

The Relationship between Staffing Pattern and Process of Care in
Patients with Chronic Kidney Disease (CKD) – An analysis of the data
from the CANPREVENT Clinical trial

By

© John Shik, BSc, MD

A thesis submitted to the School of Graduate Studies in partial
fulfillment of the requirements for the degree of Master of Science

Department of Clinical Epidemiology
Faculty of Medicine
Memorial University
May 2014

St. John's

Newfoundland

Abstract

Chronic Kidney Disease (CKD) is associated with much morbidity and mortality in the general population. It not only is a precursor for End-stage renal disease (ESRD), but also serves as a significant risk factor for cardiovascular disease.

The care of patients with CKD is complex and often involves blood pressure lowering, renin-angiotensin system interruption, lipid lowering, anemia management, and control of mineral metabolism.

Currently, the literature lacks evidence and consensus regarding how best to deliver care to this patient population. In particular, the degree of specialist involvement, care consistency, nursing expertise and multidisciplinary team involvement may all influence achievement of treatment targets and ultimately patient outcomes.

CANPREVENT was a randomized controlled multicentre trial with 500 subjects comparing usual care by a primary physician to a model of CKD care involving a nurse as a primary caregiver supported by a nephrologist. This model proposes the delivery of a chronic disease management clinic with multiple risk factor intervention for people with moderate chronic kidney disease.

By further analyzing data from this trial across the five trial sites, we examined whether differences in nursing educational background, and staffing consistency during the trial, all of which differed by site, were associated with achievement of treatment targets and surrogate outcomes. The hope was that the results would help direct future care and research into care delivery for chronic disease.

In this analysis, no major differences in the clinical practice patterns were detected amongst the interventional sites. Overall, none of the interventional sites had consistently superior adherence rates for clinical interventions. However, the small number of sites and the low numbers of eligible participants at each site, reduced the power of the analysis. Based on these results, no clear definite association can be drawn between interventional sites, nursing expertise, continuity of care and practice pattern.

Acknowledgements

First I would like to thank my wife, Jennifer, for her help, encouragement and understanding throughout this project.

I would also like to thank my parents, Maureen and Chen Fong, for instilling the importance of life-long learning in me.

I would like to thank my supervisor, Dr. Brendan Barrett, for his ideas, support, advice, and insight from the inception to the end of this project.

I would also like to thank the members of my supervisory committee: Dr. Anita Molzahn and Dr. Patrick Parfrey for helpful and invaluable advice in preparation and finalization of the manuscript.

Table of Contents

Abstract	ii
Acknowledgement	iii
List of Tables	v
Introduction	1
<i>Modifiable risk factors for CVD and CKD</i>	2
<i>Modifiable risk factors relating to CVD</i>	3
<i>Modifiable risk factors relating to CKD</i>	5
<i>Care of CKD patients</i>	7
<i>Patient care delivery by nurses</i>	9
<i>Continuity of Care</i>	11
Materials and Methods	15
<i>Study Design</i>	17
<i>Interventional Groups at each site</i>	17
Relational Continuity	18
Nursing educational background	19
<i>Clinical parameters examined</i>	20
Control of Dyslipidemia	23
Diabetic Care	24
Blood pressure control	26
Weight reduction	27
Antiplatelet Use	27
Use of Iron supplementation	28
Combined interventional analysis	28
Health Care Utilization and Costs	28
<i>Statistical analysis</i>	33
Results	34
Discussion	56
Conclusion	67
References	68

List of Figures and Tables

Figure 1: Summary of the intervention site staffing characteristics	31
Figure 2 : Overview of the study design	32
Table 1 : Baseline characteristics of interventional patients at each site	35
Table 2 : Comparison of Dyslipidemia control between the five interventional sites	38
Table 3 : Comparison of Diabetic Care at the five interventional sites	40
Table 4 : Comparison of Blood pressure management at the five interventional sites	43
Table 5 : Comparison of Overweight management at the five interventional sites	45
Table 6 : Comparison of Antiplatelet prescription at the five interventional sites	46
Table 7 : Comparison of Iron replacement therapy	48
Table 8 : Summary of the key interventions by and their combined analysis	50
Table 9 : Summary of univariate analysis for combined key interventions	51
Table 10 : Regression analysis of key interventions	53
Table 11 : Comparison of Nephrologist resource	54
Table 12 : Comparison of the nursing resource utilization	55

Introduction

Patients with multiple chronic conditions consume a significant portion of health care resources.(1) End stage renal disease (ESRD) is a leading example of such a condition given that its incidence continues to grow rapidly in North America. In particular, the incidence of ESRD grew steadily at over 7% per annum in Canada over the past decade. Moreover, in 2010, there was a 13% increase of newly diagnosed patients with ESRD when compared to 2001. It follows that the prevalence rates of patients with ESRD are also increasing. For instance, in 2010, there were 23,188 individuals receiving dialysis in Canada, representing a 189% increase from 1991. (2) Identifying individuals at risk of developing ESRD, as well as implementing cost-effective management strategies for these individuals should be a priority in controlling this chronic condition. Hence, a study of care processes to manage Chronic Kidney Disease (CKD) is vitally important. The goal of this study was to examine the role of relational continuity, nursing education and expertise, and the degree of involvement of nephrologists in the care of patients with CKD in achieving optimal care processes and outcomes.

The majority of ESRD cases result from progressive Chronic Kidney Disease (CKD).(3) This is due to the fact that in CKD, extra stress is placed on the remaining healthy nephrons, thereby shortening their lifespan. As well, the state of CKD often exacerbates certain risk factors such as hypertension and hyperglycemia, which will

further promote progressive renal damage and hence ESRD. Consequently, preventing the development of CKD will also decrease the incidence of ESRD.

Furthermore, individuals with CKD are also at risk of developing cardiovascular disease. This is because CKD shares many similar risk factors as cardiovascular disease, and these include hypertension, dyslipidemia, smoking, and diabetes. It follows that CKD and cardiovascular disease often develop and progress concurrently due to similar pathogenetic pathways. These pathways include oxidative stress, chronic inflammation, vascular (intima and media) calcifications, and atherosclerotic plaque formation. Therefore, patients with CKD often have comorbid cardiovascular disease, which leads to even greater rates of morbidity and mortality.

Nevertheless, some of the risk factors attributed to both CKD and cardiovascular disease have been shown to be modifiable in clinical trials. In particular, antagonism of the renin angiotensin system, treatment of hypertension and proper treatment of diabetes have all been shown to have both cardiovascular benefit as well as slowing the progress of CKD. Cholesterol-lowering strategies have been shown to decrease rates of cardiovascular-related complications. Furthermore, there are targeted risk-reducing strategies unique to CKD such as anemia, mineral metabolism, and metabolic acidosis management which have also been shown to confer varying degrees of clinical benefit.

Modifiable risk factors for CVD and CKD

Numerous large, randomized control trials have shown that Angiotensin-converting enzyme inhibitors (ACEIs) are superior to non-ACEI in reducing progression of renal disease, reducing ischemic heart disease and congestive heart failure event rates, and reducing mortality.(4-6) The effect of ACEI on cardiovascular disease appears to be similar in patients with and without mild to moderate renal failure.

RAS antagonism with angiotensin receptor blocker (ARB) also reduced proteinuria and lengthened the time to dialysis or doubling of serum creatinine when compared to placebo in type 2 diabetics.(7-9) One ARB trial has shown a clinically and statistically significant reduction in mortality compared to the beta-blocker atenolol in patients with hypertension and left ventricular hypertrophy.(10)

ARBs have not been proven better than ACEIs in trials in CHF or post MI. The confidence intervals in general have excluded significant superiority but have included the possibility of clinically significant inferiority, allowing the possibility that ARBs may not be as cardio-protective as ACEIs.(11, 12) In one trial comparing an ARB to an ACEI in patients with established cardiovascular disease or diabetes, patients in each group had similar rates of the primary outcome, a composite of death from cardiovascular causes, myocardial infarction, stroke or hospitalization for heart failure.(13) The results of that trial also suggest that the combination of an

ACEI and ARB was not superior to an ACEI alone, but may result in higher rates of adverse events.

Poorly controlled blood glucose is associated with progression of diabetic nephropathy as well as the development of cardiovascular disease. Controlling diabetes in Type I and Type II diabetic patients has beneficial effects for prevention of microvascular disease,(14-16) an example of which would be nephropathy.

Hypertension is a long established risk factor for premature death, ischemic heart disease, congestive heart failure and left ventricular hypertrophy in the general population. In patients with CKD, hypertension can lead to progression of renal disease, ischemic heart disease, congestive heart failure, left ventricular hypertrophy and death. The established national guidelines at the time of the study recommended a blood pressure target of below 130/80 mmHg in patients with CKD.(17-20) However, the more recent CHEP (Canadian Hypertension Education Program) guidelines recommend a blood pressure target of below 140/90 mmHg in nondiabetic patients with or without CKD.(21)

Elevated LDL (Low-Density Lipoprotein) cholesterol is a well-established risk factor for atherosclerosis, cardiovascular disease and death in certain at-risk populations.(22-24) Therefore, the national guidelines at the time of the study recommended that cholesterol reduction with HMG-CoA (5-hydroxy-3-

methylglutaryl-coenzyme A) reductase inhibitor (statin) in all patients with diabetes, established atherosclerotic disease, or persistent LDL above 2.5 mmol/L should be instituted. The recently published SHARP (Study of Heart and Renal Protection) demonstrated that reduction of LDL cholesterol in a wide range of patients with advanced CKD with simvastatin and ezetimibe reduced the incidence of major atherosclerotic events.(25)

Modifiable risk factors relating to CVD

It is well established that antiplatelet therapy is effective for prevention of cardiovascular events in patients with known atherosclerotic disease, such as peripheral vascular disease, ischemic stroke, ischemic heart disease, and post myocardial infarction as well as in diabetic patients. An observational study of outcomes following myocardial infarction in patients with CKD showed that ASA use is associated with improved post-myocardial infarction survival across a broad spectrum of renal function.(26) Antiplatelet use in diabetics was consistent with the guidelines at the time of the study, although its use is being questioned more recently in diabetics without established vascular disease.

Modifiable risk factors relating to CKD

Several cohort studies have demonstrated an association between anemia and mortality and morbidity in patients with renal disease. Anemia is a risk factor for LVH, CHF, hospitalization, and death in patients on dialysis.(27, 28) The presence of

anemia in patients with CKD also predicts development of left ventricular hypertrophy, which has been associated with cardiovascular events and death in the general population, dialysis and kidney transplant recipients.(29) However, as of now, no intervention study has demonstrated a clear survival benefit of anemia treatment with erythropoietin in patients on dialysis, or with CKD, or in kidney transplant recipients. Nevertheless, due to the benefit of reducing blood transfusion and anemia-related symptoms, the international nephrology consortium, KDIGO (Kidney Disease: Improving Global Outcomes) guidelines recommend using erythropoiesis stimulating agents to maintain a hemoglobin level between 90 to 115 g/L.(30)

Abnormalities of mineral metabolism and secondary hyperparathyroidism occur concurrently with CKD, and have numerous physiological effects on renal function, cardiovascular function and bone metabolism. Registry data have demonstrated higher mortality rates in ESRD patients with abnormal serum phosphate and serum phosphate and calcium product.(31) Higher rates of cardiac mortality are also associated with elevated serum phosphate, phosphate and calcium product, and parathyroid hormone levels.(32) However, there is currently a lack of interventional research showing improved clinical outcome with control of serum phosphate levels with dietary binders. A recently published randomized control trial in hemodialysis patients with moderate-to-severe secondary hyperparathyroidism comparing cinacalcet (a calcimimetic agent that acts by allosteric activation of the calcium-

sensing receptor on parathyroid tissue) to placebo, showed no statistical difference in the primary composite end point of time until death, myocardial infarction, hospitalization for unstable angina, heart failure, or a peripheral vascular event.(33) Although patients in the cinacalcet arm had a 50% risk reduction in requiring surgery to remove part of their parathyroid glands in order to control the hyperparathyroidism.

Another modifiable risk factor in patients in CKD is metabolic acidosis. It is associated with multiple adverse outcomes including malnutrition and abnormalities of bone mineral metabolism(34, 35). Furthermore, metabolic acidosis may activate the complement cascade, in part through increasing the need for NH_4 excretion, thus leading to increased interstitial fibrosis and possibly accelerated renal function decline(36). Recently, a small randomized controlled trial showed that bicarbonate supplementation slowed the progression of renal disease(37).

Care of CKD patients

Ideally, comprehensive care for a patient with CKD should therefore comprise of management of all of the above risk factors. Therefore, there is huge potential in recognizing and treating CKD patients at earlier stages (3 and 4) in order to prevent significant clinical endpoints and improve health outcomes, thereby limiting potential health care costs to society.

Despite this rationale for early intervention, studies suggest that clinical targets such as blood pressure control and use of cardioprotective medications for treating patients with earlier stages of CKD are generally not met, (38, 39). Care coordination and integration through primary health providers is often variable and fragmented where scheduled follow-up is often insufficient for treating chronic conditions. As a result, patients with CKD may not consistently receive optimal care. In particular, patients with CKD often experience care gaps between recommended care and actual received care. They also routinely experience underutilization of therapies with proven efficacy(39-42).

Approaches for targeting patients with CKD and related comorbidities vary across the developed world. For instance, researchers in United Kingdom have proposed a program for at risk populations, such as people with diabetes, hypertension and/or cardiovascular disease, by seeking out cases of CKD early by searching established patient electronic databases(43). The identified patients would be flagged for intensified primary care management for their risk factors (such as blood pressure and diabetes control) for CKD progression and of their cardiovascular risk, as well as facilitating earlier referrals to specialists(44).

In the United States, disease management strategies for CKD have been proposed and developed in the context of managed care.(45, 46) For example, a disease management organization can institute a comprehensive and integrated approach to

CKD care delivery which focuses on slowing the progression of CKD, identifying and treating CKD-specific complications, managing CKD-related comorbidities, and smoothing the transition to ESRD care, in an effort to improve clinical outcomes as well as providing cost savings(45, 47). This approach of intervention at earlier stages of CKD has been shown in small observational studies to improve renal-related outcomes as well as preventing complications from comorbidities(48).

In Canada, multidisciplinary team-based CKD care is common and has been shown to be clinically superior to standard nephrologist care in a multicentre observational study(49). Specifically, in a mixed Canadian/Italian cohort, there was a survival advantage for those exposed to formalized clinic care (consisting of a nurse educator, physician, social worker, nutritionist, psychologist and pharmacist) in addition to standard nephrologist follow-up. However, this was not a randomized controlled trial and major differences between the groups at baseline (age, race, and creatinine clearance at the start of dialysis) could have biased the study's results(49).

Based on the current literature, an alternative method of care delivery would be beneficial in the complex management of CKD patients.

Patient care delivery by nurses

Registered nurses involved in direct patient care can have varying levels of nursing education including a Diploma in Nursing, Baccalaureate degree in Nursing, and Master of Science in Nursing (or Master of Nursing). Level of nursing education has been shown to affect overall patient care. For instance, hospital units with a high proportion of baccalaureate-prepared nurses had more positive reports of patient teaching(50), registered nurses with baccalaureate degrees perform higher skill functions than graduates of diploma programs(51), and hospital units with registered nurses with higher education are associated with improved patient safety(52-54).

Furthermore, care by nurses with specialty certification has been associated with improved quality of patient care(55). Specifically, subspecialty certification in perioperative nurses contributed to improved self perceptions of competence, while additional nursing subspecialty certification in the intensive care unit has been associated with increased perceptions of workplace empowerment(56). In other studies, additional nursing certification was found to be associated with decreased falls in a sample of medical and surgical inpatient units(57), and in various inpatient surgical services, a positive association was found between specialty certification and 30-day mortality rates(58).

Different nursing models have also previously been explored in caring for patients with CKD.(59-63) These include nurse-run clinics, specialized nephrology nurses set

up as a group to facilitate patient care(60), or involvement of a nurse practitioner with specialty nephrology training as the primary care provider(62). The addition of a nurse practitioner as the coordinator of the medical care team may promote adherence to lifestyle recommendations. In a randomized trial, in which over 1000 largely female Hispanic middle-aged participants were recruited from multiple primary care clinics in the United States, and where nurse practitioner and physician care were compared, suggested that no significant differences in patients' health status ($p=0.92$) and satisfaction ratings ($p=0.88$), up to a follow-up of two years.(64, 65) This suggests that the quality of care delivered by nurse practitioners is comparable to that of physicians in a primary care setting for this particular patient population.

Furthermore, in a recent randomized trial from the Netherlands, with just under 800 mostly Caucasian male participants, the addition of a nurse practitioner to standard nephrologist care in CKD patients was examined. The results suggested that the intervention and control groups had similar rates of the primary composite end point (myocardial infarction, stroke or cardiovascular death) or secondary end outcomes (vascular interventions, all-cause mortality or ESRD).(66) Despite various approaches and models of care , the optimal degree of nursing background preparation and further specialty training and expertise in caring for this patient population is still unclear from the current literature.

Continuity of Care

Moreover, as patients with CKD often present with an array of complex medical issues, the implementation of a structured clinic with good continuity of care may be important. For example, continuity of care can be achieved by “relational continuity,” where a sustained interaction between patient and provider over time has been associated with improvements in care (i.e. better recognition of problems, diagnostic accuracy, medication adherence, and reduced hospitalization).(67)

The current literature supports the benefit of relational continuity across different health care domains. For instance, in primary care where relational continuity is regarded as a central concept, it is often accomplished by having a single care-provider. This has been shown to improve compliance with medical instruction, patient satisfaction, among other benefits(68). With respect to mental health care, relationship continuity is achieved through coordination of medical services by a health care team. These “continuous treatment teams” are responsible for all of the patients’ medical and psychosocial needs, integrating complex mental health care in a number of successful programs in the United States.(69) Varying degrees of relational continuity in care of patients with chronic diseases such as AIDS, diabetes, cardiovascular disease, rheumatologic conditions, and cancer have been described.(67) The emphasis is placed on delivery of services by different providers in a coherent, logical and timely fashion, ultimately resulting in reduction in hospital

length of stay, reduction in costs, improved patient quality of life, increased patient satisfaction, and reduction in the time on carrying out paperwork.(70)

In 2011, Dr. John Knight demonstrated that higher continuity of family physician care is associated with reduced specialist utilization and hospitalization for ambulatory-care sensitive conditions (i.e. avoidable admissions), as well as reduced costs associated with specialist, total physician and hospital utilization in a Canadian province.(71) Using data from cross-sectional analyses of survey and provincial health insurance registry samples, this study demonstrated even stronger associations in the case of older patients.(71) Whether relational continuity can improve outcomes in CKD patients is still unclear in the current literature.

Despite ample evidence for individual risk factor reduction, how best to implement all these clinical interventions in CKD is unknown. While other chronic diseases such as diabetes mellitus have been shown to benefit from multifactorial risk reducing strategies,(16) trials with similar clinical design and outcomes have not been replicated for management of CKD. Since there was clinical equipoise as to whether multifactorial risk reducing strategies in a managed care setting should all be applied to the care of patients with CKD, a clinical trial (CanPREVENT - Canadian Collaborative Group for the Prevention of Renal and Cardiovascular Endpoints Trial) was conducted to test the hypothesis that a specialized clinic staffed by a trained nurse in collaboration with a nephrologist using a protocol guided multiple risk

factor and disease management approach would have significant impact on clinical outcomes. This pilot study aimed to explore the feasibility of achieving pre-defined clinical care goals by the interventional group, as well as examining the quality of life and economic implications associated with such care. The primary outcomes for the pilot study were anticipated for any potential follow-up of a full trial included time to ESRD, marked decline in kidney function, myocardial infarction, stroke, hospitalization for congestive heart failure, leg amputation above the ankle or gangrene, or death due to any cause.

The results of this trial are published and will be discussed later(72, 73). However, questions remain regarding the role of relational continuity of care, nursing expertise, and the degree of involvement of nephrologists in the care of patients with CKD in achieving optimal care processes and outcomes. The CanPREVENT trial interventional sites had different research staffing consistency as well as nursing expertise. Furthermore, a preliminary scan of the data relevant to the interventional sites suggested that adherence to established clinical protocols differed across the five sites.

By further analyzing the data from the trial across five different sites in Canada and exploring the difference in practice patterns between the sites, we hypothesized that the continuity of care provided by nursing staff and nursing educational preparation would affect the degree of provider adherence to established clinical protocols.

Materials and Methods

CanPREVENT (Canadian Collaborative Group for the Prevention of Renal and Cardiovascular Endpoints Trial) was a randomized, un-blinded, parallel two group clinical trial in five urban centres in Canada. The study was conducted between 2005 and 2008. The results of the clinical trial have been previously reported.(72-74) It compared a novel integrated approach of nurse-led chronic kidney disease clinic to the usual medical care.

The interventional groups at each site in the CanPREVENT study were exposed to a protocol-guided, multiple risk factor clinic based in a hospital run by a registered nurse and supported by a nephrologist. An orientation program was offered to the nurses, Web-based resources were developed and regular teleconferences among the nurses were held. A series of medical protocols were developed regarding managing blood pressure; controlling lipids with diet and statins; disrupting the renin-angiotensin II system with angiotensin converting enzyme inhibitors (or using angiotensin II receptor blockers if angiotensin converting enzyme inhibitors were not tolerated) for all patients; treating anemia; using acetylsalicylic acid to prevent atherothrombotic events in high risk patients; and controlling serum calcium, phosphorus and parathyroid hormone (PTH) levels with diet, phosphate binders, and activated vitamin D. In addition, lifestyle modifications were encouraged in the interventional group including weight management, glycemic

control in diabetic patients, regular exercise, dietary sodium restriction and smoking cessation(74).

The five research sites across Canada were in St. John's, Newfoundland; Halifax, Nova Scotia; London, Ontario; Greenfield Park, Quebec; and Vancouver, British Columbia. A study investigator who is a nephrologist participated at each site. Each site also had at least one dedicated interventional clinic nurse who managed the interventional patients in the study. Each site followed the study protocol regarding recruitment and regular visits.

However, the details of background preparation of, and continuity of care by the intervention group nursing staff varied across the sites. For instance, while Sites A and B (coded by letter to preserve site anonymity) had a consistent research nurse (registered nurses with diplomas and baccalaureate degree respectively) who interacted with patients in the interventional group, Site D had at least three different nurses in the same role at different times during the trial. At Site E, there were also staffing changes during the study as there were at least two nurses who interacted with the patients in the interventional group at different times during the study. On the other hand, Site C had a dedicated nephrology clinical nurse specialist with a master's degree who interacted with the intervention patients from the start to the end of the study. This will be described in more detail in the Study Design section.

The inconsistency with respect to nursing staff could have impacted overall patient care and relational continuity of care across the five sites. We hypothesized that the addition of a specialized nurse with nephrology expertise as well as a consistent and continuous nursing staff (i.e. Site C) would translate into improved adherence of care providers to the defined medical protocols.

Study Design

Data from the CanPREVENT study database were used for the purposes of this study; CanPREVENT was a randomized, unblinded, parallel two-group clinical trial conducted in five urban centres in Canada. This present study is a prospective cohort study of the intervention group in the trial. The exposure variable was the staffing pattern and the outcomes were overall protocol adherence by providers in instances where changes would have been indicated.

Interventional Groups at each site

The data on nurse staffing was extracted by retroactively reviewing minutes from the monthly CanPREVENT site nurse teleconferences which occurred from July 2005 to April 2008. These meeting minutes routinely documented any staff changes, enrollment status, as well as issues relating to trial execution. The nursing educational background and clinical expertise was retrospectively identified with

each interventional site. Each interventional site will be identified using an alphabetical letter in order to preserve the confidentiality of the research staff. The summary of the nurse-staffing pattern is as follows:

Relational Continuity

Site A

One registered nurse managed the interventional group from 2005 to the end of the study in 2008.

Site B

One registered nurse was present from 2005 until February of 2006, at which point another registered nurse took over until the end of the study in 2008.

Site C

A registered nurse who was a clinical nurse specialist with a master's degree, was involved from 2005 until the end of the study in 2008.

Site D

Site D had a dedicated registered nurse with the interventional group from 2005 to April 2007. She was subsequently replaced by another registered nurse from April 2007 to Jan 2008

Site E

Two registered nurses were involved from 2005 until the Fall of 2006, at which point, two other nurses took over until the end of the study in 2008.

In summary, only Sites A and C had a dedicated interventional nurse from the beginning to the end of the trial, thereby providing the highest relational continuity of care.

Nursing educational background and specialty training

Site A

The interventional nurse had a diploma and further nephrology nursing certification. She also had an extensive background in nephrology nursing.

Site B

The interventional nurse at Site B had a baccalaureate degree as well as further certification in nephrology nursing. The educational background of the other nursing staff are unknown.

Site C

The interventional group had a clinical nurse specialist with a master's degree and specialty expertise in nephrology nursing,

Site D

Both interventional nurses had diploma preparation in nursing. One of them had extensive background in nephrology nursing.

Site E

One of the interventional nurses had a master's degree and certification in nephrology nursing. The educational background of the other three nursing staff members is unknown.

Please see Figure 1 for a summary of the interventional sites' staffing description.

Due to the retrospective nature of this part of the data collection, one could not unequivocally ascertain the educational background and expertise of all the interventional nurses at each study site.

Clinical parameters examined

The surrogate end point or treatment targets specified in the trial protocol included: an LDL level of < 2.5 mmol/L; Hba1c of < 7% in patients with diabetes mellitus; a blood pressure target of < 130/80 mmHg; weight reduction in obese patients; antiplatelet use in patients with a history of ischemic disease or diabetes; iron saturation of > 20%; serum bicarbonate > 22 mmol/L; serum phosphate of < 1.8

mmol/L; hemoglobin > 105 g/L; use of RAAS blockers; and minimization of proteinuria. These targets were consistent with the national guidelines at the time of the trial execution. (The trial protocol detailing the evidence is available through the study investigator upon request).

The specific treatment protocols in the CanPREVENT study were categorized in two tiers. Tier one interventions had stronger evidence-based indications and were more likely to be applied under the sole direction of study staff independently. They included antagonism of the renin-angiotensin system, blood pressure reduction to below 130/80 mmHg, a fasting LDL level of < 2.5 mmol/L, using aspirin for cardiovascular protection, and using beta-blockers in those with heart failure or post MI.

Tier two therapies had weaker evidence and normally involved input from multiple disciplines (dietitian, nurse educator, etc.) as well as patient compliance. They include maintenance of hemoglobin level between 105 g/L and 120 g/L, normalization of mineral metabolism parameters, and avoidance of malnutrition and correction of metabolic acidosis.

Medical protocols were developed that addressed the evidence base, rationale and guided study staff in aiming for the above targets. At the outset of the trial, an orientation was offered to all nurses to ensure consistency, while regular nationwide

teleconferences were conducted monthly to monitor and update progress. However, new staff was not given the same orientation once the trial was underway. Web-based resources were also developed as guidance for the research nursing staff.(74)

The results of the CANPREVENT trial were published previously.(72) In summary, the rate of GFR decline over a median period of 24 months (difference in marginal mean 1.4cc/min per 1.73m²) was not different in the interventional group comprised of patients attending nurse-led clinics. The clinical endpoints included cardiovascular death, all-cause mortality, ESRD, and stroke. The overall clinical endpoints rates were 5.3% and 5.2% in the intervention and control groups, respectively. Amongst the different clinical targets: a) the interventional group had a slightly higher average number of antihypertensive drugs prescribed (0.1 drug, p<0.01), b) 78% interventional vs. 66% control participants were on RAAS blockers (p=0.06), c) intervention-group patients with high LDL were more likely to be on a statin (84% vs. 51%, p= 0.0003), d) as were interventional-patients with low iron saturation to receive iron supplementation than controls (35% vs. 14%, p=0.005). Similar rates were observed in both interventional and control groups for diabetes management targets (referral to nurse educator or dietitian), mineral metabolism and acidosis care and use of antiplatelet therapy.(72)

With the diverse research nurse expertise and staffing continuity of care at the five CanPREVENT interventional sites, we hypothesized that the addition of a specialized clinical nurse (Site C) as well as a consistent and continuous nursing staff pattern would result in statistically significant improvements in adherence of nurses/team to pre-defined medical protocols between the study sites. Six clinical targets related to dyslipidemia, glycemic control, blood pressure, weight reduction, antiplatelet usage, and iron supplementation will be examined. As the results from the CanPREVENT study demonstrated that treatments were rarely required for anemia, metabolic acidosis, and mineral metabolism, no analysis will be performed for these clinical benchmarks. Furthermore, the resource utilization by interventional nurse visits and interventional nephrologists visits amongst the five sites will also be compared, in order to explore whether a differential staffing pattern translates into cost differences.

The analyses for this thesis are limited to a comparison of care administered to intervention group participants at each site, as control groups received usual care only which would not have been affected by study staffing patterns. The analysis of this was performed in a blinded fashion. In particular, during the analysis, each site was assigned an arbitrary letter for comparison.

a) Control of Dyslipidemia

LDL cholesterol levels were measured annually by research protocol. The patients within the interventional group with an LDL level of above 2.5 mmol/L and who were not on a statin at baseline were identified for each site. Then, it was determined what proportion of this subgroup were started on a statin at the 4, 8 or 12 month follow up visit at each site.

A similar analysis was performed using the LDL level measured by protocol at the twelve-month clinic visit. For those not on a statin at the 12-month visit, the proportion so prescribed within the following 12 months was determined for each site.

As the total number of patients with suboptimal LDL levels and not on appropriate treatments was small, the results from the first and second year analyses were combined in order to increase the numbers and hence the power of the analysis.

b) Diabetic Care

The analysis began by analyzing the number of diabetic patients with a Hemoglobin A1c above 7% at the baseline clinic visit and twelfth month clinic visit in the intervention groups.

Within this patient population where their glycemic control was above target, it was then determined whether any of these patients ever a) had the number of daily insulin doses increased, b) had the number of their oral hypoglycemic medications increased, c) were referred to a diabetic clinic, d) were referred to a diabetic nurse educator, e) were referred to an endocrinologist, or f) were referred to a dietitian.

For instance, the number of diabetic patients with an HbA1c above 7% was identified at the baseline clinic visit. It was then determined if any of the diabetic patients with suboptimal glycemic control had any of the above clinical maneuvers at the 4th, 8th and 12th month clinic visits. Subsequently, at the 12th month clinic visit, the number of diabetic patients with an HbA1c level above 7% was again identified. It was then determined if any of these patients had any of the above clinical interventions at their 16th, 20th or 24th clinic visits.

Due to the fact that there were low numbers of patients requiring any of the above interventions, we also examined if any of the appropriate participants had at least one of the interventions performed at the same time intervals.

As the total number of diabetic participants was small, the results from the first and second year analyses were combined in order to increase the numbers and hence the power of the analysis.

c) Blood pressure control

The number of patients who had blood pressure readings above 130/80 mmHg at the baseline clinic visit, twelve month clinic visit and twenty-fourth month clinic visit were determined in the intervention groups. This the only analysis which included the third year clinical data because of the availability of clinical data (blood pressure readings and medication lists) which was collected every four months as per trial protocol.

The first analysis involves identifying the number of patients who had blood pressure readings above 130/80 mmHg at baseline clinic visit and had their number of antihypertensive medications adjusted upward at any point within the first twelve months. The second analysis involves identifying the number of patients who had a blood pressure reading above 130/80 mmHg at the twelfth month clinic visit and had their number of antihypertensive medications increased at any point between the twelfth and twenty-fourth month. A third analysis identifies the number of patients who had a blood pressure reading above 130/80 at the twenty-fourth month clinic visit and had their number of antihypertensive medications increased at any point between the twenty-fourth and thirty-sixth month.

As the total number of suboptimal treated hypertensive participants was small, the results of the first, second and third year analyses were combined to increase the power of the overall analysis.

d) Weight reduction

Any patients with a body mass index of above 30 were identified. It was then determined whether any of these patients were referred to a dietitian at any point from the start of the study to the 24th month of the study.

e) Antiplatelet Use

Any patients with a clinical indication for antiplatelet use were identified. The indications included having a history of coronary artery disease (prior myocardial infarction, prior angina, prior percutaneous transluminal coronary angioplasty, and/or prior history of coronary artery bypass graft) having diabetes mellitus, having a history of peripheral vascular disease (prior gangrene, prior amputation, experiencing intermittent claudication and/or history of bypass intervention), and/or prior cerebral vascular accident (history of transient ischemic attacks and/or history of thrombotic stroke).

From this group of patients, it was then determined if any of them were ever on an antiplatelet medication during the study. The number of patients with at least one cardiovascular indication who were started on an antiplatelet agent during the first 24 months of the study was also determined. The number of patients who were not on an antiplatelet agent due to a past history of gastrointestinal bleeding was also noted.

f) Use of Iron supplementation in appropriate patients

Patients with an iron saturation level below 20% were identified from the database at the baseline clinic visit. Among these, we then determined whether the patients were ever started on oral or intravenous iron supplementation between 0 to 24 months of the study.

g) Combined intervention analysis – the above six clinical interventions were combined for further analysis. One analysis was performed comparing sites using a Chi-squared test in terms of the total number of interventions completed in circumstances where the protocol would have suggested them. This Chi-squared test included all the possible interventions as denominator, and thus could have counted multiple instances for specific participants. It is recognized that this violates the principle of independence, but it maximizes power. In contrast the second analysis was performed with a logistic regression (explained later) to compare sites in terms of whether indicated interventions were carried out or not and for this analysis each participant could only contribute once. The consistency of the results will be compared across both analytic approaches.

h) Health Care Utilization and Costs

The program costs per year per patient were estimated separately for study nurses and nephrologists. The data for use of nursing resources was more comprehensive

than the nephrologist resources because each nursing visit was recorded in the CANPREVENT trial database as well as nursing logs. The nephrologists were required to complete four 2-week block logs for a total of eight weeks, while the nurses were required to complete logs for six randomly selected days during the study. The data for nephrologists' time spent was less accurate as it relied on nephrologists' self-reported log sheets which were not always completed on schedule. For instance, the nephrologist at Site C did not complete the activity log and only reported weekly time spent after the conclusion of the trial. One site nephrologist submitted only four weekly logs while the remaining three site nephrologists submitted eight weekly logs. Overall, the nurses' logs were 63% reported while the nephrologists' logs were 70% reported. Even though the nurses' logs were less complete than the physicians' logs, each nursing visit was tracked in the study, enabling a more accurate calculation of the nursing resource utilization.

For the nephrologists' cost, the nephrologists at each site completed timing logs to record all events related to care for the study patients during several randomly selected two-week periods at different points during the trial. This included the extra time for meetings, communications (emails and telephone calls) relating to patient care and direct patient contacts. The sampling logs generated the average time per week spent by each nephrologist at each site. This number was then multiplied by 104 weeks (two years or the duration of the study). Costs were then

calculated by multiplying time by the physician fee (\$45.85) for a 20-minute repeat consultation according to the Ontario physicians' payment schedule.

For the nursing costs, the time logs for each nurse at each site generated an average time per visit across all the sites (69.3 minutes/visit), which was then multiplied by the average number of visits over the course of the study, and then multiplied by the maximum wage that an Ontario registered nurse receives (\$40 per hour).(73)

See Figure 2 for a summary of the study design.

Site	Relational Continuity / Staffing consistency (# of total staff during study)	Nursing Background Education
A	1	-Diploma with nursing certification
B	2	-Baccalaureate degree -Other unknown
C	1	-Master's Degree with nursing certification
D	2	-Diploma with nephrology experience -Other with Diploma
E	4	-Master's Degree -Other three unknown

Figure 1 – Summary of the Interventional Sites' Staffing Description

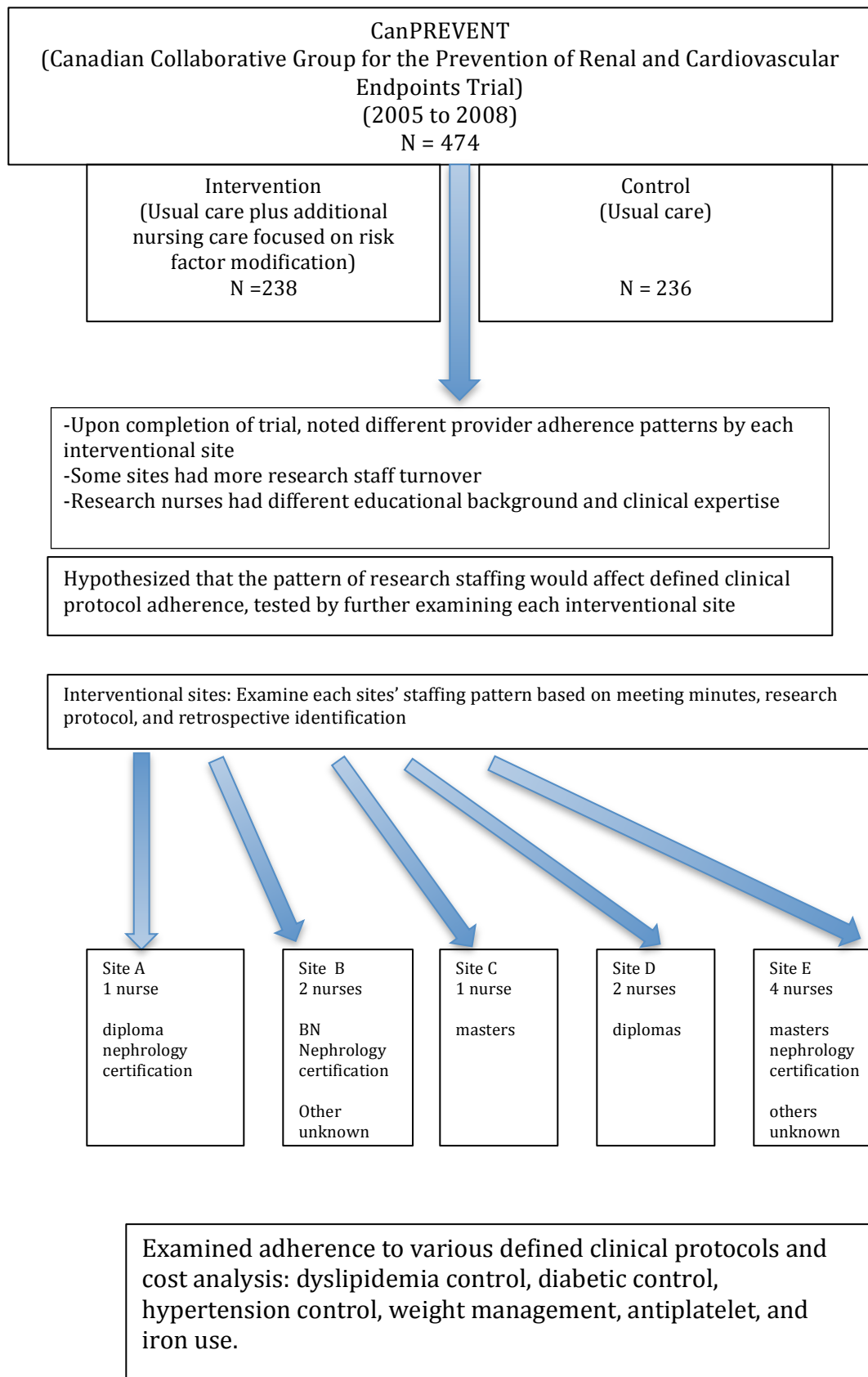


Figure 2 – Overview of study design

Statistical analysis

The study group characteristics were described as proportions, median (interquartile range) or means (standard deviation) as appropriate. Proportions were compared by χ^2 . The means were compared by *t* tests or ANOVA (for > 2 samples). Medians were compared by a median test. Analysis of data across sites was completed with the investigator blinded as to site. In stating the results, each site will be identified by an alphabetical letter in order to preserve the confidentiality of the research staff.

A logistic regression model was employed to evaluate the association between study sites and combined overall protocol adherence (explained later). Since a non-linear model was employed, confidence intervals that included 1 were considered as non-significant. Model significance was tested by the Omnibus test, Hosmer-Lemeshow test and -2loglinear likelihood ratios. Cox-Snell R^2 and Nagelkerke R^2 were considered as the equivalent to R^2 in the linear regression. Significance of individual coefficients were tested using Wald statistic technique, and odds ratios with 95% confidence intervals (CI) were obtained. Assumptions were tested, and residual analysis was performed to evaluate the model. A deviation contrast method was selected to compare each category of the predictor variable (except the reference category) to the overall effect.

All of the data were analyzed using SPSS (version 18.0.2).

RESULTS

Within the intervention groups, there were 54 patients enrolled at Site A, 59 patients at Site B, 60 patients at Site C, 29 patients at Site D and 36 patients at Site E, giving a total of 238 patients in the intervention group amongst the five sites. Their baseline characteristics are described in Table 1. The trial ran from May 2005 to June 2008. The median follow-up was 2.03 years (1.68 – 2.34).

Within each particular site, the median follow-up at Site A was 1.78 years (1.13-2.40), at Site B was 1.83 years (1.13-2.53), at Site C was 1.92 years (1.28-2.55), at Site D was 1.56 years (0.83-2.29) and at Site E was 1.47 years (1.04 – 1.90)

Table 1

Baseline characteristics of interventional trial participants at each site.

	Site A (N=54)	Site B (N=59)	Site C (N=60)	Site D (N=29)	Site E (N=36)	P Values for the Difference
The following are continuous variables presented as median (interquartile range)						
Age	66 (58-69)	63(58-69)	69(65-72)	66(59-72)	69(64-74)	0
Creatinine (µmol/L)	136(118-150)	119(110-138)	122(106-138)	134(117-145)	118(106-134)	0
Baseline eGFR (mls/min/1.73m ²)	43(37-46)	43(39-47)	44(40-48)	41(35-43)	40(36-44)	0.023
Weight (kg)	90(77-98)	84(75-102)	74(63-89)	86(74-94)	81(67-92)	0.063
Systolic blood pressure	128(113-135)	126(113-132)	140(120-150)	122(116-132)	125(117-134)	0.075
Diastolic blood pressure	70(63-80)	76(70-82)	77(65-80)	78(64-80)	73(68-79)	0.032
Proteinuria (g/Day)	0.12(0.06-0.22)	0.12(0.06-0.19)	0.10(0.06-0.15)	0.13(0.06-0.18)	0.08(0.05-0.11)	0
LDL cholesterol (mmol/L)	2.5(2.0-3.5)	2.7(2.2-3.5)	2.6(2.0-3.3)	2.4(1.8-3.3)	2.7(2.1-3.4)	0.723
Hba1c among diabetics (%)	6.8(6.4-7.5)	7.0(6.8-8.5)	7.2(6.2-8.0)	7.9(6.8-8.3)	6.3(6.2-6.6)	0
Hemoglobin (g/L)	138(124-147)	138(129-146)	134(118-142)	134(126-147)	138(122-149)	0.12
The following are binary variables presented as a frequency number (percentage)						
Female	24(44)	41(70)	30(50)	13(45)	23(64)	0.034
Caucasian	53(98)	56(95)	53(88)	29(100)	32(89)	0.380
Retired	32(59)	30(51)	44(73)	16(55)	22(61)	0.269
Working	14(24)	15(25)	10(17)	7(24)	12(33)	0.269
Post-Secondary school Education	24(44)	19(32)	21(35)	13(45)	19(53)	0.071
Married	45(83)	35(59)	33(55)	23(79)	23(64)	0.230
Living in own Home - no hired assistance	50(93)	58(98)	55(92)	28(97)	33(92)	0.814
Current Smoker	7(13)	3(5)	7(12)	2(7)	1(3)	0.571

Systolic BP > 130 mmHg	19(35)	21(36)	34(57)	16(55)	19(53)	0.049
Systolic BP ≥ 140 mmHg	9(17)	13(22)	24(40)	8(28)	11(30)	0.062
Diastolic BP > 80 mmHg	8(15)	12(20)	16(27)	15(52)	13(36)	0.003
Diastolic BP ≥ 90 mmHg	2(4)	4(7)	4(7)	4(14)	4(11)	0.473
Diabetes Mellitus	22(41)	16(27)	19(32)	9(31)	7(19)	0.278
Angina	6(11)	6(10)	1(2)	3(10)	3(8)	0.054
History of Myocardial Infarction	9(17)	6(10)	12(20)	7(24)	5(14)	0.458
History of PTCA	4(7)	3(5)	8(13)	5(17)	6(17)	0.215
History of CABG	10(18)	0(0)	7(12)	4(14)	4(11)	0.025
History of Heart Failure	6(11)	2(3)	4(7)	0(0)	1(3)	0.195
History of Cardiac Arrhythmia	11(20)	8(14)	6(10)	3(10)	4(11)	0.351
History of cerebrovascular event	1(2)	0(0)	3(5)	1(3)	1(3)	0.634
History of Hypertension	42(78)	47(80)	48(80)	21(72)	24(67)	0.378
History of Chronic Lung Disease	5(9)	4(7)	6(10)	0(0)	3(8)	0.558
History of Cancer	5(9)	6(10)	7(12)	2(7)	7(19)	0.465
Taking an ACE inhibitor or ARB	42(78)	45(76)	37(62)	17(59)	24(67)	0.165
Taking a statin	31(57)	28(49)	32(53)	13(45)	13(36)	0.338

The baseline characteristics amongst the five study sites demonstrated that Site B had the youngest patients proportionally compared to the rest of the sites and it had the highest proportion of female participants, while Sites A and D's participants had higher baseline creatinine levels when compared to the rest. The baseline diastolic blood pressure readings were lowest at Site A. Among diabetic participants, Site D

patients had the highest HbA1c levels. Site D also had the highest proportion of participants with diastolic blood pressure reading above 80 mmHg, while Site A had the lowest proportion of participants with systolic blood pressure readings above 130 mmHg. Site E had the lowest levels of proteinuria compared to the rest.

Regarding comorbidities, Site C had the lowest proportions of participants with current angina, and Site B had the lowest proportions of participants with history of CABG.

Even though there were baseline differences between the interventional sites, limiting the analysis to interventions provided to suboptimally treated participants will mitigate the bias generated by the differences.

Table 2

Comparison of Dyslipidemia control between the five interventional sites

The first row lists the number and percentage of patients with a suboptimal LDL level at the beginning of the study or at twelve months of the study. The following row lists the number of suboptimal patients not on a statin.

The following row then lists the number and percentage of those patients started on a statin during their first two years of the study.

Site	Site A N=53	Site B N=57	Site C N=58	Site D N=29	Site E N=33	Chi square	p- value
Patients with LDL Level > 2.5 mmol at baseline or at twelve months	38 (71.7)	47 (82.4)	41 (70.7)	25 (86.2)	24 (72.7)	4.60	0.33
Patients not on a statin at baseline with LDL level > 2.5 mmol/L	20/38 (52.6)	24/47 (51.1)	21/41 (51.2)	18/31 (58.1)	22/24 (91.7)	13.32	0.01
Started on a statin within the first two years	8/20 (40)	13/24 (54.2)	16/21 (76.2)	6/18 (33.3)	5/22 (22.7)	14.61	0.006

This analysis revealed that Site E had the highest proportion of participants with an LDL level above target range that was not treated with a statin. It also showed that Site C had the highest percentage of participants (76.2%) correctly started on a statin during the first two years of the study. Both Sites D and E had the lowest number of participants started on a statin appropriately.

Table 3

Comparison of Diabetic care at the five interventional sites

The first row describes the number of participants with suboptimal HbA1c. The following rows list the number of participants who had their insulin regime intensified, oral hypoglycemic increased, diabetic clinic visit, diabetic educator visit, endocrinologist visit, dietitian visit, or any one of those interventions respectively.

	Site A (N=22)	Site B (N=16)	Site C (N=19)	Site D (N=9)	Site E (N=7)	Chi square	p- value
Number of diabetic patients with HbA1C > 7% at baseline or at twelve months	12 (54.5)	10(62.5)	13 (68.4)	7 (77.8)	0	12.16	0.016
Had insulin regime intensified	2/12 (16.7)	0	1/13 (7.8)	0		2.955	0.40
Had number of oral hypoglycemic increased	1/12 (8.3)	1/10 (10)	3/13 (23.1)	0		2.674	0.44
Had at least one diabetic clinic visit	3/12 (25)	5/10 (50)	1/13 (7.8)	4/7 (57.1)		7.434	0.06
Had at least one diabetes educator visit	5/12 (41.7))	3/10 (30)	2/13 (15.4)	5/7 (71.4)		6.556	0.09
Had at least one endocrinologist visit	1/12 (8.3)	3/10 (30)	1/13 (7.8)	3/7 (42.8)		5.332	0.15
Had at least one dietitian visit	5/12 (41.7)	3/10 (30)	2/13 (15.4)	5/7 (71.4)		6.556	0.09
Had any above interventions	7/12 (58.3)	5/10 (50)	7/13 (53.8)	5/7 (71.4)		0.856	0.84

All sites had low numbers of enrolled diabetic participants, and an even lower number of participants with HbA1c >7%. This generally translated into a low number of diabetic therapeutic changes and referrals to diabetic clinics.

This analysis demonstrated that there were large variations of diabetic control among diabetic participants across the sites. For instance, none of the diabetic patients at Site E had an HbA1c% level above target range, while Site D had 77.8% of diabetic participants above the target range (p-value = 0.016). None of the observed practice patterns in the four sites for suboptimal diabetic patients was statistically significantly different across sites during the two years of the study.

Table 4

Comparison of blood pressure management at the five interventional sites

In the following tables the first row shows the number and percentage of participants with a blood pressure reading above 130/80 mmHg at their baseline clinical visit, at the twelve month clinic visit, or at their 24th month clinic visit. This is followed by the number and percentage of those participants who had the number of antihypertensive medications increased during the subsequent year of the study.

	Site A (N=54)	Site B (N=57)	Site C (N=60)	Site D (N=29)	Site E (N=36)	Chi Square	p- value
Number of patients with blood pressure above 130/80 mmHg at baseline, twelve months, or twenty-four months	22 (40.7)	38 (66.7)	43 (71.7)	17 (58.6)	19 (52.8)	13.37	0.01
Number of patients who had number of medications increased during the first, second or third 12 months of the study	10/22 (45.4)	11/38 (28.9)	8/43 (18.6)	2/17 (11.8)	7/19 (36.8)	8.275	0.08

This analysis demonstrated that during the study, the participants at Site C had the highest percentage (71.7%) of patients with suboptimal blood pressure readings at baseline, twelve months and 24 months. Site A had the highest percentage of participants with the number of antihypertensive medications increased (45.4%), although this was only a trend and not statistically significant (p=0.08).

Table 5

Comparison of Overweight management at the five interventional sites

The first row of the table describes the number and percentage of participants with a BMI of >30 at each interventional site. The second row presents the number and percentage of overweight patients who were referred to a dietitian during the course of the study.

	Site A N=(54)	Site B N = (59)	Site C N=(60)	Site D N=(29)	Site E N=(36)	Chi Square	p-value
BMI > 30 at baseline	31 (57.4)	34 (57.6)	19 (31.7)	11 (37.9)	15 (41.7)	12.02	0.017
Number of patients with at least one dietitian visit during the study	11/31 (35.5)	12/34 (35.3)	3/19 (15.8)	6/11 (54.4)	3/15 (20)	6.216	0.18

The analysis showed that Site B had the highest percentage of patients with a BMI > 30 (57.6%), followed by Site A. There was a higher proportion of participants at Site D referred to a dietitian (54.4%) and a lower proportion of participants at Site C referred to a dietitian (15.8%). However, these differences in proportions are not statistically significant.

Table 6

Comparison of Antiplatelet prescription at the five interventional sites

The first row of the table describes the number of participants with at least one cardiovascular disease or diabetes. The second row eliminated those participants with a contraindication for antiplatelet therapy (GI bleed). The next row lists the number of participants with cardiovascular disease without a contraindication (GI Bleed) and not on an antiplatelet. The final row describes the number of patients started on an antiplatelet during the study.

	Site A N = (54)	Site B N = (59)	Site C N = (60)	Site D N = (29)	Site E N = (36)	Chi Square	p- value
Patients with indication for antiplatelet use	33 (61.1)	28 (47.4)	31 (51.7)	17 (58.6)	16 (44.4)	3.596	0.46
Patients with cardiovascular indication without a history of GI Bleed	30 (55.6)	28 (47.4)	31 (51.7)	16 (55.2)	16 (44.4)	1.574	0.81
Number of patients not on an antiplatelet at baseline	5 (16.7)	5 (17.8)	1 (3.2)	6 (37.5)	3 (18.8)	9.17	0.057
Number of patients with cardiovascular indication, without GI bleed started on an antiplatelet during the trial in 24 months	1/5 (20)	5/5 (100)	0	0	2/3 (66.7)	13.89	0.08

Site B had the highest proportion of participants started on antiplatelet therapy correctly (100%), although this was not statistically significant (p=0.08).

Table 7

Comparison of Iron replacement therapy between the five interventional sites

The first row describes the number and percentage of participants with evidence of iron deficiency (based on an iron saturation level below 20% at the baseline clinic visit or at 12 months). The second row describes the number and percentage of participants with iron deficiency and not on iron supplementation. Row three describes the number and percentage of such participants started on iron supplementation during the first two years of the study.

	Site A	Site B	Site C	Site D	Site E	Chi square	p-value
Patients with Iron Saturation < 20% at baseline or at 12 months	N = 54 23	N =59 30	N =60 23	N =29 11	N =36 12	3.536	0.47
Participants with Iron Saturation < 20% and not on Iron at Baseline	19/23 (82.6)	17/30 (56.7)	19/23 (82.6)	9/11 (81.8)	6/12 (50)	9.141	0.058
Number of patients started on Iron replacement during the first 24 months of the study	4/19 (21)	13/17 (76.4)	3/19 (15.8)	1/9 (11.1)	5/6 (16.7)	25.18	0.00005

This analysis demonstrates that Site B had the highest number and percentage of participants started on iron supplementation appropriately (76.4%) which was statistically significant (p=0.00005).

Table 8

Summary of the key interventions and their combined analysis

Site	Site A	Site B	Site C	Site D	Site E	Chi-square	p-value
Dyslipidemia Intervention	8/20 (40%)	13/24 (54.2%)	16/21 (76.2%)	6/18 (33.3%)	5/22 (22.7%)	14.61	0.006
Diabetes Intervention	7/12 (58.3%)	5/10 (50%)	7/13 (53.8%)	5/7 (71.4%)	0	0.856	0.84
BP Intervention	10/22 (45.4%)	11/38 (28.9%)	8/43 (18.6%)	2/17 (11.8%)	7/19 (36.8%)	8.275	0.08
BMI Intervention	11/31 (35.5%)	12/34 (35.3%)	3/19 (15.8%)	6/11 (54.4%)	3/15 (20%)	6.216	0.18
Antiplatelet Intervention	1/5 (20%)	5/5 (100%)	0	0	2/3 (66.7%)	13.89	0.08
Iron supplementation Intervention	4/19 (21%)	13/17 (76.4%)	3/19 (15.8%)	1/9 (11.1%)	5/6 (16.7%)	25.18	0.00005
Combined key interventions	46/109 (42%)	59/128 (46%)	53/115 (46%)	20/62 (32%)	22/65 (33%)	5.86	0.21

The Chi-square test demonstrated no significant difference among the five sites when the key interventions were combined (p=0.21).

Table 9

Summary of univariate analysis for combined key interventions

Univariate analysis was performed and the enter method was used for selection of variables. The outcome variable was the combined overall protocol adherence (i.e. any correct clinical intervention based on the pre-defined protocol; specifically, if any of the six clinical interventions was positive, then the combined variable will be positive). Each step was tested for goodness of fit with 95% CI's.

Univariate analysis was performed for each predictor variable, including age, gender, weight, baseline creatinine, baseline systolic and diastolic blood pressures, baseline hemoglobin A1c, baseline urinary protein excretion rate, presence of angina and history of CABG. The significance level was 0.1 for retention in the multivariate model by default.

Variable	P value	Exp(B)	95% C.I
Age	0.777	1.005	0.971-1.039
Gender	0.630	0.882	0.529-1.470
Weight	0.049	1.015	1.000-1.030
Baseline creatinine	0.292	1.005	0.996-1.015
Baseline systolic blood pressure	0.594	1.004	0.990-1.018
Baseline diastolic blood pressure	0.300	0.988	0.965-1.011
Hemoglobin A1c	0.712	1.016	0.933-1.107
Urinary protein excretion rate	0.464	1.273	0.667-2.427
Presence of angina	0.348	3.429	0.261-45.026
History of CABG	0.395	1.443	0.620-3.360

“Weight” as a predictor in the univariate analysis was significantly associated with the positive likelihood of combined key interventions. Thus, “weight” was included in the regression analysis.

Table 10

Regression analysis of combined key interventions

The regressions analysis set the categorical independent variables as “interventional sites” and “weight”. The outcome variable was the combined overall protocol adherence (i.e. any correct clinical intervention based on the pre-defined protocol)

Site	Site A	Site B	Site C	Site D	Site E
P-value	0.038	0.053	0.824	0.536	0.465
EXP (B)	0.581	1.656	1.057	1.221	0.806
(95% C.I.)	(0.348 – 0.970)	(0.994 – 2.758)	(0.650 – 1.718)	(0.648 – 2.301)	(0.451 – 1.439)

The logistic regression analysis demonstrated a potential small difference in Site A when compared to the overall effect: exp(B) 0.581 CI (0.348 – 0.970).

The model evaluation was tested by the Omnibus test (0.037) , Hosmer- Lemeshow test (0.792) and -2 loglinear likelihood ratios (312.545) which suggested a good fit.

The pseudo R² estimates, Cox-Snell R² (0.049) and Nagelkerke R² (0.066) also supported the model.

Table 11

Comparison of Nephrologist resource utilization in the five interventional sites

The first row of this table describes the amount of time spent per week by each nephrologist at each site based on self-reported time logs. The following row converted this time spent per week per study patient. The third row describes the time spent per study (104 weeks or two years) per patient. The final row converted time spent to dollars spent based on the Ontario Medical Association wage scale.

	Site A	Site B	Site C	Site D	Site E	F	p-value
Minutes spent per week	198.8	58.1	60	212.5	100	5.588	0.03
Minutes spent per week per patient	3.68	0.985	1.00	7.33	2.78		
Minutes spent per study (104 weeks)/patient	382.72	102.44	104	762.32	289.12		
Dollars/study/patient (\$)	877.38	235	238	1,748	663		

This ANOVA analysis identified significant differences in nephrologist resource use between the five sites. In particular, there is higher resource utilization by Sites A and D.

Table 12

Comparison of the nursing resource utilization in the five interventional sites

The first row describes the mean number of clinic visits per patient per year at each site. The next row describes the time spent per patient based on an average rate of 69.3 minutes per visit. The third row then describes the dollar spent per year based on an estimated hourly rate of \$40. The final row summarizes the dollar spent per study (2 years).

	Site A	Site B	Site C	Site D	Site E	F	p-value
Visit/year/patient	4.06	3.96	3.98	3.69	3.72	0.1055	0.38
Minutes/year (x69.3)	281	274	276	256	258		
Dollars/year/patient	187	183	184	171	172		
Dollars/study/patient	374	366	368	342	344		

This ANOVA analysis demonstrated no difference in the resources used by the study nurses among the five sites.

Discussion

CANPREVENT was a randomized, unblinded, pilot clinical trial in patients with stage III and IV CKD. Its comparison of a nurse-coordinated care model versus usual care by family physicians did not show any statistically significant difference in clinical endpoints or rate of decline in kidney function. However, the interventional group participants with suboptimal LDL levels or low iron saturation levels were more likely to receive treatment than their counterparts in the control group, even though the treatment effects were similar between two groups over time.

This further sub-analysis aimed to explore practice differences among the interventional sites regarding clinician adherence to established clinical protocols. Specifically, our hypothesis was that nursing background preparation/clinical expertise and relational continuity of care would affect overall clinical practice patterns. However, no major difference in the clinical practice pattern amongst the interventional sites was found. Overall, none of the interventional sites had consistently superior rates of clinical interventions.

Nevertheless, there were specific differences with respect to various clinical interventions at each site. Specifically, at baseline, Site D had the highest proportion of diabetics and hypertensive patients (highest percentage of diastolic blood pressure above 80 mmHg).

Amongst all the clinical interventions examined, Site C had the highest proportion of participants started on statins (76.2%, $p=0.006$). Site D had the highest percentage of diabetic clinic visits (57.1%, $p=0.06$), referral to a diabetic educator (71.4%, $p=0.09$), and dietitian referral (71.4%, $p=0.09$) amongst diabetics with suboptimal HbA1c; these were trends and not statistically significant, suggesting some degree of differential practice patterns at each site.

Site A had a trend toward the highest number of hypertensive medication increases during the first three years of the study (45.4%, $p=0.08$) amongst hypertensive participants, while Site D had a trend to the highest proportion of overweight participants referred to a dietitian (54.4%, $p=0.18$) - on both of these indicators, there were no statistically significant differences among centres .

Site B had the highest proportion of new antiplatelet usage appropriately (100%, $p=0.08$), while also having the highest proportion of participants started on iron replacement therapy (76.4%, $p=0.002$).

Based on these results, no clear definite association can be drawn between interventional sites, relational continuity of care and practice pattern. All the study sites other than Site E tended to emphasize certain aspects of the examined protocols. For example, Site A had the highest protocol adherence rate with hypertension control, Site B had the highest protocol adherence rate with

antiplatelet and iron therapy, Site C had the highest protocol adherence rate with dyslipidemia control, while Site D had the highest protocol adherence rate with diabetic and weight management. It is unclear why this pattern occurred, but may certainly be a reflection of the site-specific priorities in certain aspects of patient management, or it could be due to differential accessibility to services (dietitians, diabetic educators) across the sites.

When the clinical interventions were combined, no clear association can be seen on the Chi-square analysis between sites and overall protocol adherence ($p=0.21$). The univariate regression analysis demonstrated no significant p-values for the predictors or age, gender, baseline creatinine, baseline blood pressure, baseline hemoglobin A1c levels, baseline urinary protein excretion rate, presence of angina and history of CABG. However, weight was significantly associated as a positive predictor of combined key intervention, and thus was included in the final regression model. The logistic regression did demonstrate a small potential difference with Site A, (sig.: 0.038, exp(B) 0.581, 95% C.I. 0.348 – 0.970). This site had diploma-trained interventional nursing staff and no staff turnover demonstrated the least adherence to clinical protocols - even though the overall clinical significance of the effect is small.

Based on the results of the Chi-square analysis and the small difference in the logistic regressions, we failed to definitively reject our null hypothesis. The

discrepancy in the results between the Chi-square test and the regression analysis could be due to the data sets used for each analysis. Specifically, the Chi-square test was performed on the sum of all potential interventions, thus certain interventions were potentially counted multiple instances for a single participant, thereby making the variable less independent and thus introducing bias. On the other hand the regression analysis only counted one possible occurrence in each study participant, even though each participant could have required several interventions of which more than one might have been carried out. Site B was statistical significant in the regressions analysis and not in the Chi square analysis could be due to the possibility where particular participants at Site B had several interventions indicated, therefore would have appeared to have intervened positively even if only one of those interventions were carried out, ignoring the failures in the rest of the cases. The Chi square analysis would have captured those failures, and therefore found all sites to be equal.

With respect to baseline patient factors and their influence on practice patterns, site D had the highest proportion of diabetic participants with suboptimal HbA1c, and it was demonstrated that site D also had the highest proportion of referrals to a diabetic educator. Beyond this observation, no clear association can be drawn with respect with participants' baseline clinical characteristics and practice patterns.

There could be a number of explanations for these results. The overall trial sample size was limited and this analysis is further restricted to half of the participants of the CanPREVENT trial. The small sample size significantly reduces the power to detect even relatively large differences between the interventional sites. The power for our particular analysis could not be accurately calculated as we do not know the true magnitude of our proposed intervention. Nevertheless, the limited power in the our study was demonstrated by the regression analysis in table 10, where the confidence intervals for Site B was 1.140-3.079, suggesting a potential three-fold experimental effect at the upper end of the confidence interval, reflecting poor precision and thus too a small sample size to reject or accept our null hypothesis.

This analysis was also performed on data collected from the interventional groups in each of the five sites. Due to the retrospective nature of the data collection, the intersite differences with respect to continuity and the background education of the staff were not all that clear and therefore it is difficult to unequivocally assess the impact of continuity and staff preparation on the outcomes of clinical protocol adherence.

Furthermore, this study targeted patients with stage three and four chronic kidney disease in the community and recruited patients who were generally clinically well at baseline. The intent of the trial was to recruit a general population of those with CKD, rather than those already known to a nephrologist. For reasons of ethics,

participants could only be recruited to the trial via their family doctors. This filter may have led to referral of low numbers of “at risk” patients, such as diabetic patients, patients with suboptimal LDL, HbA1c, as well as hypertensive patients. As well, most patients did not have significant established cardiovascular disease. Furthermore, most patients were already on treatment with an ACEI/ARB, not smoking, and had optimal blood pressure control and minimal proteinuria at baseline. The lack of clinical complexity and the perceived “wellness” of the interventional patients by the interventional research staff may have reduced staff enthusiasm for therapy intensification as per protocol.

Another limitation of this study is that the participants’ access to certain clinical services was variable across centres and this could not be accurately accounted for in our analysis. For instance, the access to a diabetic educator was variable across the five sites and this disparity would not have been measured or captured in our database. This could certainly have confounded the results of this analysis.

Finally, despite having an established clinical protocol and dedicated interventional research staff executing the protocols, participants’ adherence to therapy may have biased the final result. Non-adherence in Stage V CKD (dialysis) patients to prescribed oral medications was described in a systematic review, where the median non-adherence rate is 50% (75). Therefore, if a particular intervention or medication was prescribed by study staff but not ultimately carried through by the

participant, then it would appear in the database that the intervention or medication was never prescribed. This could happen because the database only included the clinical interventions each participant received at each visit although the prescription pattern by research staff was not actually recorded. For instance, attendance at a diabetic clinic rather than the referral by staff to that clinic would be recorded, as well as the drugs the patient said they were taking at each visit rather than what had been prescribed for them at an earlier time. Since this particular level of patient adherence was not captured in the study database, patient non-adherence could have been interpreted as prescriber non-adherence even though the intervention might have been prescribed. This is a limitation of the study data and patient non-compliance across each site could have significantly contributed to the relatively neutral result of this analysis.

In patients with chronic diseases, a meta-analysis previously reported that provider education (materials or instruction given to healthcare providers regarding appropriate care for patients with the condition targeted by the program), giving feedback to healthcare providers, and periodic reminders prompting specific patient care tasks were associated with improvements in provider adherence to guidelines in disease management programs.(76) Further research in CKD management could address all or some of these variables in order to elucidate their relative effects on guideline adherence. On the other hand, patient behaviour and adherence is more

difficult to accurately measure and quantify and may improve with patient education and incentives.(76)

The researcher originally hypothesized an association between nursing expertise/background education and protocol adherence. However, nursing expertise proved to be a challenging variable to quantify because of the turnover of staff and the retrospective nature of the analysis. The inability to ascertain and quantify nursing expertise is a limitation of this study.

This type of research is inherently difficult to conduct as it involves multiple complex interventions and many different care-provider characteristics. For instance, the care provider's educational preparation could influence patient-related outcomes. The literature suggests that a master's level nursing education can result in improved patient outcomes, while being specifically trained in a medical specialty could enhance clinical decision making.(77) Provider experience, especially in a specialty area (i.e. nurse subspecialty certification), could also impact on the overall patient care and outcomes although any conclusion with respect to true association is limited by the paucity of the current evidence. These areas need to be further explored in future research.

Regarding the resource utilization findings of the study, this particular analysis demonstrated that there was higher nephrologist resource utilization at Sites A and

D, although these data may be biased as they were largely based on retrospective recall and self-reporting by each site nephrologist. Nevertheless, a potential explanation for this statistically significant higher nephrologist resource utilization could be due to the absence of a clinical nurse specialist. The presence of the clinical nurse specialist at site C could have resulted in reduced nephrologist cost because a clinical nurse specialist could manage a greater number of issues normally managed by a nephrologist. On the other hand, the nursing resource (time) utilization was similar between the sites despite the difference in nursing expertise and staffing continuity. This confirmed the notion that nursing clinic visits and hence resources utilization were largely driven by the pre-defined protocol for the trial with little deviation in the form of extra clinic visits. Another limitation to the nephrologist resource utilization analysis was that the nephrologist costs (time) were heavily influenced by the personal practice patterns of each study nephrologist whose personal commitment and engagement in the trial or in patient care may not have been heavily influenced by the nursing practice pattern and expertise.

There are several limitations to this research: Firstly, this was a post-hoc analysis of the original CanPREVENT clinical trial data, which might not have generated enough power to detect any statistical difference between the interventional sites. Secondly, the relational continuity of care within the interventional sites was determined retrospectively which limited the robustness of the results. The nature of the relationship between the nurses and patients, between physicians and patients, and

physicians and nurses was not measured. It may be that the specific nature of those relationships has an impact on patient care and outcomes. This research involves many complex interventions and many different patient characteristics and protocol adherence patterns, making the identification of a single positive effect difficult. It would be more desirable from an evidence-based point of view to have separate treatment groups defined a priori to test the hypothesis of an association between relational continuity of care or nursing preparation level/expertise and clinical outcomes.

If the present research question had been identified a priori and the CanPREVENT trial were to be redesigned, there would be separate treatment arms with nurses with varying degrees of expertise and educational background, as well as introducing a variable of different levels of relational continuity (e.g. a treatment arm with one provider vs. a treatment arm with two or three providers).

For example, to test the hypothesis that different levels of nursing education and training can affect patient outcomes; one could have a predefined group of interventional nurses with and without nephrology nursing subspecialty preparation. Within each of these two groups, one could further define groups of registered nurses with diploma, baccalaureate, and/or a master's preparation.

Different levels of relational continuity can be achieved by predefined groups where site A would have one nurse as interventional nurse for the duration of the study, and site B would have one nurse per year for the duration of the study. To incorporate both independent variables of nursing expertise and relational continuity of care into the study design, one could generate a 2 X 3 factorial design template.

Conclusion

It was not possible to detect a significant difference between the relational continuity or nursing background educational/clinical expertise in the management of the care of stage III and IV CKD patients and their surrogate clinical outcomes. However, this study design was retrospective in nature and a larger participant sample with increased power may provide different results. A more definitive randomized clinical trial with a larger sample size (sites and patients) and longer follow-up, thereby increasing the power, is required to examine this hypothesis.

The management of patients with CKD is becoming more complex as more interventions are becoming available to treat its complications and co-morbid conditions. Research is also elucidating interventions to prevent the risk of progression to end stage renal disease. The current model of a single nephrologist-delivered CKD care is not optimal and likely not sustainable in the future. More studies are needed to examine the most effective and efficient means of delivering care to CKD patients.

Reference

1. Tinetti ME, Studenski SA. Comparative effectiveness research and patients with multiple chronic conditions. *N Engl J Med.* 2011 Jun 30;364(26):2478-81.
2. Canadian Organ Replacement Register Annual Report: Treatment of End-Stage Organ Failure in Canada, 2001 to 2010. 2011.
3. Landray MJ, Emberson JR, Blackwell L, Dasgupta T, Zakeri R, Morgan MD, et al. Prediction of ESRD and death among people with CKD: the Chronic Renal Impairment in Birmingham (CRIB) prospective cohort study. *Am J Kidney Dis.* [Research Support, Non-U.S. Gov't]. 2010 Dec;56(6):1082-94.
4. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med.* [Clinical Trial
Multicenter Study
Randomized Controlled Trial
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.]. 1993 Nov 11;329(20):1456-62.
5. Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *N Engl J Med.* [Clinical Trial
Randomized Controlled Trial
Research Support, Non-U.S. Gov't]. 1996 Apr 11;334(15):939-45.
6. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). *Lancet.* [Clinical Trial
Randomized Controlled Trial
Research Support, Non-U.S. Gov't]. 1997 Jun 28;349(9069):1857-63.
7. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med.* [Clinical Trial
Multicenter Study
Randomized Controlled Trial
Research Support, Non-U.S. Gov't]. 2001 Sep 20;345(12):861-9.
8. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med.* [Clinical Trial
Comparative Study
Multicenter Study
Randomized Controlled Trial
Research Support, Non-U.S. Gov't]. 2001 Sep 20;345(12):851-60.

9. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med.* [Clinical Trial Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2001 Sep 20;345(12):870-8.
10. Lindholm LH, Ibsen H, Dahlof B, Devereux RB, Beevers G, de Faire U, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet.* [Clinical Trial Comparative Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2002 Mar 23;359(9311):1004-10.
11. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial--the Losartan Heart Failure Survival Study ELITE II. *Lancet.* [Clinical Trial Comparative Study Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2000 May 6;355(9215):1582-7.
12. Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. *Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan.* *Lancet.* [Clinical Trial Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2002 Sep 7;360(9335):752-60.
13. Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med.* [Comparative Study Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2008 Apr 10;358(15):1547-59.
14. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998 Sep 12;352(9131):837-53.
15. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. *N Engl J Med.* 2000 Feb 10;342(6):381-9.

16. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. [Clinical Trial Comparative Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2003 Jan 30;348(5):383-93.
17. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet*. [Clinical Trial Comparative Study Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 1998 Jun 13;351(9118):1755-62.
18. Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis*. [Consensus Development Conference Guideline Research Support, Non-U.S. Gov't Review]. 2000 Sep;36(3):646-61.
19. Toto RD, Mitchell HC, Smith RD, Lee HC, McIntire D, Pettinger WA. "Strict" blood pressure control and progression of renal disease in hypertensive nephrosclerosis. *Kidney international*. [Clinical Trial Randomized Controlled Trial Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 1995 Sep;48(3):851-9.
20. Lazarus JM, Bourgoignie JJ, Buckalew VM, Greene T, Levey AS, Milas NC, et al. Achievement and safety of a low blood pressure goal in chronic renal disease. The Modification of Diet in Renal Disease Study Group. *Hypertension*. [Clinical Trial Multicenter Study Randomized Controlled Trial Research Support, U.S. Gov't, Non-P.H.S. Research Support, U.S. Gov't, P.H.S.]. 1997 Feb;29(2):641-50.
21. 2012 CHEP Recommendations for Management of Hypertension. 2012.
22. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. [Clinical Trial Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 1995 Nov 16;333(20):1301-7.
23. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. [Clinical Trial

Randomized Controlled Trial

Research Support, Non-U.S. Gov't]. 1994 Nov 19;344(8934):1383-9.

24. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. [Clinical Trial

Multicenter Study

Randomized Controlled Trial

Research Support, Non-U.S. Gov't]. 2002 Jul 6;360(9326):7-22.

25. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. [Comparative Study

Randomized Controlled Trial

Research Support, Non-U.S. Gov't]. 2011 Jun 25;377(9784):2181-92.

26. Wright RS, Reeder GS, Herzog CA, Albright RC, Williams BA, Dvorak DL, et al. Acute myocardial infarction and renal dysfunction: a high-risk combination. *Ann Intern Med*. [Research Support, Non-U.S. Gov't]. 2002 Oct 1;137(7):563-70.

27. Silberberg JS, Rahal DP, Patton DR, Sniderman AD. Role of anemia in the pathogenesis of left ventricular hypertrophy in end-stage renal disease. *Am J Cardiol*. 1989 Jul 15;64(3):222-4.

28. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. The impact of anemia on cardiomyopathy, morbidity, and mortality in end-stage renal disease. *Am J Kidney Dis*. [Comparative Study

Research Support, Non-U.S. Gov't]. 1996 Jul;28(1):53-61.

29. Levin A, Thompson CR, Ethier J, Carlisle EJ, Tobe S, Mendelssohn D, et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis*. [Multicenter Study

Research Support, Non-U.S. Gov't]. 1999 Jul;34(1):125-34.

30. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work group. KDIGO Clinical Practice guideline for Anemia in Chronic Kidney Disease. *Kidney Int, Suppl*. 2012;2:279-335.

31. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis*. 1998 Apr;31(4):607-17.

32. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol*. 2001 Oct;12(10):2131-8.

33. Effect of Cinacalcet on Cardiovascular Disease in Patients Undergoing Dialysis. *N Engl J Med*. 2012 Nov 3.

34. Bushinsky DA. The contribution of acidosis to renal osteodystrophy. *Kidney international*. [Case Reports

Clinical Conference

Research Support, Non-U.S. Gov't

- Research Support, U.S. Gov't, P.H.S.]. 1995 Jun;47(6):1816-32.
35. Ballmer PE, Imoberdorf R. Influence of acidosis on protein metabolism. *Nutrition*. [Research Support, Non-U.S. Gov't Review]. 1995 Sep-Oct;11(5):462-8; discussion 70.
 36. Mazouz H, Kacso I, Ghazali A, El Esper N, Moriniere P, Makdassi R, et al. Risk factors of renal failure progression two years prior to dialysis. *Clin Nephrol*. 1999 Jun;51(6):355-66.
 37. de Brito-Ashurst I, Varaganam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J Am Soc Nephrol*. [Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2009 Sep;20(9):2075-84.
 38. Coresh J, Wei GL, McQuillan G, Brancati FL, Levey AS, Jones C, et al. Prevalence of high blood pressure and elevated serum creatinine level in the United States: findings from the third National Health and Nutrition Examination Survey (1988-1994). *Arch Intern Med*. [Comparative Study Research Support, U.S. Gov't, P.H.S.]. 2001 May 14;161(9):1207-16.
 39. Tonelli M, Bohm C, Pandeya S, Gill J, Levin A, Kiberd BA. Cardiac risk factors and the use of cardioprotective medications in patients with chronic renal insufficiency. *Am J Kidney Dis*. [Multicenter Study Research Support, Non-U.S. Gov't]. 2001 Mar;37(3):484-9.
 40. Nissenson AR, Collins AJ, Hurley J, Petersen H, Pereira BJ, Steinberg EP. Opportunities for improving the care of patients with chronic renal insufficiency: current practice patterns. *J Am Soc Nephrol*. [Research Support, Non-U.S. Gov't]. 2001 Aug;12(8):1713-20.
 41. Parikh NI, Hwang SJ, Larson MG, Meigs JB, Levy D, Fox CS. Cardiovascular disease risk factors in chronic kidney disease: overall burden and rates of treatment and control. *Arch Intern Med*. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. 2006 Sep 25;166(17):1884-91.
 42. Fischer MJ, Ahya SN, Gordon EJ. Interventions to reduce late referrals to nephrologists. *Am J Nephrol*. 2011;33(1):60-9.
 43. Stevens PE, O'Donoghue DJ, de Lusignan S, Van Vlymen J, Klebe B, Middleton R, et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. *Kidney international*. [Research Support, Non-U.S. Gov't]. 2007 Jul;72(1):92-9.
 44. Klebe B, Farmer C, Cooley R, de Lusignan S, Middleton R, O'Donoghue D, et al. Kidney disease management in UK primary care: guidelines, incentives and information technology. *Fam Pract*. [Research Support, Non-U.S. Gov't]. 2007 Sep;24(4):330-5.
 45. Rastogi A, Linden A, Nissenson AR. Disease management in chronic kidney disease. *Adv Chronic Kidney Dis*. [Research Support, Non-U.S. Gov't]. 2008 Jan;15(1):19-28.
 46. Thorp ML, Eastman L, Smith DH, Johnson ES. Managing the burden of chronic kidney disease. *Dis Manag*. [Review]. 2006 Apr;9(2):115-21.

47. Chen RA, Scott S, Mattern WD, Mohini R, Nissenson AR. The case for disease management in chronic kidney disease. *Dis Manag.* 2006 Apr;9(2):86-92.
48. Rettig R, Vargas R, Norris K, Nissenson AR. A 'quiet revolution' in nephrology. *Nephrol News Issues.* [Research Support, N.I.H., Extramural]. 2010 Nov;24(12):18-9, 23.
49. Curtis BM, Ravani P, Malberti F, Kennett F, Taylor PA, Djurdjev O, et al. The short- and long-term impact of multi-disciplinary clinics in addition to standard nephrology care on patient outcomes. *Nephrol Dial Transplant.* [Comparative Study Research Support, Non-U.S. Gov't]. 2005 Jan;20(1):147-54.
50. Minnick AF, Roberts MJ, Young WB, Kleinpell RM, Marcantonio RJ. What influences patients' reports of three aspects of hospital services? *Med Care.* 1997 Apr;35(4):399-409.
51. Young WB, Lehrer EL, White WD. The effect of education on the practice of nursing. *Image J Nurs Sch.* [Comparative Study Research Support, Non-U.S. Gov't]. 1991 Summer;23(2):105-8.
52. Ridley RT. The relationship between nurse education level and patient safety: an integrative review. *J Nurs Educ.* [Review]. 2008 Apr;47(4):149-56.
53. Blegen MA, Vaughn TE, Goode CJ. Nurse experience and education: effect on quality of care. *J Nurs Adm.* [Evaluation Studies]. 2001 Jan;31(1):33-9.
54. Blegen MA, Goode CJ, Park SH, Vaughn T, Spetz J. Baccalaureate education in nursing and patient outcomes. *J Nurs Adm.* 2013 Feb;43(2):89-94.
55. Wade CH. Perceived effects of specialty nurse certification: a review of the literature. *Aorn J.* [Review]. 2009 Jan;89(1):183-92.
56. Krapohl G, Manojlovich M, Redman R, Zhang L. Nursing specialty certification and nursing-sensitive patient outcomes in the intensive care unit. *Am J Crit Care.* [Research Support, Non-U.S. Gov't]. 2010 Nov;19(6):490-8; quiz 9.
57. Boltz M, Capezuti E, Wagner L, Rosenberg MC, Secic M. Patient safety in medical-surgical units: can nurse certification make a difference? *Medsurg Nurs.* [Research Support, Non-U.S. Gov't]. 2013 Jan-Feb;22(1):26-32, 7.
58. Kendall-Gallagher D, Aiken LH, Sloane DM, Cimiotti JP. Nurse specialty certification, inpatient mortality, and failure to rescue. *J Nurs Scholarsh.* [Research Support, N.I.H., Extramural]. 2011 Jun;43(2):188-94.
59. Graham J. Nursing theory and clinical practice: how three nursing models can be incorporated into the care of patients with end stage kidney disease. *CANNT journal = Journal ACITN.* [Review]. 2006 Oct-Dec;16(4):28-31.
60. Neyhart CD, McCoy L, Rodegast B, Gilet CA, Roberts C, Downes K. A new nursing model for the care of patients with chronic kidney disease: the UNC Kidney Center Nephrology Nursing Initiative. *Nephrology nursing journal : journal of the American Nephrology Nurses' Association.* 2010 Mar-Apr;37(2):121-30; quiz 31.
61. Polaschek N. Negotiated care: a model for nursing work in the renal setting. *Journal of advanced nursing.* 2003 May;42(4):355-63.
62. Van Zuilen AD, Wetzels JF, Bots ML, Van Blankestijn PJ. MASTERPLAN: study of the role of nurse practitioners in a multifactorial intervention to reduce

- cardiovascular risk in chronic kidney disease patients. *Journal of nephrology*. [Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2008 May-Jun;21(3):261-7.
63. Wong FK, Chow SK, Chan TM. Evaluation of a nurse-led disease management programme for chronic kidney disease: a randomized controlled trial. *International journal of nursing studies*. [Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2010 Mar;47(3):268-78.
64. Lenz ER, Mundinger MO, Kane RL, Hopkins SC, Lin SX. Primary care outcomes in patients treated by nurse practitioners or physicians: two-year follow-up. *Med Care Res Rev*. 2004 Sep;61(3):332-51.
65. Mundinger MO, Kane RL, Lenz ER, Totten AM, Tsai WY, Cleary PD, et al. Primary care outcomes in patients treated by nurse practitioners or physicians: a randomized trial. *JAMA*. 2000 Jan 5;283(1):59-68.
66. van Zuilen AD, Bots ML, Dulger A, van der Tweel I, van Buren M, Ten Dam MA, et al. Multifactorial intervention with nurse practitioners does not change cardiovascular outcomes in patients with chronic kidney disease. *Kidney international*. 2012 Jun 27.
67. Haggerty JL, Reid RJ, Freeman GK, Starfield BH, Adair CE, McKendry R. Continuity of care: a multidisciplinary review. *Bmj*. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Review]. 2003 Nov 22;327(7425):1219-21.
68. Rogers J, Curtis P. The concept and measurement of continuity in primary care. *Am J Public Health*. 1980 Feb;70(2):122-7.
69. Torrey EF. Continuous treatment teams in the care of the chronic mentally ill. *Hosp Community Psychiatry*. [Comparative Study]. 1986 Dec;37(12):1243-7.
70. Campbell H, Hotchkiss R, Bradshaw N, Porteous M. Integrated care pathways. *Bmj*. [Research Support, Non-U.S. Gov't Review]. 1998 Jan 10;316(7125):133-7.
71. Knight JC. The Association of Continuity of Family Physician Care with Health Care Services Utilization and Costs in Newfoundland and Labrador [Ph.D]. St. John's: Memorial University of Newfoundland; 2011.
72. Barrett BJ, Garg AX, Goeree R, Levin A, Molzahn A, Rigatto C, et al. A Nurse-coordinated Model of Care versus Usual Care for Stage 3/4 Chronic Kidney Disease in the Community: A Randomized Controlled Trial. *Clin J Am Soc Nephrol*. 2011 Jun;6(6):1241-7.
73. Hopkins RB, Garg AX, Levin A, Molzahn A, Rigatto C, Singer J, et al. Cost-effectiveness analysis of a randomized trial comparing care models for chronic kidney disease. *Clin J Am Soc Nephrol*. [Research Support, Non-U.S. Gov't]. 2011 Jun;6(6):1248-57.
74. Molzahn AE, Hibbert MP, Gaudet D, Starzomski R, Barrett B, Morgan J. Managing chronic kidney disease in a nurse-run, physician-monitored clinic: the CanPREVENT experience. *Can J Nurs Res*. 2008 Sep;40(3):96-112.

75. Schmid H, Hartmann B, Schiffl H. Adherence to prescribed oral medication in adult patients undergoing chronic hemodialysis: a critical review of the literature. *Eur J Med Res.* [Review]. 2009 May 14;14(5):185-90.
76. Weingarten SR, Henning JM, Badamgarav E, Knight K, Hasselblad V, Gano A, Jr., et al. Interventions used in disease management programmes for patients with chronic illness-which ones work? Meta-analysis of published reports. *Bmj.* 2002 Oct 26;325(7370):925.
77. Cotterill-Walker SM. Where is the evidence that master's level nursing education makes a difference to patient care? A literature review. *Nurse Educ Today.* [Review]. 2012 Jan;32(1):57-64.