Nephrol Dial Transplant (2023) 38: 1249–1259
https://doi.org/10.1093/ndt/gfac268
Advance Access publication date 13 September 2022

Impact of a continuous quality improvement program on contrast-induced nephropathy in outpatients with chronic kidney disease: an interrupted time-series study

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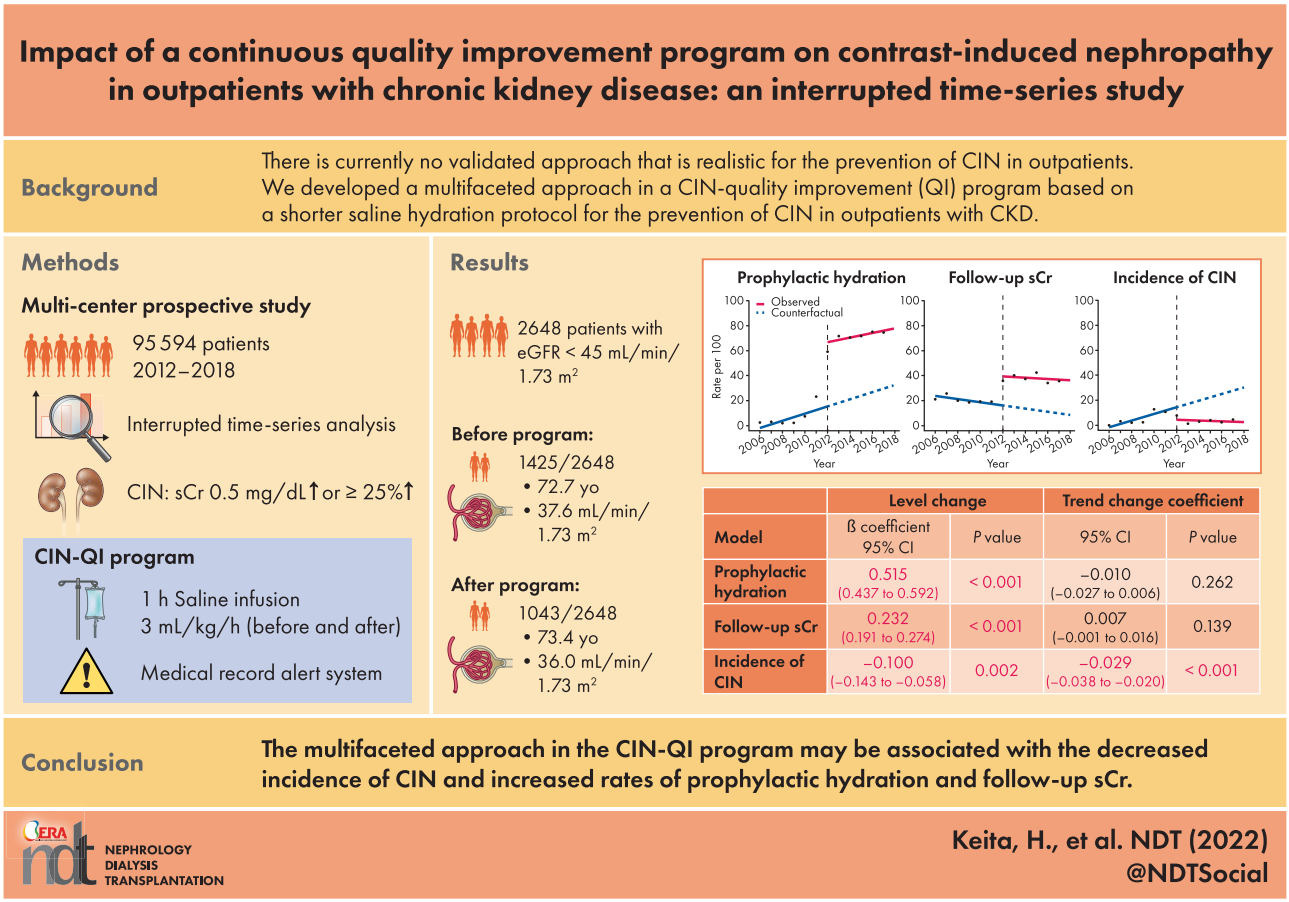
GRAPHICAL ABSTRACT



ABSTRACT

Background. Contrast-induced nephropathy (CIN) caused by exposure to radioactive contrast media can cause acute kidney injury in patients with chronic kidney disease (CKD). We developed a multifaceted approach in a CIN-quality improvement (QI) program based on a shorter saline hydration

KEY LEARNING POINTS

What is already known about this subject?

•Saline hydration is a useful method of preventing contrast-induced nephropathy (CIN). However, the typical protocol for prophylactic hydration recommends 6–24 h of infusion, which is not feasible for outpatients undergoing contrast-enhanced imaging studies.

•There is currently no validated approach that is realistic for the prevention of CIN in outpatients.

What this study adds?

•A multifaceted approach in a CIN-quality improvement (QI) program, which included a shorter prophylactic saline hydration protocol during contrast-enhanced computed tomography procedures for outpatients, was found to be effective in preventing CIN and decreasing the number of contrast studies.

What impact this may have on practice or policy?

•Widespread implementation of the CIN-QI program may help prevent the development of CIN in outpatients undergoing contrast-enhanced imaging studies, thereby preventing complications from CIN and reducing the associated costs to healthcare systems.

protocol for the prevention of CIN in outpatients and assessed the effect of our CIN-QI program on decreasing both the incidence rate of CIN and overall use of contrast agents in patients undergoing contrast-enhanced computed tomography (CT).

Methods. We conducted a multi-center prospective interrupted time-series study from 2006 to 2018 investigating the efficacy of a CIN-QI program in preventing CIN among outpatients with CKD. An automatic medical record system alert was implemented to instruct physicians to consult a nephrologist and administer prophylactic hydration and follow-up when ordering contrast-enhanced imaging in patients with an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2. The primary outcomes were the rates of prophylactic hydration and follow-up kidney function assessment, and the incidence of CIN for eligible patients. The usage rate of contrast-enhanced CT was also examined.

Results. A total of 95 594 patients who underwent contrast-enhanced CT were included in the study. The annual prophylactic hydration rate before the CIN-QI program ranged from 2.0% to 23.2% but increased to 59.2%–75.2% during the CIN-QI program ($P < .001$). The annual rate of follow-up kidney function testing also improved from 18.6%–25.8% to 34.1%–42.5% after implementation of the CIN-QI program ($P < .001$). The rate of CIN significantly declined in level by 10.0% at the start of the CIN-QI program ($P = .002$) and in trend by 2.9%/year ($P < .001$). The number of contrast-enhanced CT orders showed a positive level change in patients with advanced CKD, who were the CIN-QI program target group of patients with eGFR <45 mL/min/1.73 m^2, at the start of the implementation of the CIN-QI program. After implementing the CIN-QI program, the number of contrast-enhanced CT orders showed a negative trend change across all patients, which decreased from −1.4%/year to −10.0%/year for patients with advanced CKD.

Conclusion. The multifaceted approach in the CIN-QI program may be associated with the decreased incidence of CIN and increased rates of prophylactic hydration and follow-up kidney function testing.

Keywords: acute kidney injury, chronic kidney disease, contrast-induced nephropathy, interrupted time-series analysis, quality improvement

INTRODUCTION

Contrast-induced nephropathy (CIN) is a kidney injury caused by the administration of radioactive contrast agents during transvenous diagnostic contrast-enhanced computed tomography (CT) scanning or a transarterial cardiovascular intervention. Notably, CIN is the third most common causes of acute kidney injury (AKI) in hospitalized patients [1]. Patients with CIN have a high incidence of adverse events and a 13% higher annual mortality rate than patients without CIN, which causes a significant economic and healthcare burden [2]. Specifically, patients who develop CIN are at an increased risk of cardiovascular events, resulting in extended hospital stays, poor renal outcomes and increased mortality [3–6]. As a result of the public health implications of CIN and AKI, there have been large-scale global awareness campaigns about these conditions [7].

Patients with chronic kidney disease (CKD) are at an increased risk for CIN [8, 9]. The guidelines of the Contrast Safety Committee of the European Society of Urogenital Radiology (ESUR) recommend prophylactic intravenous crystalloid infusions for 6–24 h before and after contrast agent use for patients with an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 [10]. Although there are few randomized controlled trials (RCTs) investigating crystalloid infusion to prevent CIN, Nijssen *et al.* [11] recently conducted the AMACING study, which showed that no prophylaxis is non-inferior to prophylactic intravenous fluids in the prevention of CIN. However, much of the evidence from the A MAstricht Contrast-Induced Nephropathy Guideline (AMACING) trial is based on interventional radiography studies for inpatients who used large amounts of contrast agents. A shorter prophylactic protocol is needed in the outpatient setting as prolonged prophylactic hydration is impractical for most outpatient contrast-enhanced CT studies. To date, such shorter prophylactic protocols have not been adequately investigated.

We developed a multifaceted approach in a CIN-quality improvement (QI) program based on the shorter protocol for CIN prevention in outpatients proposed by Goldfarb *et al.* [12]. We assessed the effect of our CIN-QI program on decreasing both the incidence rate of CIN and the overall use of contrast agents in all patients undergoing contrast-enhanced CT. To this end, we conducted a longitudinal cohort study with a long follow-up period in patients with CKD. The multifaceted approach in the CIN-QI program was evaluated using an interrupted time-series analysis, also known as a "pseudo-RCT," which allowed us to assess the impact of the interventions on the entire population.

MATERIALS AND METHODS

Study design

We conducted a multi-center prospective longitudinal study using medical record data from all patients 18 years or older with eGFR <45 mL/min/1.73 m² scheduled for contrast-enhanced CT in three branches of St Luke's International Hospital between April 2006 and March 2018. To account for potential covariates, we obtained data about the participants' medical history and previous laboratory measurements. The following information was collected: age, sex, serum creatinine level from registration to the end of the observation period, baseline eGFR, comorbidities (hypertension and diabetes), volume of radiocontrast agents used and details of the saline hydration administration protocol. We excluded all patients who opted out of having their anonymized data used in the study. In addition, patients were excluded if their baseline kidney function was not measured. Patients who required regular dialysis, whether hemodialysis or peritoneal dialysis, were excluded.

The outcome measures were the implementation rate of prophylactic saline hydration, rate of kidney function assessment after contrast-enhanced CT and incidence of CIN. The kidney function assessment rate was defined as the percentage of patients whose kidney function was measured within 1 week of undergoing contrast-enhanced CT, and the hydration implementation rate was defined as the percentage of patients who received intravenous hydration according to the CIN-QI protocol described below. Contrast agent use was also assessed based on the annual number of contrast-enhanced CT scans obtained in patients with all stages of CKD [10, 13]. Finally, the trends in contrast medium utilization were evaluated and compared between imaging regions. Patient outcomes were compared before and after the 2012 implementation of the CIN-QI program. The Ethics Committee Institutional Review Board approved this study with the approval number R21-013.

Definition of CIN

CIN is diagnosed when kidney function declines after using radiocontrast agents, and other causes of AKI—such as dehydration, sepsis and drug-induced AKI—can be ruled out. We used the following definition of CIN in patients with CKD: a serum creatinine ratio before and after CT or more or a ≥25% increase from the previous serum creatinine value measured within 1 week of iodine contrast agent administration. Baseline kidney function was defined as the most recent serum creatinine value measured on the day closest to and within 1 year retrospectively from the CT order date, and patients were excluded if their baseline creatinine level was not measured. This definition is based on the joint guideline from the Japanese Society of Nephrology, Japan Radiological Society and Japanese Circulation Society [13], which is consistent with the guidelines outlined by the ESUR Contrast Media Safety Committee [10] and Consensus Statements from the American College of Radiology and the National Kidney Foundation [14]. As all patients included in this study were outpatients, the follow-up period after the administration of iodinated contrast medium was 1 week, which is consistent with the usual outpatient follow-up schedule.

Development and implementation of the CIN-QI program

The development, dissemination and evaluation of the CIN prevention program was conducted as a hospital-wide QI activity. This included the development of a CIN prevention protocol, a CIN risk assessment using a risk score, an automatic medical record system alert and monitoring of CIN prevention protocol implementation rates as monthly quality indicator measurements [15]. CIN-QI program committees met monthly to review and assess progress toward achieving the target implementation rate of 80%. Department heads who participated in the committee meetings provided feedback to the physicians in their respective departments. The CIN-QI program also promoted the awareness of the need to avoid unnecessary contrast studies in accordance with clinical guidelines [10, 13]. A CIN working group, QI committee and specialist teams were closely involved in the QI activities from April 2012 to March 2018. The detailed composition and roles of the involved groups are summarized in Supplementary data, Table S1.

As a preliminary study, the CIN prevention protocol was implemented for patients with CKD undergoing contrast-enhanced cardiac CT, as this procedure typically requires a smaller volume of contrast agent than abdominal CT. We adopted the following procedure reported by Goldfarb *et al.* [12]: an outpatient CIN prevention protocol in which a 3 mL/kg/h isotonic solution of either sodium bicarbonate or saline is infused before the test and for at least 1 h after the test. After confirming the safety of this CIN prevention protocol, educational conferences were held for the entire hospital regarding the appropriate time to order contrast-enhanced CT prior to initiating CIN-QI. Here, we explained the need for prophylactic infusions before and after contrast CT. For example, we explained that necessary contrast-enhanced CT should not be avoided because of renal dysfunction. The CIN-QI program recommended that this protocol be used for patients with CKD stage 3b or higher. Next, after the CIN-QI was initiated, educational interventions that included guidance on the appropriate contrast by body region were conducted for each clinical department. For example, simple CT is first indicated for the diagnosis of stones in the urinary tract and should

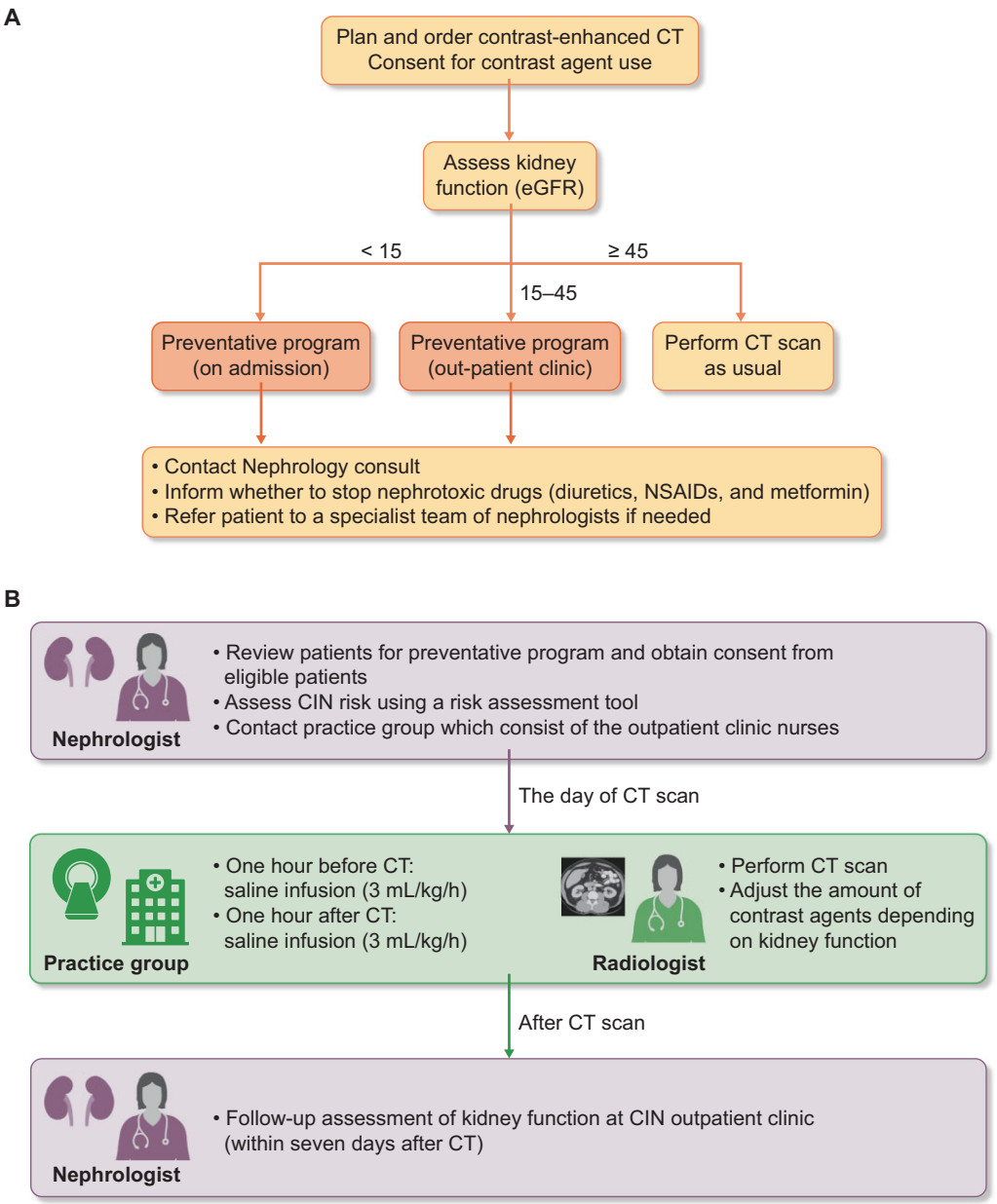


Figure 1: CIN-QI program.

be avoided in patients with renal dysfunction. To identify high-risk patients to physicians ordering contrast-enhanced CT, the Hospital Health Information Centre developed an automatic medical record system alert to identify high-risk patients with CKD stage 3b or higher. When a physician orders a contrast CT for a patient with eGFR <45 mL/min/1.73 m^2, the system is activated, and the electronic medical record system automatically notifies the ordering physician that the patient is at a high risk of CIN and then recommends prophylactic hydration and a nephrologist consultation (Supplementary data, Fig. S1). The nephrologist explains the risk of CIN to the patient and plans prophylactic hydration before and after contrast-enhanced CT. Based on the clinical guideline [13], the nephrologist may consider stopping medications such as non-steroidal anti-inflammatory drugs, metformin or loop diuretics depending on the patient's risk factors. Next, the radiologist and radiographer assess the patient's renal function and decide to adjust and administer the minimum contrast dose within the range that would maintain diagnostic performance. All contrast media used are hypo-osmotic, non-ionic contrast media. Lastly, the nephrologist performs follow-up kidney function testing within 1 week of the contrast-enhanced CT. Patients with kidney dysfunction at follow-up are subjected to ongoing follow-up at the CKD outpatient clinic (Fig. 1).

For QI monitoring, the Hospital Health Information Centre collected data on patients undergoing contrast-enhanced CT and identified whether a nephrologist was consulted and prophylactic intravenous hydration was performed as appropriate. Furthermore, the changes in patients' serum creatinine

levels following the administration of the iodinated contrast medium were recorded. As part of the monthly monitoring and feedback program, the results were analyzed and reported at the monthly QI committee meeting.

Statistical analysis

We used an interrupted time-series approach to analyze the collected longitudinal data [14, 16, 17]. This strategy enables the evaluation of the effectiveness of population-level health interventions. Using this approach, we examined the changes in the prevalence of CIN following the implementation of the CIN-QI program compared with an outcome of a group not targeted by the CIN-QI program. We also performed an interrupted time-series analysis with a non-intervention control group with eGFR ≥45 mL/min/1.73 m^2 to evaluate the effect of educational intervention. Various models of the data were tested including the autoregressive, moving average and autoregressive moving average models [16]. We also used the Durbin–Watson test to assess for autocorrelation. We used different potential covariates in each of the models and adjusted for participant age, sex, comorbidities (hypertension and diabetes) and volume of contrast medium, as indicated in the model descriptions. To mitigate the effects of autocorrelation, which is often a challenge in an interrupted time-series analysis, we based our conclusions on the model with the lowest Akaike's information criteria for each condition. Sensitivity analyses were performed using the ratio of post- to pre-contrast serum creatinine level as a continuous variable and the diagnosis of CIN based on a 25% increase in serum creatinine level as a categorical variable. All analyses were performed using R version 4.0.2 (R Foundation, Vienna, Austria).

RESULTS

Annual patient characteristics before and after the implementation of the CIN-QI program

As patients were excluded if their baseline Cr levels were not measured, there was a missing rate of 10.2% among patients who underwent contrast CT, and the records of 95 594 patients who underwent contrast-enhanced CT between April 2006 and March 2018 were reviewed. A total of 2468 participants met the CKD inclusion criteria. Participants were divided into pre (2006–11) and post (2012–17) CIN-QI program implementation groups for analysis. Pre-implementation participants had a mean age of 72.7 ± 10.2 years, whereas post-implementation participants had a mean age of 73.4 ± 10.3 years. There was no statistical difference in the average age or sex breakdown between the groups; however, patients in the post-implementation group were more likely to have diabetes, hypertension and poor renal function than those in the pre-implementation group. The mean volumes of the contrast agents used in the pre- and post-implementation groups were 83.9 ± 15.4 and 76.8 ± 19.0 mL, respectively (Table 1). There was no difference between the time from physicians ordering and performing contrast-enhanced CT before CIN-QI {mean 39 [interquartile range (IQR) 15–84] days} and after CIN-QI [29 (IQR 12–72.5) days] ($P = .644$), suggesting no significant delay of performing contrast-enhanced CT due to nephrologist consultation.

Prophylactic saline hydration implementation rate and protocol adherence during the CIN-QI program

To evaluate the adherence to the CIN prevention protocol outlined in the QI program, we examined the rate of kidney function assessment after contrast-enhanced CT and the rate of prophylactic saline hydration administration. The results showed that the implementation rate of prophylactic saline hydration before and after the CIN-QI program differed significantly (P for level change <.001, P for trend change = .262). Before the CIN-QI program began (2006–11), the annual rate of intravenous saline hydration before contrast-enhanced CT ranged from 2.0% to 23.2%; after the CIN-QI program began in 2012, the annual rate immediately increased to approximately 59.2% and further to 75.2% by the end of the study period in 2018 (Fig. 2A). Next, a significant difference was also seen in the rate of kidney function evaluation after contrast-enhanced CT (P for level change <.001, P for trend change = .139); precisely, the annual rate of follow-up blood tests for kidney function assessment after contrast-enhanced CT improved from 18.6%–25.8% before implementing the CIN-QI program to 34.1%–42.5% after implementing the CIN-QI program (Fig. 2B). The rates before and after the implementation of the CIN-QI program were significantly different based on the interrupted time-series analysis.

The CIN-QI program was associated with a decreased rate of CIN

The median (IQR) time from contrast-enhanced CT to the episode of CIN was 2.9 (IQR 1.8–4.9) days. Our results showed that the CIN-QI program had a significant association with the decreased rate of CIN (P for level change = .002, P for trend change <.001). Time-series analysis revealed that the incidence of CIN decreased significantly after implementing the CIN-QI program in 2012 (Fig. 2C). Importantly, the rate of CIN significantly declined in level by 10.0% with the start of the CIN-QI program and subsequently in trend by 2.9% per year for the remainder of the study period. Our CIN-QI program contributed to the decreased incidence of CIN, even after accounting for confounding factors including age, sex, contrast use and history of comorbidities such as diabetes and hypertension (Table 2). In addition, sensitivity analysis showed that there was a significant level change in the proportion of patients with CIN after the implementation of the CIN-QI program when considering a pre- to post-contrast serum creatinine ratio as the definition of CIN (Supplementary data, Fig. S2A, Table S2). A similar level change was observed when a ≥25% increase in serum creatinine level from baseline was used as the definition of CIN (Supplementary data, Fig. S2B, Table S2). We also performed an interrupted time-series analysis on a control group with eGFR ≥45 mL/min/1.73 .m^2, without CIN-QI intervention. The difference in level and trend changes between before and after the CIN-QI pro-

Table 1: Annual characteristics of patients with CKD stage 3b or higher, before and after the initiation of the CIN-QI program.

	CIN-QI program		Year												
	Before	After	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	*P*-value
Total number of patients	1425	1043	242	264	252	226	243	198	218	204	192	174	129	126	
Age, mean (SD)	72.7	73.4	71.9	71.9	72.1	73.3	73.4	73.7	72.9	72.9	73.2	74.0	74.4	73.6	.070
	(10.2)	(10.3)	(10.9)	(10.4)	(10.2)	(8.7)	(9.9)	(10.8)	(10.2)	(10.2)	(10.6)	(10.4)	(10.6)	(9.4)	
Age <65 years, *n* (%)	1146	863	182	207	201	190	204	162	177	163	161	143	112	107	.158
	(80.4)	(82.7)	(75.2)	(78.4)	(79.8)	(84.1)	(84.0)	(81.8)	(81.2)	(79.9)	(83.9)	(82.2)	(86.8)	(84.9)	
Male, *n* (%)	848	637	141	158	142	135	147	125	142	120	113	106	75	81	.458
	(59.5)	(61.1)	(58.3)	(59.8)	(56.3)	(59.7)	(60.5)	(63.1)	(65.1)	(58.8)	(58.9)	(60.9)	(58.1)	(64.3)	
Hypertension, *n* (%)	885	786	143	151	150	138	162	141	160	161	149	122	104	90	<.001
	(62.1)	(75.4)	(59.1)	(57.2)	(59.5)	(61.1)	(66.7)	(71.2)	(73.4)	(78.9)	(77.6)	(70.1)	(80.6)	(71.4)	
Medicated, *n* (%)	619	613	101	105	88	101	115	109	125	122	122	97	80	67	<.001
	(43.4)	(58.8)	(41.7)	(39.8)	(34.9)	(44.7)	(47.3)	(55.1)	(57.3)	(59.8)	(63.5)	(55.7)	(62.0)	(53.2)	
Diabetes, *n* (%)	554	490	88	98	87	89	102	90	93	107	93	82	53	62	<.001
	(38.9)	(47.0)	(36.4)	(37.1)	(34.5)	(39.4)	(42.0)	(45.5)	(42.7)	(52.5)	(48.4)	(47.1)	(41.1)	(49.2)	
Medicated, *n* (%)	301	327	50	53	47	43	53	55	69	65	60	58	32	43	<.001
	(21.1)	(31.4)	(20.7)	(20.1)	(18.7)	(19.0)	(21.8)	(27.8)	(31.7)	(31.9)	(31.2)	(33.3)	(24.8)	(34.1)	
Volume of contrast agents used, mean (SD)	83.9	76.8	87.2	88.0	89.7	84.6	77.5	73.4	72.5	74.8	76.8	78.3	79.2	83.0	<.001
	(15.4)	(19.0)	(12.6)	(13.7)	(12.3)	(12.5)	(16.7)	(17.9)	(17.2)	(18.7)	(19.1)	(19.7)	(18.6)	(19.9)	
Patients treated with prophylactic hydration, *n* (%)	88	726	6	8	5	5	18	46	129	146	135	125	97	94	<.001
	(6.2)	(69.6)	(2.5)	(3.0)	(2.0)	(2.2)	(7.4)	(23.2)	(59.2)	(71.6)	(70.3)	(71.8)	(75.2)	(74.6)	
Cr, mean (SD)	1.52	1.75	1.43	1.60	1.42	1.51	1.44	1.80	1.90	1.90	1.73	1.71	1.57	1.55	<.001
	(1.37)	(1.82)	(1.03)	(1.81)	(1.19)	(1.21)	(0.69)	(1.91)	(2.15)	(2.08)	(1.61)	(1.76)	(1.59)	(1.30)	
eGFR, mean (SD)	37.6	36.0	38.0	38.1	38.7	37.4	37.5	35.7	35.6	34.3	35.8	36.5	37.7	37.4	<.001
	(7.8)	(9.6)	(6.9)	(7.8)	(6.7)	(7.8)	(7.7)	(9.6)	(10.2)	(10.2)	(9.8)	(9.6)	(8.1)	(8.2)	
Cr measurement after CT, *n* (%)	297	395	51	68	51	42	47	38	78	82	72	74	44	45	<.001
	(20.8)	(37.9)	(21.1)	(25.8)	(20.2)	(18.6)	(19.3)	(19.2)	(35.8)	(40.2)	(37.5)	(42.5)	(34.1)	(35.7)	
Post-CT Cr/pre-CT Cr, mean (SD)	1.01	1.01	0.99	0.97	0.99	1.01	1.11	1.04	1.03	0.99	1.00	1.01	0.99	1.01	.628
	(0.26)	(0.17)	(0.09)	(0.14)	(0.11)	(0.19)	(0.56)	(0.15)	(0.26)	(0.10)	(0.17)	(0.17)	(0.12)	(0.11)	
Number of patients with a 25% increase (%)[a]	10	13	0	2	1	1	3	3	4	1	2	3	1	2	1.000
	(3.4)	(3.3)	(0.0)	(2.9)	(2.0)	(2.4)	(6.4)	(7.9)	(5.1)	(1.2)	(2.8)	(4.1)	(2.3)	(4.4)	
CIN, *n* (%)[a]	14	15	0	2	1	1	6	4	6	1	2	3	1	2	.396
	(4.7)	(3.8)	(0.0)	(2.9)	(2.0)	(2.4)	(12.8)	(10.5)	(7.7)	(1.2)	(2.8)	(4.1)	(2.3)	(4.4)	

[a]Denominator is the number of patients whose Cr levels were measured after CT.
Cr, serum creatinine.

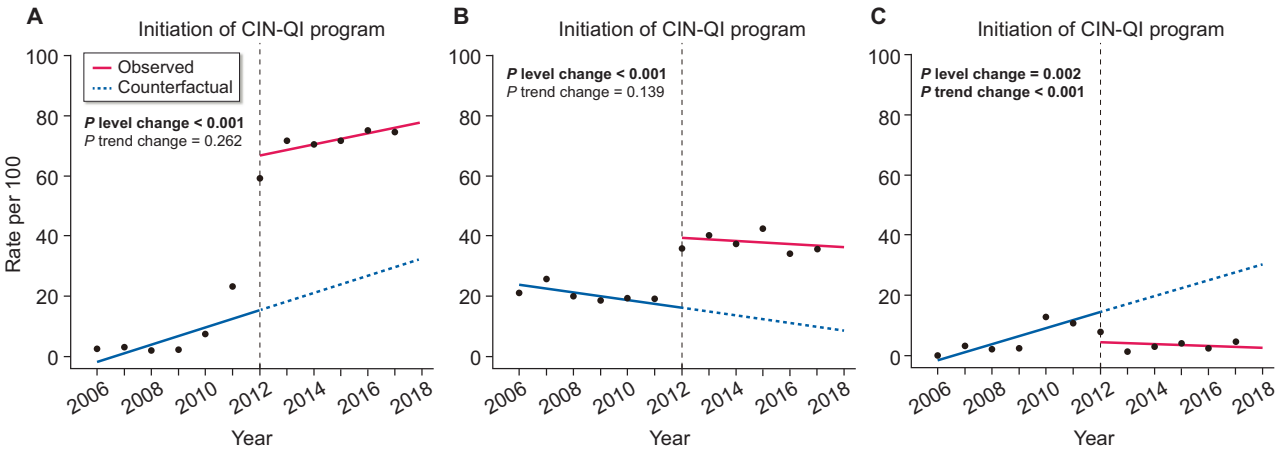


Figure 2: CIN-QI program improves quality indicators of CIN. (**A**) Implementation rate of prophylactic hydration. (**B**) Rate of kidney function evaluation after contrast-enhanced CT. (**C**) Incidence rate of CIN. Statistical analysis by interrupted time series analysis pre- and post-implementation of the CIN-QI program. *P* level change: *P*-value for the level change after initiation of the CIN-QI program. *P* trend change: *P*-value for the rates of level change of the slope of the trend line before and after the initiation of the CIN-QI program. The vertical dotted line indicates the initiation of CIN-QI program. Bold font indicates statistical significance ($P < .05$).

gram in the intervention group (−10.0%, −2.9%/year) was significantly greater than that in the non-intervention group (1.0%, −0.6%/year) (Supplementary data, Fig. S3A, Table S3, $P < .001$).

The CIN-QI program was associated with a decreased number of contrast-enhanced CT scans

As a secondary outcome, we evaluated the records of 95 594 patients who underwent contrast-enhanced CT between 2006 and 2018 (Supplementary data, Table S4). We also evaluated the number of contrast-enhanced CT scans stratified by anatomical regions. When we stratified patients by CKD stage, the number of contrast-enhanced CT orders showed a positive level change for patients with CKD stage 4 at the start of the implementation of the CIN-QI program (*P* for level change = .038, Fig. 3, Supplementary data, Table S5). After the implementation of the CIN-QI program, we found that the number of contrast-enhanced CT orders showed a negative trend change with the start of the CIN-QI program across patients with any CKD stage including in the CIN-QI program target group of patients with an eGFR <45 mL/min/1.73 m^2. As the patient's CKD stage progressed, the trend changes decreased from −1.4% to −10.0% per year. In addition, sub-analysis by imaging region showed a negative trend change in the use of contrast agents for several anatomical regions—including the heart, abdomen, kidney, ureter and bladder—and whole body (Supplementary data, Fig. S4, Table S6).

We also performed an interrupted time-series analysis with a non-intervention control group with eGFR ≥45 mL/min/1.73 m^2 (this group did not have any alert to recommend nephrologist consultation) to evaluate the effect of educational intervention. The difference in level change between before and after the CIN-QI program in the intervention group (0.7%) was significantly greater than that in the non-intervention group (−1.4%) (Supplementary data, Fig. S3B, Table S3, $P = .043$).

DISCUSSION

This is the first study to demonstrate the effectiveness of a QI program for CIN prevention in outpatients with CKD using an interrupted time-series analysis over an extended period. We examined the incidence of CIN in a large patient cohort over a 12-year period from 2006 to 2018. Following the development and implementation of the CIN-QI program in 2012, there was a significant increase in the rate of follow-up kidney function assessment after contrast-enhanced CT and in the rate of prophylactic saline hydration administration. Furthermore, the incidence of CIN and the rate of CT scans performed with contrast agents decreased across all patients with CKD, in addition to the target patient group. These results provide important information for physicians ordering and performing contrast-enhanced CT in outpatients with CKD.

Previous studies in outpatient settings have suggested that the incidence of CIN ranges from 5% to 14% [17, 18]. The incidence of CIN increases in patients with multiple comorbidities, such as diabetes and CKD [19]. According to previous reports, the use of contrast media is considered as a risk factor for AKI in patients with CKD stage 3b or higher [20, 21]. Given that our study included high-risk patients with CKD stage 3b or higher and the mean patient age and prevalence of diabetes were high, the incidence of CIN in the study population is lower than expected based on previous studies of this population. Our CIN prevention protocol included a 1-h infusion of isotonic saline before and after contrast-enhanced CT, which was designed to be feasible and practical to administer to outpatients undergoing CT. As there was a decrease in the incidence of CIN after the initiation of the CIN-QI program, this prophylactic hydration protocol may have been able to decrease the risk of CIN by increasing blood volume prior to CT.

Clinical guidelines state that the most important way of preventing CIN is to perform iodine-free procedures as much as possible [13]. According to our study, the number of contrast-enhanced CT studies decreased after implementing

Table 2: Interrupted time-series analysis for the model used in Fig. 2 (adjusted and unadjusted).

		Intercept		Pre-intervention trend		Level change		Trend change	
	Model[a]	β-coefficient 95% CI[a]	*P*-value	β-coefficient 95% CI	*P*-value	β-coefficient 95% CI	*P*-value	β-coefficient 95% CI	*P*-value
Figure 2A	Unadjusted[b]	−0.018 (−0.057 to 0.021)	.403	0.029 (0.014 to 0.043)	**.005**	0.515 (0.437 to 0.592)	**<.001**	−0.010 (−0.027 to 0.006)	.262
	Adjusted	13.304 (4.553 to 22.056)	.059	0.038 (−0.005 to 0.081)	.180	0.344 (0.231 to 0.457)	**.009**	0.064 (0.038 to 0.091)	**.017**
Figure 2B	Unadjusted	0.236 (0.216 to 0.257)	**<.001**[c]	−0.013 (−0.020 to −0.005)	**.013**	0.232 (0.191 to 0.274)	**<.001**	0.007 (−0.001 to 0.016)	.139
	Adjusted	9.055 (8.213 to 9.896)	**<.001**	0.011 (0.006 to 0.015)	**.016**	0.174 (0.163 to 0.185)	**<.001**	0.033 (0.030 to 0.035)	**<.001**
Figure 2C	Unadjusted	−0.016 (−0.037 to 0.006)	.190	0.026 (0.019 to 0.034)	**<.001**	−0.100 (−0.143 to −0.058)	**.002**	−0.029 (−0.038 to −0.020)	**<.001**
	Adjusted	1.302 (0.513 to 2.092)	**.048**	0.017 (−0.001 to 0.035)	.155	−0.166 (−0.213 to −0.119)	**.006**	−0.001 (−0.025 to 0.024)	.959

[a]Model was adjusted for age, sex, comorbidities (hypertension and diabetes) and volume of contrast agent used.
[b]Moving average (1) was selected for the unadjusted model and autoregressive moving average (1,1) was selected for the adjusted model.
[c]Bold font indicates statistical significance ($P < .05$).

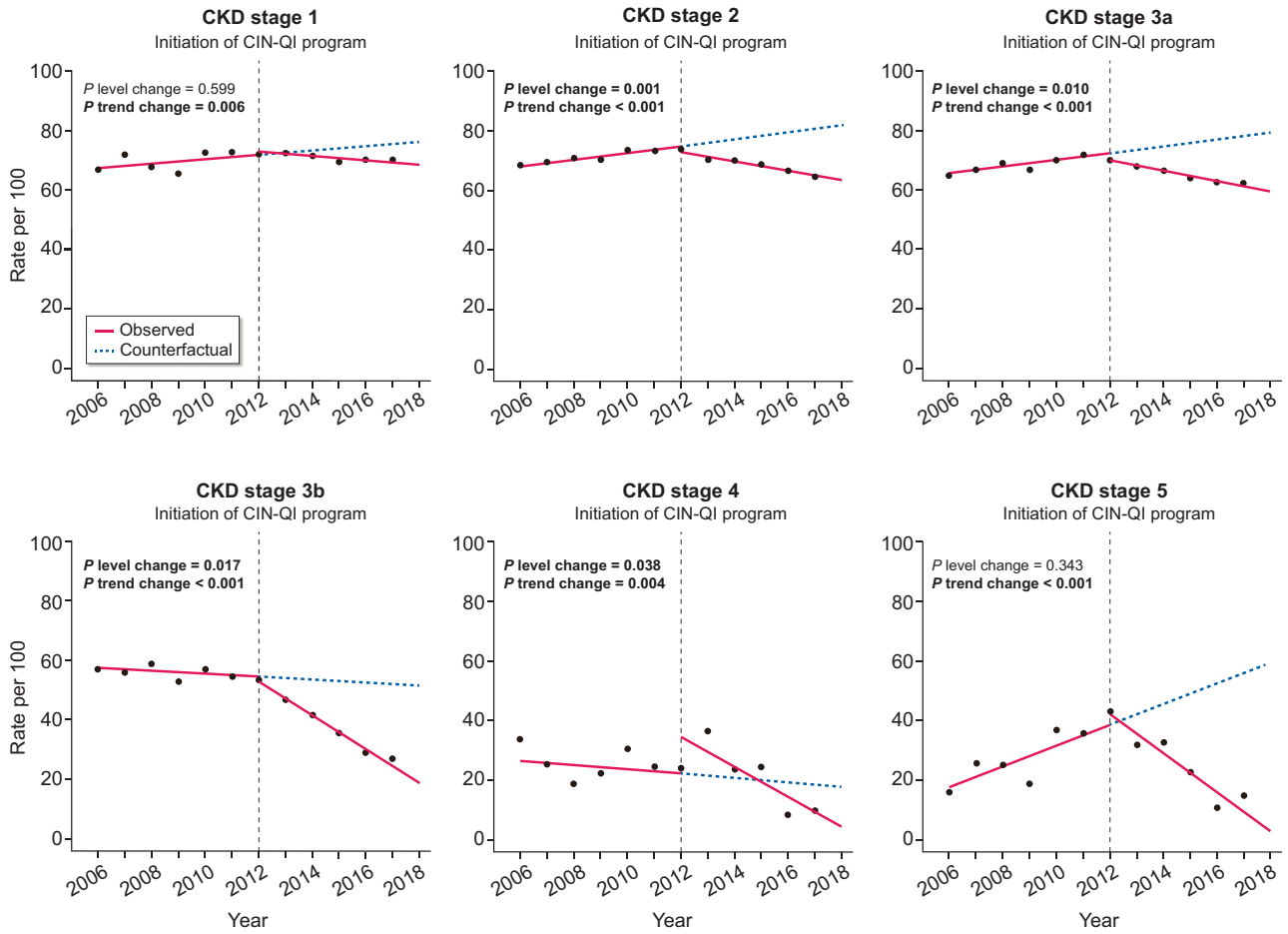


Figure 3: Change in the rate of contrast agent use of patients stratified by CKD stage. Statistical analysis by interrupted time-series analysis pre- and post-implementation of the CIN-QI program. *P* level change: *P*-value for the level change after initiation of CIN-QI program. *P* trend change: *P*-value for the rates of level change of the slope of the trend line before and after the initiation of the CIN-QI program. Solid trend lines indicate the observed trend line. Dashed trend lines indicate the counterfactual line. Vertical dotted lines indicate the initiation of the CIN-QI program. Bold font indicates statistical significance ($P < .05$).

the CIN-QI program. This was the case both in patients with CKD and in patients with normal kidney function. In the sub-analysis by imaging region, the rate of contrast media use was decreased for regions that typically have high contrast usage, including the heart, abdomen, kidney, ureter and bladder and whole body. Considering that the incidence rates of CIN decreased even after adjusting for the overall decrease in contrast agent use after implementing the CIN-QI program, we believe that the impact of the CIN-QI program has implications beyond simply decreasing the incidence rate of CIN. Specifically, we believe that the CIN-QI program led to a decrease in the number of tests performed with unnecessary contrast agents by reminding physicians of the potential adverse renal outcomes, outlining preventative measures to ensure that tests requiring contrast agent use could be performed safely and alerting physicians to high-risk patients when contrast-enhanced CT was ordered through the electronic medical record system so that indications could be strictly reviewed [22, 23]. Interestingly, in patients with CKD stage 4 who were eligible for the CIN-QI program, there was a positive level change in 2012 when the CIN-QI program started; this result was not seen in patients with lower CKD stages. In addition, our interrupted time-series analysis also revealed a positive level change compared with the group without educational intervention. We believe that a decrease in "renalism"—the behavior of avoiding the use of contrast media that may increase the risk of CIN or AKI in patients with poor renal function—may have temporarily increased the rate of contrast media use in these patients [24].

QI is a systematic approach to studying and improving the provision of healthcare services to meet the needs of patients and healthcare systems. It involves identifying a problem, examining and applying solutions, and monitoring outcomes for improvement [25–30]. QI seeks to ensure that medical treatment is performed according to the highest level of evidence, such as adherence with clinical practice guidelines, and to identify and close the evidence–practice gap in clinical medicine [31, 32]. Previous studies have shown that sustained QI programs can reduce mortality after cardiac surgery and nephrotoxic medication–associated AKI [33–35]. However, the positive results associated with QI initiatives are often due to the intense resources devoted to the project, which

may have been achieved without a clear plan to maintain the initiative after completing the project. The sustainability of a QI program can only be achieved through the trusted procedures that become part of the organizational culture [33, 36–38]. As a result of constructing a simple but robust and effective CIN-QI program, we were able to maintain a high program implementation rate for six years. Importantly, the implementation rate of the CIN prevention protocol was evaluated monthly as a quality indicator. Within 1 year of initiating the CIN-QI program, the implementation rate reached the target of approximately 80%, which was maintained for the remainder of the study period. Thus, a simple but multifaceted approach to CIN prevention implemented by a trusted team may contribute to a sustainable decrease in the incidence of CIN.

This study has some limitations. First, a key assumption of interrupted time-series analysis is that the intervention occurred independently of other changes over time and that other interventions, therefore, did not affect the outcome. Given that we also showed the effects on contrast agent use in patients with lower CKD stages, who were not targeted by the electronic medical record alert of the CIN prevention program, this suggests that other interventions likely affected the outcome. In parallel with the main CIN prevention program, we conducted educational activities and lectures to decrease the unnecessary use of contrast media for all patients at the hospital, including those with less severe CKD. We believe that these activities had an effective and positive impact on decreasing the incidence rate of CIN. Second, although serum creatinine measurement is necessary to estimate the incidence of CIN, several patients did not have their creatinine levels measured after the CT despite being administered with prophylactic saline hydration. If the increased number of kidney function follow-ups after the CIN-QI program were from lower risk groups, this would result in a lower incidence of CIN. However, we found that the baseline serum creatine level was higher in patients who were assessed after implementation than those who were assessed before the implementation of the CIN-QI program. Furthermore, the sources and methods of data collection were the same before and after our intervention, the intervention itself did not affect the data collection, and the primary endpoints were reliable and objectively measured. As a sensitivity analysis was performed, we believe that this selection bias will not significantly affect the results. Third, the incidence of CIN was low. We suspect that there are several reasons for this, including the development of low-damage contrast media and appropriate prophylactic administration, in addition to the fact that the incidence of CIN was generally low in the first place. However, we believe that our findings are clinically significant as there are reports that CIN leads to irreversible AKI, which may require dialysis and significantly impact healthcare economics [2, 39]. Fourth, this QI program is resource-intensive owing to the need for nephrologists to examine all patients and may not be generalizable to all healthcare systems. However, we plan to reduce the need for these resources by developing an algorithm to recommend prevention orders according to patient risk, except in complicated cases. Finally, we could not gather sufficient data on the appropriateness of the contrast-enhanced CT ordered to evaluate the effect of educational intervention on renalism. However, we believe that an additional interrupted time-series analysis on a non-intervention control group with eGFR $\geq$45 mL/min/1.73 m^2 can enable us to evaluate the effect of educational intervention. In addition, we believe that this study offers important insights that may guide the development and implementation of appropriate CIN prevention protocols for patients at risk of CIN who are undergoing contrast-enhanced procedures.

In conclusion, the incidence of CIN decreased in patients who underwent contrast-enhanced CT after the implementation of a multifaceted approach in the CIN-QI program, which included a CIN risk assessment tool as an automated electronic medical record alert system for patients with eGFR <45 mL/min/1.73 m^2 and monthly QI monitoring and feedback to physicians. These findings may help physicians determine the safety of CT contrast media in high-risk patients with CKD and ensure contrast-enhanced CT is performed safely in this patient population.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

ACKNOWLEDGEMENTS

We would like to thank Hideki Nakashima, Data Center at St Luke's International Hospital, Masahiko Nagahama, and Masaaki Nakayama for their work on the development and implementation of the CIN-QI protocol. We would also like to thank the Department of Nephrology and the Data Center at St Luke's International Hospital for supporting the recruitment of participants.

FUNDING

This research received no specific grant from any funding agency in the public, commercial or non-profit sectors.

AUTHORS' CONTRIBUTIONS

K.H. was involved in the conception, design and execution of the study. K.H. analyzed the data, performed the statistical analysis and wrote the paper. D.K., T.S. and Y.K. participated in the study design and coordination. All authors discussed the results and implications, commented on the manuscript at all stages and approved the final manuscript.

DATA AVAILABILITY STATEMENT

Due to the nature of this research, patients' data were not shared publicly due to participants' privacy, so supporting data are not available.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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Received: 16.5.2022; Editorial decision: 6.9.2022