The Association of eGFR Reporting with the Timing of Dialysis Initiation

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ABSTRACT

Automated reporting of eGFR by laboratories has been widely implemented during the last decade. Over this same period, a steady increase in eGFR at dialysis initiation has been reported. This study examined trends in eGFR at dialysis initiation over time among incident dialysis patient populations before and after eGFR reporting. All patients who initiated dialysis between January of 2001 and December of 2010 in four Canadian provinces that implemented province-wide automated eGFR reporting and had an eGFR measure at dialysis initiation were included in the study (n=22,208). The primary outcome was change over time in eGFR among patients at dialysis initiation. An interrupted time series and adjusted multilevel regression models were used to determine the differences in eGFR at dialysis initiation before and after reporting. We observed a linear increase in the mean eGFR at dialysis initiation from 9.1 to 10.8 ml/min per m^2 during the study period. There was no change in the trajectory of the eGFR at dialysis initiation before or after eGFR reporting in crude or adjusted models accounting for case mix and facility characteristics. These findings were consistent among age and sex strata and when the proportions of patients with an eGFR$\geq$10.5 or $\geq$12 ml/min per m^2 were examined. In conclusion, automated laboratory-based eGFR reporting did not influence eGFR at dialysis initiation among incident dialysis patient populations. Concerns that widespread eGFR reporting leads to earlier dialysis initiation are not supported by this study.

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Automated laboratory-based reporting of eGFR has been widely adopted globally in the last decade to aid in the early recognition of CKD.[1–4] There remains, however, limited knowledge regarding the impact of this public health intervention on patient outcomes and health care resource use. Several studies have shown that, although routine eGFR reporting seems to result in an increase in appropriate referral for specialist care and medication prescription, it may also increase the number of unnecessary referrals and the number of patients inappropriately labeled with a chronic disease.[1,5–8] Furthermore, with eGFR reporting, the identification of kidney disease is not uniform, because older individuals with normal creatinine values are disproportionately reclassified as having CKD and subsequently referred for specialist care.[1,8,9]

In parallel with the introduction of automated eGFR reporting, a steady rise in the eGFR at dialysis initiation has been observed over the same decade.[10–12] This trend is concerning, because the initiation of dialysis at higher levels of eGFR is associated with early mortality and excess costs.[11,13–15] Reasons for why these trends are occurring seem multifactorial.[16–18] Dialysis patients are, on average, older with substantial comorbid illnesses; therefore, determining whether nonspecific symptoms, such as fatigue, are attributed to uremia or underlying illness is difficult. Dialysis

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initiation at higher eGFR levels seems to occur more commonly in elderly individuals, the identical cohort with an increase in nephrology referrals because of eGFR reporting.

From a clinical and health policy perspective, it is important to understand whether automated eGFR reporting has contributed to earlier dialysis initiation. Thus, we hypothesized that automated eGFR reporting may be leading to earlier dialysis initiation based on eGFR level. The objectives of this study were, therefore, to examine the association of eGFR reporting and the change in eGFR level at dialysis initiation over time among incident dialysis patient populations.

RESULTS

Characteristics Pre- and Post-eGFR Reporting

During the study period, 23,674 patients initiated dialysis, of whom 22,208 (93.4%) had serum creatinine measure at dialysis initiation; 9666 and 12,542 patients initiated hemodialysis in the provinces of interest during the pre- and post-eGFR reporting periods, respectively. Compared with the prereporting interval, patients in the postreporting interval were of similar age, more commonly men, and had a higher body mass index. In the postreporting interval, malignancy, coronary artery bypass grafting, and any serious illness were more common, whereas cardiovascular disease (excluding stroke), pulmonary edema, and hypertensive medication usage decreased (Table 1). Hypertension as a cause of ESRD was more frequent in the recent era, whereas the average hemoglobin and serum phosphate decreased. Use of an arteriovenous fistula (AVF) for hemodialysis and use of peritoneal dialysis both declined over time.

Table 1. Baseline characteristics of incident dialysis patients pre- and post-eGFR reporting

Characteristic	Pre-eGFR Reporting	Post-eGFR Reporting	*P* Value
N	9666	12,542	
Patient characteristics			
Age, mean±SD (yr)	64.4±15.1	64.8±15.0	0.10
Age categories, % (*N*)			0.43
Age<60 yr	33.3 (3220)	32.8 (4120)	
Age=60–73 yr	34.2 (3307)	33.9 (4246)	
Age>73 yr	32.5 (3139)	33.3 (4176)	
Sex, % men	58.4 (5646)	60.3 (7558)	0.01
Body mass index, mean±SD	26.8±6.1	27.7±6.7	<0.001
Distance from facility, % (*N*)			0.001
<50 km	79 (7447)	81.1 (9954)	
50–150 km	13.9 (1329)	12.4 (1528)	
>150 km	7.1 (676)	6.5 (795)	
Race, % (*N*)			<0.001
Caucasian	73.6 (7110)	69.2 (8677)	
East Asian	7.2 (696)	7.6 (949)	
Aboriginal	3.5 (343)	4.1 (513)	
Other	12.6 (1218)	14.8 (1860)	
Unknown	3.1 (299)	4.3 (543)	
Comorbidities, % (*N*)			
Angina	27.3 (2635)	21.0 (2636)	<0.001
Acute coronary syndrome	24.4 (2359)	23.0 (2885)	0.02
Pulmonary edema	27.6 (2663)	25.2 (3159)	<0.001
Diabetes mellitus	46.8 (4523)	47.7 (5978)	0.20
Stroke	15.1 (1464)	15.2 (1904)	0.96
Peripheral vascular disease	21.7 (2098)	19.2 (2402)	<0.001
Malignancy	12.0 (1164)	14.9 (1869)	<0.001
Lung disease	11.8 (1139)	12.1 (1518)	0.48
Hypertension medications	87.9 (8493)	86.4 (10,842)	0.002
Current smoker	14.7 (1299)	14.9 (1567)	0.79
Coronary artery bypass graft	13.9 (1343)	16.7 (2095)	<0.001
Serious illness	11.7 (1128)	16.9 (2114)	<0.001
Cause of ESRD % (*N*)			<0.001
Hypertension	20.3 (1965)	22.3 (2801)	
Diabetes mellitus	38.2 (3689)	35.6 (4466)	
GN	16.1 (1559)	13.7 (1717)	
Other	17.4 (1677)	19.7 (2480)	
Unknown	8 (776)	8.6 (1078)	
Hemoglobin, mean±SD (g/L)	103.8±17.9	102.1±17.1	<0.001
Albumin, mean±SD (g/L)	30.0±8.0	30.3±8.0	0.15
Phosphorous, mean±SD (mmol/L)	1.93±0.65	1.90±0.65	0.003
Peritoneal dialysis, % (*N*) within 90 d	27.0 (2605)	25.1 (25.1)	0.002
Facility characteristics			
AVF at initiation of dialysis, % (*N*)	17.0 (1639)	15.0 (1879)	<0.001

Changes in the eGFR Level at Dialysis Initiation after eGFR Reporting

The mean eGFR and proportion of patient populations with eGFR≥10.5 and ≥12 ml/min per m^2 at dialysis initiation increased after eGFR reporting was implemented (Table 2); however, in the unadjusted interrupted time series, the increase was linear, with no discernable change in trend because of eGFR reporting (Figure 1A) (*P* value for change in slope=0.66, *P* value for change in intercept=0.66). This finding was consistent when examining mean eGFR and proportion of patients with eGFR≥10.5 or ≥12 ml/min per m^2 (Figure 1, B and C). Within age and sex strata, the mean eGFR was higher in the postreporting period in all categories except elderly men (*P*=0.26); however, in the unadjusted interrupted time series (Table 3), there were no significant changes in trend because of eGFR reporting (*P* values for change in slope were all nonsignificant).

Table 2. Mean and proportional changes in the eGFR level at dialysis initiation among incident dialysis patient populations pre- and post-eGFR reporting

	Pre-eGFR (ml/min per m^2)	*N*	Post-eGFR (ml/min per m^2)	*N*	*P* Value
Total cohort					
Mean eGFR±SD	9.46±4.27	9666	10.04±4.48	12,542	<0.001
≥10.5 (%)	36.3	—	42.4	—	<0.001
≥12 (%)	27.4	—	31.4	—	<0.001
Mean eGFR±SD by sex and age subgroups					
Women<60 yr	8.02±3.57	1307	8.79±3.99	1631	<0.001
Men<60 yr	9.20±4.23	1913	9.59±4.66	2489	0.004
Women=60–73 yr	8.52±3.59	1367	9.49±3.98	1665	<0.001
Men=60–73 yr	10.08±4.44	1940	10.70±4.71	2581	<0.001
Women>73 yr	9.17±3.81	1346	9.73±3.88	1688	<0.001
Men>73 yr	11.0±4.78	1793	11.23±4.66	2488	0.26

Association of eGFR Reporting and eGFR at Dialysis Initiation

In the multilevel adjusted models, there was no change in the slope of eGFR level at dialysis initiation over time among incident patient populations between the pre- and postreporting intervals (change in eGFR at dialysis initiation between pre- and postreporting β=0.01 [P=0.64] per 90-day period) (Table 4). This finding was similar in sensitivity analyses examining trends within the higher strata of eGFR (eGFR≥10.5: odds ratio, 1.02; 95% confidence interval, 1.0 to 1.05; P=0.09; eGFR≥12: odds ratio, 1.01; 95% confidence interval, 0.98 to 1.03; P=0.61). There were no significant changes in slope before or after eGFR reporting in any of the age and sex strata (P values for each stratum were nonsignificant) (Table 4). When stratified by province, there were no significant changes after eGFR reporting in Ontario (β=0.0, P=0.75 per 90-day period) and British Columbia (β=−0.01, P=0.80 per 90-day period). In Alberta, there was a decrease in the slope after eGFR reporting (β=−0.12, P<0.001 per 90-day period).

DISCUSSION

In this large, population-level study of incident patients starting dialysis over the last decade, we found that laboratory-based automated eGFR reporting was not associated with changes in the eGFR level at dialysis initiation. The proportion of patients initiating dialysis with an eGFR≥10.5 or ≥12 ml/min per m^2 did not change after eGFR reporting. There was no association with eGFR reporting and the level of eGFR at dialysis initiation in specific high-risk patient populations, such as the elderly, or women. Based on our findings, concern that widespread, automated eGFR reporting may be leading to initiation of dialysis at higher levels of eGFR are unwarranted.

This study is the first clinical study to investigate the relationship between eGFR reporting and the timing of dialysis initiation. There are plausible concerns for why eGFR reporting may be contributing to early dialysis initiation. The decision to start dialysis is not purely objective; rather, it depends on a combination of objective laboratory and clinical examination findings as well as a patient's self-reported symptoms of uremia. Recognizing this subjectivity, clinical guidelines are deliberately vague (because of limited evidence) and merely suggest that dialysis be considered when eGFR drops below 15 ml/min per m^2.[19] Given this context, patient and physician biases may influence the decision to start dialysis. A portion of physicians has traditionally believed that starting dialysis earlier is better. For example, in a recent European survey of nephrologists, 11% felt that starting dialysis in patients with eGFR≥10.5 ml/min per m^2 was always beneficial, even in the absence of symptoms.[20] The clinical uncertainty about when to start dialysis was reported in Canada, where facility-level variation in eGFR at dialysis initiation was found to be 4.5% after accounting for case mix and facility-level factors.[21] A recent international survey study randomized clinical vignettes presented to nephrologists to contain one of eGFR or serum creatinine and assessed opinions regarding the initiation of dialysis. The survey found that participants randomized to scenarios reporting the eGFR modestly increased the likelihood of initiating dialysis.[22] There was no difference in responses from participants among the different countries (Canada included), and therefore, it is plausible that automated eGFR reporting might sway physicians to recommend dialysis earlier and more strongly, irrespective of symptom severity. Reasons for discrepant findings between the two studies may include limited generalizability in the survey study (response rate=19%), a relatively small number of respondents from Canada (n=119), and actual practice patterns differing from theoretical scenarios.

eGFR reporting has led to an increase in the detection of kidney disease, specifically in the elderly and women, and they are the same cohort susceptible to dialysis initiation at higher eGFR levels. Because elderly individuals may have a higher burden of comorbid conditions causing clinical symptoms, these individuals may be started early on dialysis, because nephrologists may falsely attribute symptoms to uremia rather than a coexisting condition. Reports have shown an increase of 3–6 years in the mean age of the referral population to

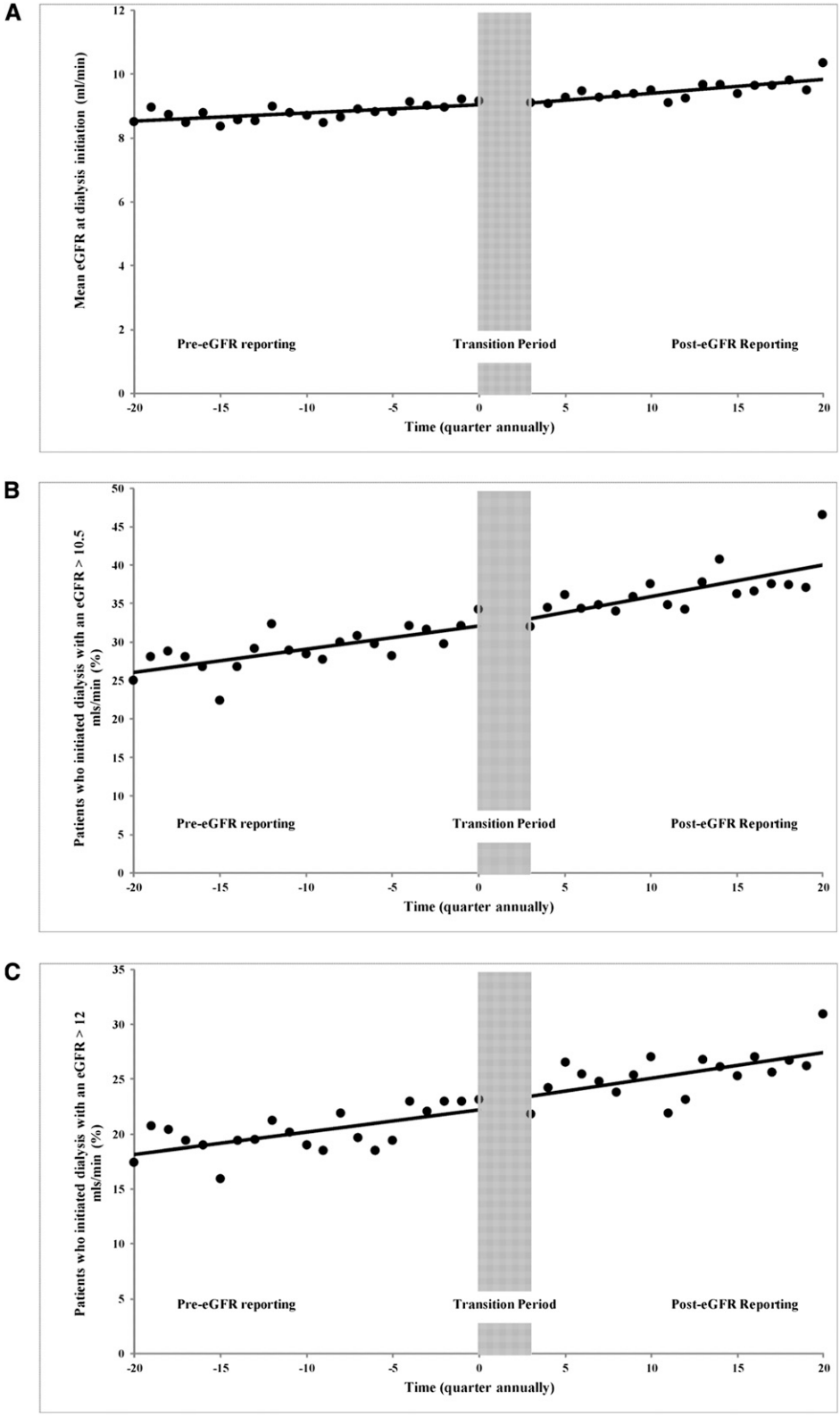

Figure 1. Unadjusted interrupted time series of (A) mean eGFR, (B) proportion of patients initiated with an eGFR≥10.5 ml/min per m^2, and (C) proportion of patients initiated dialysis with an eGFR≥12 ml/min per m^2 before and after eGFR reporting. Each point represents the mean or proportion among incident dialysis patients in that 3-month period. Gray bars represent the 6-month transition periods. The solid line represents the linear trend line. Significance testing for the change in slope and the change in intercept: mean eGFR: *P*(slope)=0.66, *P*(intercept)=0.66; eGFR≥10.5 ml/min per m^2: *P*(slope)=0.18, *P*(intercept)=0.47; eGFR≥12 ml/mi per m^2: *P*(slope)=0.47, *P*(intercept)=0.57.

Table 3. Unadjusted change in the slope and intercept of the eGFR level over time among incident dialysis patient populations initiating dialysis before and after automated eGFR reporting

Sex	Age (yr)	*P* Value for Intercept	*P* Value for Slope
Women	<60	0.12	0.23
Men	<60	0.17	0.46
Women	60–73	0.09	0.10
Men	60–73	0.39	0.86
Women	>73	0.73	0.93
Men	>73	0.05	0.17

Data are presented for eGFR as a continuous variable. The results were similar when examining the proportion of patients initiated with eGFR≥10.5 and ≥12 ml/min per m^2 (data not shown). Results were based on an unadjusted interrupted time series.

Table 4. Adjusted change in slope of the eGFR level at dialysis initiation among incident dialysis patient populations post-eGFR reported in age and sex subgroups

Age (yr)	Sex	Point Estimate	*P* Value
Total cohort	Total cohort	β=0.01; SEM=0.019	0.64
<60	Women	β=−0.02; SEM=0.02	0.33
<60	Men	β=0.01; SEM=0.02	0.34
60–73	Women	β=−0.01; SEM=0.02	0.57
60–73	Men	β=−0.01; SEM=0.02	0.58
>73	Women	β=0.01; SEM=0.02	0.53
>73	Men	β=−0.01; SEM=0.02	0.48

β-Value for post-eGFR reporting×time (90 days) in each age and sex strata interaction term in a multilevel linear regression adjusted for calendar year, post-eGFR reporting in age and sex strata, case mix (age, sex, body mass index, race, comorbidities, laboratory values, distance from center, and modality), and facility-level variables (percent AVF, transplant facility, peritoneal dialysis facility, and center size).

nephrologists post-eGFR reporting.[1,23,24] Concurrently, there have been increases of 6%–25% in women detected and referred to nephrology care with eGFR reporting.[2,23] With advanced CKD, ongoing sarcopenia, malnutrition, and higher comorbidity have led to this same population being initiated on dialysis at higher levels of eGFR. In a United States dialysis cohort study of greater than 800,000 patients, the mean age of patients starting dialysis with an eGFR>15 ml/min per m^2 was 68.4 versus 59.3 years in those patients started with an eGFR<5 ml/min per m^2.[25] A similar upward trend of age and initiating eGFR was reported in greater than 11,000 patients from the French Ramipril Efficacy in Nephropathy registry, where the mean age of those patients with an eGFR≤5 ml/min per m^2 was 60.6 compared with 71.8 in those patients with an eGFR>20 ml/min per m^2.[14] Our findings may help in alleviating some of these concerns. Although the mean eGFR levels were significantly higher in the post-eGFR period (Table 2), there was no increase in the eGFR at dialysis initiation after eGFR reporting in the interrupted time series or the adjusted models. This finding was consistent when eGFR was examined as a continuous variable or proportions≥10.5 or ≥12 ml/min per m^2 and in all subgroups (*P* value=NS), especially among those patients considered to be the most susceptible to early initiation (for example, elderly women). In one province (Alberta), it seemed that there was a decline in the eGFR level after eGFR reporting; however, reasons for this finding are unclear.

Initiation of dialysis at higher eGFR levels remains highly controversial. Numerous studies and a recent meta-analysis have consistently shown the lack of benefit and potential harm with early dialysis initiation.[10,15,26–28] The Initiating Dialysis Early and Late (IDEAL) randomized control trial showed no difference in mortality between the two study arms: a high (10–14 ml/min per m^2) and low eGFR (5–7 ml/min per m^2) at dialysis initiation; however, there was a high degree of crossover between the two study groups.[29] Furthermore, patients in the IDEAL trial started in the higher eGFR arm were initiated, on average, 6 months earlier than patients in the low eGFR arm, with a direct dialysis cost increase of greater than $10,000 per patient.[30] eGFR reporting also has led to increases in resource use by increasing the referral rate from 3% to 270%.[9] Subsequently, it would be concerning if eGFR reporting was associated with an increase in early dialysis initiation, because the benefit of early CKD detection, cardiovascular disease protection, and planning for dialysis would be offset by potential harm for those patients who initiate early dialysis and a significant increase in costs and health resource use.

Our findings strengthen the evidence for automated eGFR reporting as an important public health tool. To date, there is limited evidence on important health outcomes associated with eGFR reporting; evidence is often limited to short-term effects in CKD care, such as transient increases in the nephrologist referral rate, modest increases in angiotensin-converting enzyme inhibitor/angiotensin receptor blocker prescription, and a decline in nonsteroidal anti-inflammatory drug use.[9,31,32] Our study is the first study to assess the association of eGFR reporting with a downstream, dialysis-related outcome, such as eGFR level at dialysis initiation. Additional studies to assess the association of eGFR reporting and dialysis-related outcomes, such as early optimization and adoption of home modalities and AVF creation, are required.

A major strength of our study is the unique implementation of eGFR reporting in Canada. Canada's provincially administered health care system allowed for a staggered approach to eGFR reporting, thereby creating a natural experiment that enabled us to study the effects of reporting independent of era. Canada's universal health care system is ideal for these types of population health studies in that all residents have access to a primary care system and in most cases, multidisciplinary kidney health prevention clinics. In other jurisdictions/countries, where eGFR reporting would be universally applied or applied at the level of each individual laboratory provider, such a study would not have been possible. Our findings are generalizable, because there was little missing data for eGFR at dialysis initiation (<7%); also, the findings represented population-level data of incident dialysis patients

from the study provinces. Methodologically, we used an interrupted time series, a well established method of determining the temporal effects of an intervention. Furthermore, we formally examined the change in slope with multilevel models to avoid underestimation in the post-eGFR reporting period, a known limitation of using interrupted time series with upward-trending data.[33,34] The 5-year follow-up window would adequately allow for patients to be detected by eGFR reporting, be referred, and progress to ESRD. A study conducted in two of four provinces included in our cohort (British Columbia and Ontario) reported that 24% of CKD patients reached kidney failure by approximately 3 years.[35] Lastly, we were able to account for a substantive number of patient- and facility-level characteristics in our multivariable models because of the validated national registry Canadian Organ Replacement Registry (CORR), which tracks all new dialysis starts.

There are limitations to our work. There were possible unaccounted era effects (residual confounding); however, they would be minimized in our study, because the four provinces included initiated widespread eGFR reporting over an extended time period of 5 years (2003–2008), and we adjusted our model for calendar year. Laboratory creatinine measurements may not have been uniformly standardized with the implementation of eGFR reporting in each province. We attempted to minimize this lack of uniformity by the use of multilevel modeling that adjusted for facilities, thereby minimizing differences in the laboratory standardization of creatinine measurements.[36] We lacked additional patient-level information, including the indication for dialysis initiation and patient functional measures.

In conclusion, widespread laboratory automated eGFR reporting was not associated with an increase in the eGFR level at dialysis initiation over time among incident dialysis patient populations. These findings help strengthen the evidence for eGFR reporting as an important public health initiative and alleviate concerns that it may be causing harm by leading to dialysis initiation at a higher level of eGFR, independent of uremic symptoms. Additional studies to establish the downstream impacts of eGFR reporting on dialysis-related outcomes are required.

CONCISE METHODS

Population and Data Sources

All adult (>18 years old) incident dialysis patients from four Canadian provinces with automated laboratory-based eGFR reporting (Ontario, British Columbia, Alberta, and Newfoundland) with a measure of eGFR at dialysis initiation from January of 2001 to December 31, 2010, were included in the cohort (n=22,208; 93.4% of all incident patients started during that period). Data were obtained from the CORR, a validated registry that includes demographics, comorbidities, dialysis modality, vascular access, transplantation, and mortality on all ESRD patients in Canada.[37,38] Data are collected by dialysis facilities and housed centrally with the Canadian Institute for Health Information. Data were collected until death, loss of follow-up, or end of study period (2010).

Cohort Definitions

Information regarding the timing and extent of province-wide automated eGFR reporting was obtained by surveying dialysis program heads and administrators. Provinces included in the study met the following criteria: (*1*) province-wide conversion to automated eGFR reporting, (*2*) conversion occurred within 1 year, and (*3*) there were adequate pre- and postintervention study periods (>1 year). The four provinces with automated eGFR reporting and the month and year of conversion were Ontario (January of 2006), Alberta (October of 2004), British Columbia (October of 2003), and Newfoundland (January of 2008). Manitoba and Nova Scotia also had eGFR reporting but were excluded because of a less than 1-year follow-up period (Manitoba implemented eGFR reporting in January of 2010) and a conversion period of greater than 1 year (occurred over 6 years in Nova Scotia). Because the four provinces had varying implementation time for eGFR reporting, we examined all patients initiating dialysis up to 5 years pre- and post-eGFR reporting. To allow for referrals and CKD care because of automated eGFR reporting, we excluded data from the first 6 months in the postreporting period (transition period).

First visit date with a nephrologist was used to estimate the length of predialysis nephrology care. Comorbidities (angina, chronic obstructive pulmonary disease, diabetes, malignancy, serious illness, hypertension, lung disease, coronary artery bypass grafting, pulmonary edema, peripheral vascular disease, stroke, cigarette smoking, and acute coronary syndrome) were recorded at the initiation of dialysis. Serious illness was defined as any illness that could shorten life expectancy to less than 5 years. Race was self-reported. Distance to facility was calculated as the direct linear distance in kilometers between a patient's primary residence (estimated from the postal code at the time of dialysis initiation) to the nearest dialysis provider using the formula by Vincenty.[39] Facility variables included the proportion of patients who received dialysis through an AVF, whether the facility offered renal transplantation and/or peritoneal dialysis, and the center size. Individual patients and dialysis facilities were deidentified for analytic purposes. Additional laboratory values (hemoglobin, albumin, and phosphate) were recorded in cross-section at dialysis initiation.

Outcome

The primary outcome was the change in eGFR level at dialysis initiation over time among incident dialysis patient populations. Kidney function was estimated using the abbreviated Modification of Diet in Renal Disease equation based on the patients serum creatinine, age, and sex at dialysis initiation.[40] The secondary outcome was the eGFR level over time among patients at dialysis initiation stratified by age in tertiles and sex.

Statistical Analyses

Patient and facility characteristics were compared between the pre- and post-eGFR reporting periods. Continuous variables of

interest were summarized as mean or median with SD or interquartile range as appropriate. Differences in characteristics were determined by *t* test or the Mann–Whitney test for continuous variables and chi-squared or the Fisher-exact test for dichotomous variables.

The association between eGFR reporting and the eGFR level at dialysis initiation over time among incident dialysis patient populations was examined by two methods. First, an unadjusted interrupted time series was created for the time interval of 5 years before and after eGFR reporting.[33] Time was divided into 3-month intervals, and the quarterly average or proportion was examined for trends. Second, sequential adjusted multilevel regression models were used to examine changes in the eGFR at dialysis initiation in the pre- and postreporting time intervals.[41,42] Changes in trends among the populations were measured by examining changes in the slope of the eGFR at dialysis initiation after eGFR reporting using an interaction term (model equation is presented in Supplemental Appendix). Two levels were included in the multilevel model: patients and facilities. A two-level model was used to account for significant facility-level variability in the eGFR at dialysis initiation, a finding that we had previously reported.[21] Fully adjusted models included variables for case mix (age, sex, body mass index, race, comorbidities, laboratory values, distance from center, and modality), facility-level variables (percent AVF, transplant facility, peritoneal dialysis facility, and center size), and calendar year. In a series of sensitivity analyses, we also examined the primary outcome as the proportion of patients with an eGFR at dialysis initiation $\geq$10.5 and $\geq$12 ml/min per m^2. Results were further stratified by age in tertiles, sex, and province. When examining the provincial subgroups, only Ontario, Alberta, and British Columbia were examined, because Newfoundland had a small number of facilities.

Multiple imputation was used for missing values.[43] Analyses were performed using PASW version 18 and SAS version 9.3. All hypothesis tests were two-sided, with statistical significance determined at a P value <0.05.

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M.M.S. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DISCLOSURES

M.M.S. has been on advisory boards for Roche and Amgen and received speaking honoraria from Roche, Amgen, and Sanofi US.

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Supplemental Appendix 1:

Model Equation

Y_{ij} Represents observation on individual i in facility j

X_{cij} Represents the calendar year of treatment for individual i in facility j

X_{gij} Represents variable indicating if the treatment occurred after the GFR reporting period intervention for individual i in facility j

X_{tij} Represents time before (negative) or after (positive) GFR reporting period on individual i in facility j

$b_j^{(2)}$ Represents error term for facility j

e_{ij} Represents error term for individual i in facility j

$$Y_{ij} = \beta_0 + \beta_1 X_{1ij} + \beta_2 X_{2ij} + \cdots + \beta_c X_{cij} + \beta_g X_{gij} + \beta_{tg} X_{tij} X_{gij} + b_j^{(2)} + e_{ij}$$

$$b_j^{(2)} \sim N(0, \sigma_2^2)$$

$$e_{ij} \sim N(0, \sigma_1^2)$$