inhibitor

Availability and Exposure to other Resources

Table 4.7 lists the resources available to patients at the participating centres, and the percentage of patients who got exposure in the different delivery settings at first encounter. Despite 86% of patients being treated at centers with availability of educational programs, nutritional counseling and allied health care professionals, a smaller number could actually take advantage by coming into contact with these resources. However, patient exposure to all resources increased to 92 - 98% (data not shown) if the program had a formal structure with protocolized follow-up and predetermined goals for CKD care (e.g. exposure was driven by eGFR).

Table 4.7 CKD resource availability and utilization at first encounter

	Resource Available to the Patient (%)	Patient Exposed to the Resource (%)*	
		Formal	Informal
CKD Educational Program	86	7	3
Nutritional Counselling**	86	20	4
Dedicated CKD Multidisciplinary Team	83	10	0.4
Nephrologist	98	70	27
Nurse	86	36	11
Social Worker	85	7	0.2
Dietician	85	19	2
Pharmacist	54	8	0.2

*See text for details about Formal versus Informal Resources
**includes counselling by dietician, nursing staff and / or physician

4.4 Discussion

We describe a Canadian group of patients at their first encounter with nephrologists. Their treatments appear to be suboptimal before the encounter. Transmission of clinical information with the referral or consultation is limited. We further document the evaluation at the encounter and changes in medications. Further, we describe what additional resources and allied health care services are available to nephrologists and patients with CKD at our centers. The Canadian health care system is one of national universal health care coverage similar to that in Australia, the United Kingdom and parts of Europe where direct cost to the patient are not likely to result in underutilization. Physician services are free to patients at point of care and paid from government sources. All allied health care workers in this study were employed by the health care facilities and provided CKD care without charge to the patient. Similarly, patients do not have to pay for diagnostic assessments. However, patients may have to pay for their own outpatient pharmaceuticals either out of pocket or through private insurance. Provinces differ with respect to which patients groups can access various medications on a publicly funded formulary. In general, patients over 65 years of age or those receiving social welfare payments would be entitled to such access. In some jurisdictions (eg British Columbia and Ontario) patients with specific disease conditions (eg anemia of kidney disease) may be entitled to access specific therapies (eg erythropoiesis stimulating agents).

Our data reveals that relatively late nephrology referral persists in Canada despite attempts to address this issue [40]. In our study enrolment occurred just after the

Canadian CKD guidelines were published but before extensive uptake. The median wait time of 43 days for stage IV CKD may be reasonable given that the patients' estimated GFR did not decline very much, and the fact that lower estimated GFR predicted shorter wait times. Guidelines establishing wait time benchmarks for CKD referral do not currently exist, and further data would be required to determine these.

More importantly, despite the burden of CVD illness in this cohort, there remained incomplete investigation of CKD, incomplete evaluation for CVD co-morbid diseases, and lack of complete application of proven effective therapies for cardiovascular disease and CKD co-morbidities. Indeed others have shown that prevalent CKD patients do not get adequate care [9, 164, 171, 172, 174-176] in keeping with documented 'therapeutic nihilism' that may exist in the approach to treatment of these patients [164, 174, 177-179]. It is important to highlight this point given that Canadian nephrologists believe that CKD referral should occur at Stage III [180] and that nephrologists should represent the reference of CKD care.

Other interesting points in this study are the descriptions of missing data or data not available to the nephrologists at the time of referral. This study was not designed to evaluate referring physicians' practices per se as their charts may not have been available—we thus cannot determine whether the investigations were not done versus done and not available. Both are important as the potential repeating of laboratory testing by the nephrologist in some cases may reflect a costly redundancy without benefit. Future studies should determine the amount of duplicate testing in this patient group, and define

better methods for information transfer. Currently there is no expectation regarding transmission of 'standard' information at time of referral to nephrologist: this may contribute to the variation seen in this study. Despite guidelines and education to Family Physicians, a widespread standard referral form with essential information (a tool to improve communication, reduce redundancies, and indirectly educate) does not exist. The potential improvements in care and cost savings of such a tool should be explored.

Our data also demonstrates that there is variability in nephrology care; the reasons for this are not readily explained from the present study. It appears that at first visit nephrologists are intervening with CKD specific therapies (e.g. anemia therapies) but may not address the addition of renin angiotensin system blockade, reduction in proteinuria or cardiovascular risk profiles. Moreover, nephrologists are not discontinuing medications that may increase risk for both poor cardiovascular outcomes and progression of CKD (e.g. NSAIDs) [181]. There is also inconsistency amongst nephrologists in the initial evaluation 'panel', which may further confuse referring physicians as to the necessity of evaluation in CKD. This study is unable to answer the question as to the proportion of the variability explained by patient or situational issues versus individual practice pattern. This would be the target of future studies.

Weaknesses of this study include those inherent in its design and possible limitations of external validity. As a non-interventional study, the data collected were simply tabulations of information available at the first nephrology encounter. To our knowledge these patients and their characteristics are representative of those first encountered by

nephrologists across Canada; however we did not collect data in centres that were not participating, and regional differences cannot be ruled out. As this descriptive study did not directly question referring physicians nor nephrologists, other referral biases may exist. For example, physicians may be only referring patients that they consider "difficult" and have patients in their practice with similar GFR but that they are able to manage according to guidelines. As this study was conducted to understand the care of patients referred for CKD care, those with imminent dialysis initiation were excluded. This exclusion likely results in under-estimation of the problem.

Furthermore, we cannot infer causes or to judge "appropriateness" in detail (eg. reasons for not using angiotensin converting enzyme inhibitors). It is quite possible that interventions not implemented at the first encounter would be initiated later. Other non-pharmacological interventions such as protein restriction or exercise counselling were also not captured. Finally, because the study was conducted prior to any creatinine standardization or calibration, some patients may have been misclassified. However, we chose a conservative cut-off for estimated GFR of 50 mL/min/1.73m^2 and the mean level of estimated GFR was well in the range of CKD stage III.

Unique to this study are the findings of incomplete transmission of clinical information on patient evaluation and sub-optimal application of appropriate medical therapies by referring physicians, and after the first visit to a nephrologist. The current referral practice does not reflect a sophisticated understanding of the complexity of caring for

CKD patients by the referring physicians. Furthermore, there appears to be room for improvement in the care delivered by nephrologists at the first encounter.

The resources available to nephrologists are variable, and irrespective of the variability the majority of patients do not access these resources at first visit. The data suggest that if the various resources are offered in a formal protocolized manner, patients are more likely to be exposed to them. Further analysis will explore the relationship between care resource exposure and outcomes.

This study represents the first attempt to prospectively document and evaluate the care of CKD patients at the time of first nephrology encounter in a universal health care system. It enhances our understanding of the referral process and evaluates care patters to identify opportunities for improvement. Interventions to improve transmission of referral information implementation of comprehensive care plans should be the focus of future studies. Improved care with appropriate resources should ultimately improve patient outcomes.

4.5 Addendum

Further analysis of this cohort completed since original publication includes follow-up of clinical outcomes (unpublished data). After a median follow-up of 28 [17, 41] months, 78 (16%) patients died, 55 (11%) initiated kidney replacement therapy (KRT), 26 (5%) were discharged from nephrology care, and 38 (8%) were lost to follow-up. Significant univariate predictors of death were baseline age, history of cardiac disease, estimated

GFR, hemoglobin, and phosphate. Univariate predictors of a composite endpoint of death or KRT were baseline history of cardiac disease, estimated GFR, hemoglobin, albumin, calcium, phosphate, hypertension, and proteinuria. Multivariate Cox-proportional hazards modeling revealed age (β=1.08 / year), initial phosphate (β=3.48 / mmol/L), and initial Hb (β=1.02 / g/L) as significant predictors for death. Baseline estimated GFR (β=1.07 / mL/min), history of cardiac disease (β= 3.6) and initial phosphate (β=6.5) and LDL (β=1.4 / mmol/L) were significant predictors for composite death or KRT. Only proteinuria was a significant predictor of estimated GFR decline in both univariate and multivariate linear regression modeling.

Chapter 5: Conclusion

Ensuring that patients are adequately prepared for dialysis is no longer a sufficient primary goal of CKD care. In chapter 1 it was suggested that patient outcomes could be improved by intervening earlier in the course of CKD, and on many levels. Thus, the overall paradigm of CKD care appropriately changed to focus on the prevention of the progression of CKD in conjunction with the prevention of its concomitant morbidity and mortality.

The question remains—how best to achieve these goals? The findings in Chapter 2 suggest that substantial numbers of patients across Canada started dialysis with suboptimal clinical and laboratory parameters despite being previously followed by a nephrologist. The main limitations of the survey were inherent in its design. It was unable to examine what happened to these patients during their prior CKD care (i.e. those patients not progressing were not in the study population). It may be possible that nephrologists were successful with other goals: a) preventing progression, and thus not having patients progress to require dialysis therapy; or b) preventing other co-morbidities that accompany CKD. Furthermore, an alternate explanation for some of the findings would include the possibility that, despite the best intentions of the nephrology care team, patients may have declined recommendations (e.g. refused to start dialysis earlier) or had an unexpected precipitating event (e.g. myocardial infarction or infection) contributing to the poor clinical and laboratory parameters. Finally, quality of life, an important aspect from the patients' perspective, was not examined formally. Despite these limitations, the

study's findings provide useful baseline information that may be used for comparison across the country.

Similar limitations apply to the study presented in Chapter 3. CKD care and survival prior to dialysis start was not examined formally. A second limitation includes a potential bias associated with the type of patient that is willing to attend these multidisciplinary clinics. There may be some inherent patient characteristic (e.g. attitude, interest, motivation, etc) that would make them more likely to do better (e.g. more compliant with medications). The study's strength lies in its ability to examine an important clinical outcome—survival. However, the optimal way to address this question of how to best care for CKD patients may be through a randomized control trial.

Finally, Chapter 4 suggests there is room for improvement in evaluation and treatment of CKD patients before they reach dialysis. In fact, it may in part explain the findings of Chapter 2. As discussed previously, the main limitations of the study include external validity and referral bias. Finally, the inability to make causal inferences reinforces the need for further studies to determine if intervention in phosphate and haemoglobin control, for example, will translate into better outcomes in this population.

Although there appears to be evidence to support the idea that a multidisciplinary care model would be appropriate for CKD care, barriers to the implementation of MDC models remain before embracing this fully. The first issue is cost. Team's staff salaries and infrastructure must be taken into account within a complex system with other

competing issues (e.g. cancer care and wait-times). Data from a randomized control trial of CKD care supporting the effectiveness of a MDC model is necessary before endorsing this type of model as a national recommendation. The study would also need to incorporate some form of economic analysis before governments or other health care payers would be willing to make this a fiscal priority. Another barrier would be nephrology buy-in as this would mean a paradigm shift for many nephrologists accepting that there may be a more optimal method for CKD care. However, overcoming the barrier of changing physician practice may be made easier through further study and education. Of course this must not only include the issue of CKD care itself, but also research into optimal ways of changing physician practice. Patient and family buy-in would also be required. Even if it was known that this multidisciplinary care model was best for CKD care, the team may not be able to help those patients who are just not interested.

A further important issue in Canada is access to care in general. Given the country's low population density, with a significant proportion of the population living in rural areas, even access to family physicians is a potential barrier to care and would contribute to low or late CKD referral. Other practical difficulties also arise such as the physical distance between where patients live and where specialist care exists. This not only entails the time for travel, but must also include patient and family travel costs.

Other questions remain about CKD care. These include how early should specific care begin or what aspects of nephrology care should occur when (i.e. at the first nephrology

encounter or later)? Furthermore, not all CKD care may be so "complex" to necessitate a multidisciplinary care model and may not benefit or be relevant for patients that choose conservative management (i.e. no dialysis). Finally, it is not clear where in the health system certain issues should be dealt with (e.g. lipid or diabetes management). Many would argue that some of these should be the focus of primary versus specialist care. Indeed, given that a significant number of CKD patients a) have already had a cardiovascular event prior to referral, b) are referred on inadequate cardiovascular risk reduction therapy, and c) may be more likely to die from cardiovascular disease then progress to dialysis, it may be more important and appropriate to focus health care efforts on improving overall primary and secondary cardiovascular care independent of CKD. Regardless, a main issue should be a focus on communication and integration of care.

Overall, this thesis incorporates novel data at various points along the spectrum of CKD care whereby patient care might be improved. However, nephrologists alone may not be adequate for this chronic disease care model. Data herein should also allow for nephrology programs to focus on improved CKD care along different points of the CKD spectrum. For example, setting continuous quality improvement targets for access placement prior to dialysis, or haemoglobin target achievement for late stage CKD. Earlier along the course of disease it might be more appropriate to examine practice with respect to blood pressure targets or medication review. Centres with available fiscal and staffing resources have already been incorporating some aspects of this model into their CKD care program. Despite this, enough equipoise exists such that randomized control trials are still needed to address some of these questions in CKD care.

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