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ORIGINAL ARTICLE

The impact of renal protection clinics on prescription of and adherence to cardioprotective drug therapy in chronic kidney disease patients

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Abstract

Background: The aim of this study was to assess the impact of follow-up in renal protection clinics on the prescription of and adherence to cardioprotective drugs in patients with chronic kidney disease (CKD).

Methods: We studied stage 4 and 5 CKD patients who initiated follow-up in three renal protection clinics. The prescription pattern of antihypertensive agents (AHA) and lipid-lowering agents (LLAs) was measured as the percentage of patients who are prescribed the agents of interest at a given time. Adherence to drug therapy was defined as the percentage of days, during a pre-defined observation period, in which patients have an on-hand supply of their prescribed medications.

Results: A total of 259 CKD patients were enrolled and followed for up to 1 year after referral to renal protection clinics. There was a significant increase in the prescription of angiotensin-converting enzyme inhibitors (34–39%), angiotensin II receptor blockers (11–14%), beta-blockers (40–51%), calcium channel blockers (62–74%), diuretics (66–78%) and LLAs (39–47%) during follow-up in the renal protection clinic compared with baseline (P-values <0.01 for all comparisons). The proportions of patients with good ($\geq 80\%$) and poor ($< 80\%$) adherence to AHA ($P = 0.41$) and LLAs ($P = 0.11$) were similar in the year preceding and the year following the first visit to the renal protection clinics.

Conclusion: Our results suggest that referral and follow-up in a renal protection clinic may increase the prescription of cardioprotective agents in CKD patients, but does not appear to improve adherence to these medications.

Key words: cardioprotective medications, chronic kidney disease, renal protection clinic

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Introduction

Cardiovascular disease is a major cause of morbidity and mortality among patients with chronic kidney disease (CKD) [1]. The prevalence of cardiovascular risk factors in CKD is elevated, with 87–90% of CKD patients suffering from hypertension, 43% from dyslipidaemia and 37–38% from diabetes [2–5]. Actual guidelines on management of CKD emphasize the importance of recognizing and addressing cardiovascular risk factors using appropriate cardioprotective drug therapy, with consideration for aggressive blood pressure and lipid management [6, 7].

Despite these recommendations, many studies have reported underprescription of cardioprotective drug therapy in patients with CKD [2, 4, 8]. Another challenge in cardiopreventive care is low patient adherence to preventive medications such as antihypertensive agents (AHA) and lipid-lowering agents (LLAs) [9, 10]. Because of the involvement of health professionals from diverse backgrounds, including physicians, pharmacists, nurses and dieticians, renal protection clinics offer a patient-centered, multidisciplinary organization of care that may impact both prescription rates and adherence to cardioprotective drugs.

In this study, we sought to examine the impact of referral and follow-up in a renal protection clinic for patients with CKD. More specifically, we examined the prescription patterns of and adherence to AHAs and LLAs over a 1-year follow-up period following referral to the renal protection clinic.

Materials and methods

Patient population

This cohort study included patients with CKD seen in the renal protection clinics of three participating centers in the Montreal area. All consecutive patients who had a first visit to the participating renal protection clinics during the observation period were included in the study. Exclusion criteria were initiation of renal replacement therapy in the 15 days after the first visit or transfer to another center in the year following the first visit and age <18 years. Patients entered the cohort at the date of their first visit to the renal protection clinic and were followed up until death, transfer to another center or last follow-up date, whichever occurred first. Approval from the participating centers' ethics committees was obtained as well as authorization from the Quebec information access committee.

Renal protection clinics

Patients were referred to the renal protection clinics by their primary nephrologist when diagnosed with chronic and progressive renal failure, typically with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, without requirement for imminent dialysis initiation. Direct referral to the predialysis clinic by a primary care physician or other specialist was not permitted. Patients were seen approximately every 3 months by their nephrologists and kidney function and metabolic complications were monitored by blood and urine tests every 1–3 months. Medical prescriptions were re-evaluated at every consultation by the nephrologist and the nurse after a clinical and biological evaluation. Patient education, by a specialized clinic nurse, dietician and nephrologists, included information about progression and complications of CKD and the medical management and lifestyle modifications required to delay progression of CKD and target cardiovascular risk factor reduction. Preparation for dialysis and kidney transplantation was also completed. When required, patients were referred to a social worker.

Data collection

Data were collected in two different ways. First, trained medical archivists collected data from patient's medical records using a data abstraction form on an Access database. The following data were collected: demographic variables, AHA and LLA medication use (date of onset, discontinuation and dose), medical history at the time of referral, laboratory data (eGFR, haemoglobin and albumin levels) and events occurring during follow-up (hospitalization, dialysis, cardiovascular, transplantation, death). Second, the Quebec province's health insurance database [Régie de l'assurance-maladie du Québec (RAMQ)] was used to collect information on prescribed medication dispensation starting 1 year before the first visit to the renal protection clinic. This database contains records of prescribed medications dispensed to elderly Quebec residents ($\geq$65 years of age) not covered by a private drug insurance plan. More specifically, it includes information on drug dispensations that were given to patients by their pharmacists, including the number of pills provided at each refill and the dose that was prescribed.

Measurements

Prescription of LLAs and AHAs. The prescription of AHAs and LLAs was evaluated at the time of the first visit to the renal protection clinic (index date) and during follow-up at the renal protection clinic. The prescription of AHAs and LLAs followed Canadian guidelines [11]. Data on medication use (date of onset and discontinuation of prescription) from medical records were used to determine for each patient if they had an active prescription of an AHA or LLA at the index date and during follow-up separately. AHA evaluation included angiotensin II receptor blockers, beta-blockers, diuretics and angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers. LLA evaluation included HMG-Coa reductase (statins) and fibrates. The prescription was evaluated by therapy (AHA and LLA) and individually for each class of AHA and LLA mentioned above. Prescribers of new medications (i.e. nephrologists from the renal protective clinics or specialists outside the clinics) were also recorded.

Adherence to AHAs and LLAs. Data on prescribed medication dispensation (number of prescription refills) provided by the RAMQ database were used to measure adherence to AHAs and LLAs, respectively. Adherence was calculated as follows: the sum of the number of days in which the medication was dispensed divided by the total number of days included in the observation period for the year preceding and the year following the first visit to the renal protection clinic. Patients were separated into two categories of adherence for each observation period: good medication adherence (patients with an adherence $\geq$80%) and poor medication adherence (patients with an adherence $<$80%) [12, 13]. Patients who started medication 2 months before the first visit to the renal protection clinic were excluded. Adherence calculations were performed for AHA therapy (combining ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers and diuretics) and LLA therapy (combining statins and fibrates) and for each drug separately.

Statistical analyses. Descriptive statistics were used to assess the demographic and clinical characteristics of all patients, patients who started at least one AHA and/or LLA during

follow-up in the renal protection clinic (group 1) and patients who did not start any AHA and/or LLA during follow-up in the renal protection clinic (group 2). The demographic and clinical characteristics of group 1 and 2 were compared using non-parametric statistics including Mann–Whitney for continuous variables. Chi-squared test and Fisher exact test were used for categorical variables. McNemar test for paired samples was used to evaluate whether there is a significant change in the prescription of AHA and LLA between the index date and during follow-up in the renal protection clinic. The same test was used to evaluate whether there is a significant change between good (≥80%) and poor (<80%) adherence to AHA and LLA between the year preceding and the year following the first visit to the renal protection clinic. Adherence analyses were performed by SAS version 9.2 (SAS Institute Cary, NC, USA). All other analyses were performed with PASW statistics 18 software (SPSS Chicago, IL, USA). Statistical significance was defined as a P-value < 0.05.

Results

A total of 259 CKD patients were enrolled in the cohort. Two patients were excluded for incomplete medical history. Demographic and clinical characteristics are shown in Table 1. The mean age was 64 (± 13) years and the mean eGFR was 15 (± 6) mL/min/1.73 m^2. The most common causes of CKD were diabetes (38%) and hypertension (25%). The majority of patients were Caucasian (91%), with a slight male predominance (59%). The mean body mass index was 27.92 (± 6.1) kg/m^2, with a mean haemoglobin of 108.0 (± 17.8) g/L and a mean serum albumin of 37.5 (± 5.5) g/L. Patients had a high prevalence of cardiovascular risk factors, including diabetes (53%), hypertension (95%) and coronary artery disease (43%).

Table 1. Demographic and clinical characteristics of study participants ($N = 257$)

Characteristics	Values
Age, years, mean ± SD	64.2 ± 12.9
Body mass index, m^2/kg, mean ± SD	27.9 ± 6.1
Ethnicity and gender, %	
Female	40.9
Caucasian	91.4
Black	3.5
Other	5.1
eGFR, mL/min/1.73 m^2, mean ± SD[a]	15.2 ± 5.6
Stage of chronic kidney disease, %	
Stage 3	2.5
Stage 4	40.1
Stage 5	57.4
Comorbid conditions, %	
Diabetes	53.1
Hypertension	94.9
Coronary artery disease	42.5
Peripheral vascular disease	29.0
Smoking, %	
Never	36.9
Past	39.2
Active	23.9
Haemoglobin, g/L, mean ± SD	108.1 ± 17.8
Albumin, g/L, mean ± SD	37.5 ± 5.5
Primary causes of CKD, %	
Diabetes	37.9
Hypertension	24.9
Renovascular	7.9
Glomerulonephritis	12.3
Other[b]	17.0
Number of hospitalizations, mean ± SD	4.6 ± 3.6

[a]eGFR by Modification of Diet in Renal Disease four-variable equation.
[b]Includes polycystic, interstitial, congenital and obstructive kidney disease.

Prescription of AHAs and LLAs

At the time of their first visit to the renal protection clinic, 33.9% of patients were using ACE inhibitors, 11.3% angiotensin II receptor blockers, 40.1% beta-blockers, 62.9% calcium channel blockers, 66.1% diuretics and 39% LLAs (Table 2). Changes in prescribed medication during follow-up are shown in Table 2. There was a significant increase in the prescription of all AHAs (from 94% to 97%) ($P = 0.016$) during follow-up. The prescription rate also increased for each AHA drug class separately during follow-up: ACE inhibitors (34–39%), angiotensin II receptor blockers (11–14%), beta-blockers (40–51%), calcium channel blockers (62–74%) and diuretics (66–78%) (all P-values <0.001 on McNemar test). The proportion of patients prescribed one (22–14%) and two AHAs (34–26%) decreased, whereas the proportion of patients prescribed three (28–37%) and four AHAs (9–19%) increased significantly (all P-values <0.001 on McNemar test). The proportion of patients prescribed five AHAs remained similar. The proportion of patients prescribed LLAs and statins alone increased significantly, to 47% and 41%, respectively, during follow-up (P-values <0.001 on McNemar test). The proportion of patients prescribed fibrates alone remained similar. Fifty-nine percent of the new prescriptions of AHAs and 43.0% of the new prescriptions of LLAs were made by nephrologists from the renal protection clinics.

Characteristics of new users of LLAs and AHAs during follow-up in renal protection clinics

Ninety-two patients started at least one AHA and/or LLA during follow-up in the renal protection clinic (group 1), while 165 patients did not (group 2) (Table 3). Groups 1 and 2 were not significantly different in terms of most demographic and clinical characteristics. Both groups had similar age, body mass index, levels of haemoglobin and serum albumin. Both groups were predominantly Caucasian (91%) and male (59%). There were more patients with stage 3 CKD in patients who started at least one AHA and/or LLA during follow-up. The proportions of patients suffering from diabetes (52.2% in group 1 versus 53.6% in group 2) and hypertension (group 1, 95.6%; group 2, 94.5%) were similar. The prevalence of coronary artery disease was significantly lower in group 1 (group 1, 31.5%; group 2, 48.5%). Medication use on the day of the first visit to the renal protection clinic was lower in group 1 compared with group 2 for all classes of medication except ACE inhibitors and angiotensin II receptor blockers.

Adherence to AHAs and LLAs

Information on prescribed medication from the RAMQ database was available for 155 patients in the cohort. Data were not available for the other patients covered by private insurance. Eighty-one patients were taking LLAs and 151 patients were taking AHAs consecutively from the year preceding and the year following the first visit to the renal protection clinic. The proportions of patients with good (≥ 80%) and poor (< 80%) adherence to LLAs and AHAs during the year preceding and the year following the first visit to the renal protection clinic are shown in Table 4. Between the year preceding and the year following the

Table 2. Prescription of AHAs and LLAs at index date and during follow-up (N = 257)

Medication	Index date, *n* (%)	During follow-up, *n* (%)	P-value[a]
Total AHA[b,c]	241 (94%)	248 (97%)	0.016
ACE inhibitors	87 (34%)	99 (39%)	<0.001
Angiotensin II receptor blockers	29 (11%)	36 (14%)	0.016
Beta-blockers	103 (40%)	132 (51%)	<0.001
Calcium channel blockers	158 (62%)	189 (74%)	<0.001
Diuretics	170 (66%)	201 (78%)	<0.001
Monotherapy	57 (22%)	37 (14%)	<0.001
Combination therapy:			
- Two AHAs	88 (34%)	66 (26%)	<0.001
- Three AHAs	72 (28%)	95 (37%)	<0.001
- Four AHAs	23 (9%)	48 (19%)	<0.001
- Five AHAs	1 (0.4%)	2 (0.8%)	1.0
Total LLAs[d]	101 (39%)	122 (47%)	<0.001
Statin	86 (33%)	105 (41%)	<0.001
Fibrate	15 (6%)	17 (7%)	0.4795

[a]McNemar for paired samples; $P < 0.05$ is defined as statistically significant.
[b]Numbers do not add up because of combination therapy.
[c]Includes ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers and diuretics.
[d]Includes statins and fibrates.

Table 3. Demographics and clinical characteristics of new users of AHA or LLAs during follow-up in the renal protection clinic

Characteristics	New users of AHAs/LLAs (*n* = 92)	No new AHA/LLA use (*n* = 165)	P-value[a]
Age, years, mean ± SD	64.9 ± 13.8	63.9 ± 12.6	0.55
Body mass index, m^2/kg, mean ± SD	27.7 ± 5.2	27.9 ± 6.6	0.75
Ethnicity and gender, %			
Female	41.3	40.1	0.85
White	91.2	91.4	0.33
Black	4.4	3.0	
Chronic kidney disease stage, %			
Stage 3	4.6	1.3	0.05[a]
Stage 4	47.1	36.1	
Stage 5	48.3	62.6	
Comorbid conditions, %			
Diabetes	52.2	53.6	0.82
Hypertension	95.6	94.5	0.71
Coronary artery disease	31.5	48.5	0.01[a]
Peripheral vascular disease	26.1	30.5	0.45
Smoking, %			
Never	37.4	36.6	0.70
Past	36.3	40.9	
Active	26.4	22.6	
Primary causes of CKD, %			
Diabetes	35.6	39.3	0.51
Hypertension	27.8	23.3	
Renovascular	8.9	7.4	
Glomerulonephritis	11.1	12.9	
Medication at index date, %			
LLAs	29.3	44.8	0.02[a]
ACE inhibitors	30.4	35.8	0.39
Angiotensin II receptor blockers	8.7	12.7	0.33
Beta-blockers	27.2	47.3	0.002[a]
Calcium channel blockers	53.8	68.1	0.02[a]
Diuretics	56.5	71.5	0.02[a]

[a]Group 1 versus group 2; $P < 0.05$ is defined as statistically significant.

Table 4. Good (≥80%) and poor (<80%) adherence to AHAs and LLAs at 1 year preceding and 1 year following the first visit to the renal protection clinic ($N = 155$)

		1-year pre-index		1-year post-index		
Medication	n[a]	<80%, n (%)	≥80%, n (%)	<80%, n (%)	≥80%, n (%)	P-value[b]
Total AHAs[c]	151	12 (8%)	139 (92%)	11 (7%)	140 (93%)	0.81
Total LLAs[d]	81	16 (20%)	65 (80%)	22 (27%)	59 (73%)	0.11

[a]Patients who started medication 2 months before the first visit to the renal protection clinic were excluded.
[b]McNemar test for paired samples.
[c]Includes ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers and diuretics.
[d]Includes statins and fibrates.

first visit to the renal protection clinic, the proportion of patients with good (≥80%) and poor (<80%) adherence to LLAs was similar (P = 0.11). The proportion of patients with good (≥80%) and poor (<80%) adherence to AHAs was also similar during the two observation periods (P = 0.81).

Discussion

In this multicentre, cohort study, we show that the proportion of CKD patients who were prescribed AHAs and LLAs increased during follow-up in the renal protection clinic compared with the proportion of users on the day of the first visit to the renal protection clinic. Adherence to AHAs and LLAs was high and similar in the year before and the year following the first renal protection clinic visit. Our observations suggest that referral to renal protection clinics may have a positive impact on the prescription of cardioprotective drug therapy in CKD patients but it does not seem to modify adherence to cardioprotective drugs.

The overall increase in AHAs associated with follow-up in renal protection clinics suggests that this modality of care delivery may incentivize physicians to strive for stricter blood pressure control in CKD patients. We observed the greatest increases for beta-blockers, calcium channel blockers and diuretics (11–12% absolute increase), while the use of ACE inhibitors and angiotensin II receptor blockers was only modestly increased (3–5% absolute increase). Increased diuretic use was expected, given CKD-associated volume expansion and salt-sensitive hypertension [14]. ACE inhibitors and angiotensin II receptor blockers have been shown to reduce the progression of CKD in diabetics [15, 16] and non-diabetic proteinuric CKD patients [17], a finding that extends to patients with stage 4 CKD [18]. Fear of hyperkalaemia and hastening the need for renal replacement therapy may explain the relatively modest increase in the use of renin–angiotensin system inhibitors that we observed.

Although the most prevalent lipid abnormalities observed in CKD are elevated triglycerides and low high-density lipoprotein (HDL) cholesterol [19], we observed a significant increase in statin but not in fibrate use during follow-up in renal protection clinics. The efficacy of statin use to reduce cardiovascular risk in patients with CKD has been questioned in the past. Earlier randomized controlled trials in CKD patients undergoing hemodialysis did not show beneficial effects of statin therapy [20, 21]. However, a large trial in patients with CKD (with and without renal replacement therapy) demonstrated a 2.4% reduction in the absolute risk of coronary death, myocardial infarction, ischaemic stroke and revascularization procedures [22]. Although lowering triglycerides with fibrates may be associated with a reduction in cardiovascular events in patients with mild to moderate CKD [23], there are currently no data to support the use of fibrates in patients with stage 4 and 5 CKD [24]. Furthermore, a fibrate-associated decrease in eGFR has been reported in patients with CKD [23], while combined statin and fibrate therapy may increase the risk of rhabdomyolysis in this patient population [25]. In light of these observations, the change in prescription patterns that we observed in the year following the first visit to the renal protection clinic may have a positive impact on the cardiovascular risk of patients suffering from CKD.

We tried to evaluate whether the patients who were started on new AHAs and LLAs were different from those who were not in terms of cardiovascular risk factors or cardiovascular disease prevalence. The demographic characteristics and prevalence of cardiovascular risk factors were similar in both groups. However, the prevalence of coronary artery disease and the use of cardioprotective medications on the index date were higher in patients who were not started on new agents during follow-up. Due to their known history of coronary artery disease, these patients may already have had more stringent control of lipids and blood pressure [26], explaining a lesser need for the use of new cardioprotective agents.

Low adherence to medication is an important challenge in the management of hypertension and dyslipidaemia [10, 27]. In this study, we sought to evaluate the impact of referral and follow-up in a renal protection clinic on adherence to AHAs and LLAs. We observed high adherence figures for AHAs and LLAs in the year preceding the visit to renal protection clinics, as the proportion of adherent patients (≥80% of on-hand supply during the study period) was >80% for both AHAs and LLAs. These high figures may be due to the fact that patients were prevalent, not incident users. Studies in the general population have documented that the greatest decrease in persistence for LLAs occurred in the sixth month of use [28], and the selection of observant patients is probably likely when prevalent users are studied. No association could be found between follow-up in the renal protection clinics and adherence to AHAs and LLAs in our cohort of patients.

The study's strengths should be balanced against its limitations. First, an indication bias and residual confounding remain possible. Second, the cross-sectional design of the study cannot confirm causality. All observational cohort studies have limitations. The models derived in the present study may not apply to non-referred patients with CKD or those with higher eGFR values: by design, we studied only those with established advanced CKD known to nephrologists. In addition, missing laboratory and clinical data made it impossible to verify the lipid and blood pressure levels of patients at the first visit in the renal protection clinic and during follow-up. Hence, we cannot determine whether the proportion of patients managed according to guidelines improved with follow-up in renal protection clinics. Second, adherence was measured using data on drug dispensation by pharmacists, a technique that has been validated but that does not directly measure drug intake by patients [29]. Finally, modifications of the prescription of cardioprotective drug therapy were not only the consequence of the referral to renal protection clinics, as a proportion of the new prescriptions were made by other specialists outside the clinics.

Patients with CKD present multiple comorbidities and an elevated cardiovascular risk [1]. While low use of cardioprotective drugs has previously been reported in this patient

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population [2], renal protection clinics offer a multidisciplinary environment that favours a comprehensive approach to patient care, promoting stricter adherence to guidelines and medications. We observed an increase in the prescription of AHAs and LLAs during follow-up in renal protection clinics. However, adherence to these drugs was not modified. In conclusion, follow-up in renal protection may positively impact cardiovascular outcomes in CKD patients through more aggressive pharmacological management of hypertension and dyslipidaemia.

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Conflict of interest statement

None declared.

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