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# Economic burden of contrast-induced nephropathy: implications for prevention strategies

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## Summary

Contrast-induced nephropathy (CIN) is the third most common cause of hospital-acquired acute renal failure. There is increasing evidence that CIN has a significant adverse impact on patient morbidity and mortality. The objective of this study was to estimate the in-hospital and 1-year direct healthcare costs related to CIN. Using the values obtained from the literature review, a decision analytic model was developed to estimate the in-hospital and 1-year costs of CIN. Patients who develop CIN are more likely to experience adverse events, to undergo prolonged dialysis, to have longer hospital and intensive care unit stays and to have higher mortality rates. The average in-hospital cost of CIN is $10,345. The 1-year cost of treating a patient with CIN is $11,812. Overall, the economic burden associated with CIN is high. Adopting targeted interventions will reduce the incidence of CIN and its overall economic burden.

*Key words: contrast-induced nephropathy, economic burden, outcomes*

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# Background

Contrast-induced nephropathy (CIN) is the third most common cause of hospital-acquired acute renal failure after hypotension and surgery[1]. CIN is defined as acute renal failure occurring after the administration of iodinated contrast media and involves the interplay of multiple factors[2]. CIN was first recognised over 50 years ago but the long-term clinical and economic consequences are not yet fully understood. Over the past few decades, the number of procedures that use contrast media has vastly expanded and, simultaneously, the volume of patients with risk factors for CIN, including diabetes and renal insufficiency, has also increased. Given this trend, there is an urgent need to better understand the clinical and economic burden of CIN.

There is increasing evidence that CIN has a significant adverse impact on patient morbidity and mortality. A few studies have documented the adverse effects of CIN both on short- and long-term outcomes[3,4], but very limited information is available on the cost and economic burden of CIN. A cost study published in the early 1990s estimated that the average cost to the hospital for treating adverse events related to CIN was $459. This cost estimate was based on clinical trial data and limited to the index hospitalisation[5]. Other studies have compared the cost effectiveness of using low versus high osmolality contrast agents[6–9] as well as iso-osmolar versus low osmolar radiocontrast media[10].

Currently, there has been no systematic assessment of the economic burden of CIN. The objective of this study was to estimate the in-hospital and 1-year direct healthcare costs related to the disease. A thorough literature review was performed to identify the short- and long-term clinical consequences of CIN and a decision analytic model was used to estimate the economic burden.

# Methods

A thorough literature search was performed using several databases including Medline® and the Cochrane Library to estimate the incidence and understand the short- and long-term sequelae of CIN. The key words used were 'contrast induced nephropathy (CIN)', 'renal failure & percutaneous coronary intervention (PCI)', 'renal failure & contrast material', 'renal insufficiency', 'cost of CIN', 'outcomes of CIN' and 'impact of CIN'. Only studies that met the inclusion criteria were retained, which included studies published after 1990 with a sample size of at least 100 patients. In addition, studies were only retained if they reported on the incidence of CIN, or compared outcomes or resource use of patients with and without CIN. Studies not published in English, review articles and studies specifically related to the prevention of CIN were excluded. In addition, articles whose specific stated goal was to assess prevention strategies for CIN, even when these studies compared patients with and without CIN, were also excluded as the objective was to assess the economic burden associated with the baseline cohort of CIN patients without the use of any specific interventions.

However, some of the studies included in the analysis did use hydration and others did not specifically state whether specific prevention strategies were employed. Abstracts of all articles identified in the search were reviewed and the relevant articles were obtained. References for all articles retrieved were reviewed to identify additional studies. Experts were also consulted to ensure that all relevant studies were included.

Data abstraction was performed using standardised forms. Two independent researchers abstracted the necessary information from the selected studies and these results were summarised in Microsoft Excel spreadsheet format. When discrepancies were identified, the data elements were re-abstracted and reviewed for accuracy. The information abstracted included overall incidence rates for CIN (whenever available stratified by patient risk factors), details on the characteristics of the study patients and the definitions of CIN used. In addition, index hospitalisation-related outcomes (those pertaining to the first admission for the initial PCI procedure), including dialysis rate and length of stay, were abstracted. Whenever available, in-hospital and 1-year mortality and major adverse cardiac events (MACEs) were also identified. In studies where the incidence and outcome rates were provided separately for males and females, or stratified by risk factors, weighted rates were calculated. Pooled unweighted means, 95% confidence intervals (CIs) and ranges for all incidence and outcome measures were generated.

The objective of this review was to attempt to understand the real-world incidence of CIN, to quantify the clinical consequences of CIN and to estimate the economic burden associated with these sequelae. No systematic scoring system was developed to rate the quality of articles reviewed, given the nature of the topic studied. It is not clear, for instance, what type of study will produce superior results compared with others. Randomised controlled trials are not appropriate, as no specific intervention is being studied. Most studies reporting the incidence and sequelae of CIN are retrospective analysis of cardiac registry databases or prospective cohort studies. Therefore, instead of developing a scoring system, details on factors that can impact the incidence and outcomes of CIN have been provided, including the type of procedure performed, sample size, definition of CIN and patient characteristics.

To estimate the in-hospital and 1-year cost of CIN, a decision analytic model was developed in Microsoft Excel using the model parameters obtained through literature review. For example, the cost of an additional day of hospitalisation was used to estimate the incremental cost for CIN patients who stay in hospital longer than patients without CIN. The costs presented were not derived through microcosting (i.e. estimating cost based on detailed resources used by CIN versus non-CIN patients during the initial hospital admission). We assumed that the additional cost potentially borne by CIN patients is reflected in the overall average cost per hospital day. The cost analysis is presented from the perspective of the Medicare

programme in the US, and Medicare expenditures primarily from the years 2002 and 2004 were used as a proxy for cost.

As only 1-year costs are reported, no discounting was performed. One- and two-way sensitivity analyses were performed using low- and high-cost values and by varying the rate of CIN. In addition, extrapolations were performed to assess the future costs of CIN using various population risk profiles. The risk profiles developed by Mehran *et al*[11], which were based on total number of co-morbid conditions, were used to estimate the per procedure cost for patients at low, medium, high and very high risk for CIN. In addition, using these risk profiles the cost associated with an increase in the overall incidence of CIN (due to an increase in patient risk factors for CIN) and the impact of different risk reduction scenarios were estimated.

# Results

The initial literature search yielded more than 60 journal articles, 10 of which met the inclusion criteria and were retained. The majority of the studies identified reported the incidence and consequence of CIN for patients undergoing PCIs or coronary angiography. Only two studies were identified that reported on other interventions: one on computed tomography angiography and perfusion imaging[12], and another on general radiocontrast imaging procedures[3]. Given the limited number of studies on non-coronary interventions, only coronary diagnostic and intervention procedures were included in the review.

## Overall incidence of CIN and by risk factors

Table 1 presents information abstracted from studies that report on the overall incidence of CIN. Studies that focused on specific population subgroups, such as those with diabetes, were excluded to provide an estimate of the average rate of CIN for patient cohorts undergoing coronary procedures. Almost all of the selected studies reported rates based on analysis of hospital-based prospective registries[4,11,13–18]. Information on the year the study was published, the specific procedure performed, the sample size, the definition of CIN used, the proportion of patients with diabetes, a description of specified exclusions, the proportion of elderly patients and the rate of CIN was provided. The definition of CIN varied across papers and was defined as a 25%, 50%, 0.5 mg/dl, 1 mg/dl or 44 mmol/l increase in serum creatinine level from baseline. The proportion of patients with diabetes ranged from 15.7 to 30.7% and the overall rate of CIN was 9.8% (95% CI 8.6–11.1%) for all studies reviewed, with a range of 2.0–16.5%. The incidence rate was 12.0% (95% CI 8.2–15.9%) for studies that used the definition of 25% increase in serum creatinine level.

In addition to the results presented in Table 1, the incidences of CIN in patients with pre-existing renal conditions and with diabetes mellitus were also identified. One recent study found that patients with pre-existing renal insufficiency were more than six times as likely to acquire CIN following contrast medium administration compared with patients without any pre-existing co-

**Table 1. Incidence of CIN among patients undergoing cardiac procedures.**

| *Reference* | *Year* | *Procedure studied* | *Sample size* | *Definition of CIN* | *Patient risk factors and sample exclusions* | | | Overall incidence of CIN (%) |
|---|---|---|---|---|---|---|---|---|
| | | | | | *Diabetics (%)* | *Exclusions from sample* | *Age (years)* | |
| 16 | 2005 | PCI | 7,230 | >0.5 mg/dl or 25% increase in SCr level | 30.4 | Patients with acute ST-elevation MI within 48 h, cardiogenic shock and baseline ESRD requiring dialysis | | 14.8 |
| 14 | 2004 | PCI | 1,383 | 25% increase in SCr level | 15.7 | Patients with cardiogenic shock, mechanical ventilation and ESRD requiring dialysis | Average age: males 63 ± 0, females 68 ± 10 | 10.1 |
| 11* | 2004 | PCI | 5,571 | >0.5 mg/dl or 25% increase in SCr level | 30.7 | Patients with pre-existing ESRD requiring dialysis and other contrast exposure within ≤ 1 week from the index procedure, patients treated with PCI for AMI and patients in shock | Average age 63.8 ± 11.2 (derivation set), 17.1% >75 years | 13.1 |
| 13 | 2004 | PCI | 20,479 | 1 mg/dl increase in SCr level | 26.5 | Patients with any form of prior dialysis ($n$=356) and those having in-hospital coronary artery bypass grafting surgery ($n$=334) | 36.95% >70 years | 2.0 |
| 17 | 2003 | PCI | 5,967 | 50% increase in SCr level | 24.1 | No history of renal insufficiency and baseline SCr >1.2 mg/dl, non-successful opening of all targeted stenoses, major in-hospital complication (Q wave, MI, CAB surgery), patients with AMI <48 h prior to PCI | | 3.5 |

CIN, contrast-induced nephropahty; PCI, percutaneous coronary intervention; SCr, serum creatinine; MI, myocardial infarction; CAB, coronary artery bypass; ESRD, end-stage renal disease; AMI, acute myocardial infarction; CI, confidence interval.

*Used only the derivation set statistics.

**Table 1. Incidence of CIN among patients undergoing cardiac procedures (continued).**

| *Reference* | *Year* | *Procedure studied* | *Sample size* | *Definition of CIN* | *Patient risk factors and sample exclusions* | | | Overall incidence of CIN (%) |
|---|---|---|---|---|---|---|---|---|
| | | | | | *Diabetics (%)* | *Exclusions from sample* | *Age (years)* | |
| 18 | 2003 | PCI | 8,628 | 25% increase in SCr level | | | | 16.5 |
| 15 | 2002 | PCI | 7,586 | 0.5 mg/dl increase in serum creatinine level | 21.7 | Patients who denied research access to their medical records | | 3.3 |
| 4* | 1997 | PCI | 1,826 | 25% increase in SCr level | 24.8 | Patients previously on dialysis and those with repeated procedures within study period | | 14.5 |
| 1 | 1990 | Cardiac catheteri-sations | 199 | ≥ 44 mmol/l increase in SCr level | 16.4 | Patients with insufficient data on renal function or cardiogenic shock. | All >70 years | 10.5 |
| Mean (95% CI) (all procedures) | | | 23.8 (22.5–25.2) | | | | 9.8 (8.6–11.1) | |
| Range | | | 15.7–30.7 | | | | 2.0–16.5 | |
| Mean (95% CI) (only studies with 25% increase definition) | | | | | | | 12.0 (8.2–15.9) | |

CIN, contrast-induced nephropahty; PCI, percutaneous coronary intervention; SCr, serum creatinine; MI, myocardial infarction; CAB, coronary artery bypass; ESRD, end-stage renal disease; AMI, acute myocardial infarction; CI, confidence interval.

*Used only the derivation set statistics.

morbidities (0.6 vs. 6.4%)[13]. Among individuals with diabetes undergoing coronary procedures, the rate of CIN ranges from 19.2 to 26%[11,19]. Overall, patients both with pre-existing renal insufficiency and diabetes mellitus are at a very high risk of developing CIN[20, 21].

## Clinical consequences of CIN

Table 2 reports the rate of dialysis and the in-hospital and 1-year mortality rates for patients with and without CIN. The average rate of dialysis was 3.3% (95% CI 2.5–4.1%). The in-hospital and long-term survival rates of patients requiring dialysis were poorer than patients who do not require dialysis (data not shown). McCullough *et al*[4] found that 81.2% of the patients with CIN who underwent dialysis died within 2 years. Gruberg *et al*[22,23] also found in two separate studies that the 1-year mortality among patients undergoing dialysis was extremely high (45.2 and 54.5%, respectively).

All seven studies comparing mortality rates between those with and without CIN consistently reported that patients with CIN had much higher short- and long-term mortality than patients who underwent the same procedure but who did not have CIN. The average in-hospital mortality rate pooled across studies was 12.9% (95% CI 7.5–18.4%) for patients with CIN and 2.3% (95% CI 0.5–4.1%) for patients without CIN, a difference of 10.6% (95% CI 5.4–15.9%). The difference in mortality rates at 1 year was even greater, estimated to be 13.4% (95% CI 11.3–15.5%) based on four studies that reported this information.

Two studies[16,18] were found that reported the actual length of in-hospital stay for patients with and without CIN ( Table 3). Patients with CIN stayed an additional 3.75 days (95% CI 1.9–5.6 days) on average in hospital compared with patients without CIN. Iakovou *et al*[18] found that patients with CIN also stayed 1.7 days longer in ICUs compared with patients without CIN. In addition, a recent study by Bartholomew *et al*[13] found that patients with CIN were 15 times more likely to have an extended hospitalisation of more than 4 days (90 vs. 20%).

A few studies were also identified that reported on the incidence of MACEs among patients with CIN either during hospitalisation or during 1 year of follow-up. The two studies that reported in-hospital incidence of MACEs indicated that patients with CIN are more likely to experience these events than patients without CIN. Dangas *et al*[16] reported a difference of 6.7% (7.7% among CIN patients vs. 1.0% among non-CIN patients), whilst Bartholomew *et al*[13] showed an even greater difference of 24% (26 vs. 2%). In addition, there is evidence that patients with CIN are more likely to have non-Q-wave myocardial infarction than non-CIN patients (28.7 vs. 15.9%)[22]. The higher incidence of MACEs is reported even during 1 year of follow-up: 8.8% differential (31.4 vs. 22.6 %)[16]. In another study[17] that also reported 1-year outcomes, the rates of acute myocardial infarction (24.0 vs. 11.6%) and target vessel revascularisation (28.8 vs. 20.3%) were both higher for patients with CIN.

**Table 2. Consequences of CIN: rate of dialysis and mortality.**

| *Reference* | *Year* | *Procedure studied* | *Sample size* | *Definition of CIN* | *Dialysis rate (patients with CIN)* | *In-hospital mortality* | | | *1-year mortality* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *Patients without CIN* | *Patients with CIN* | *Difference* | *Patients without CIN* | *Patients with CIN* | *Difference* |
| 16 | 2005 | PCI | 7,230 | 25% or 0.5 mg/dl increase in SCr level | | 0.3 | 3.9 | 3.6 | 3.8 | 13.2 | 9.4 |
| 14 | 2004 | PCI | 1,383 | 25% increase in SCr level | 1.4 | | | | | | |
| 13 | 2004 | PCI | 20,479 | 1 mg/dl increase in SCr level | | 1 | 21 | 20 | | | |
| 17 | 2003 | PCI | 5,967 | 50% increase in SCr level | 1.4 | | | | 2.7 | 9.5 | 6.8 |
| 18* | 2003 | PCI | 8,628 | 25% increase in SCr level | 3.9 | 0.9 | 4.7 | 3.8 | 13.9 | 32.3 | 18.4 |
| 15 | 2002 | PCI | 7,586 | 0.5 mg/dl increase in SCr level | 7.9 | 1.4 | 22 | 20.6 | | | |
| 23 | 2000 | Cardiac catheterisations | 439 | 25% increase in SCr level within 48 h or required dialysis | | 5.4 | 16.1 | 10.8 | 19.4 | 38.5 | 19.1 |
| 4† | 1997 | PCI | 1,826 | 25% increase in SCr level | 5.0 | 1.1 | 8.6 | 7.5 | | | |
| 1 | 1990 | Cardiac catheterisations | 199 | ≥ 44 mmol/l increase in SCr level | 0.0 | 6.2 | 14.3 | 8.1 | | | |
| | | | | **Mean (95% CI)** | 3.3 (2.5–4.1) | 2.3 (0.5–4.1) | 12.9 (7.5–18.4) | 10.6 (5.4–15.9) | 10.0 (7.2–12.7) | 23.4 (18.6–28.2) | 13.4 (11.3–15.5) |

CIN, contrast-induced neptopathy; PCI, percutaneous coronary intervention; SCr, serum creatinine; CI, confidence interval.

* Aggregated results from Nikolsky *et al* (2003)[24]. Rates for mortality based on 743 patients.

† Results are based on the derivation set of 1,826 observations.

Source: RTI International.

**Table 3. Length of in-hospital stay related to CIN.**

| *Ref.* | *Year* | *Procedure studied* | *Sample size* | *Definition of CIN* | *In-hospital stay (non-ICU)* | | | *ICU stay* | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | *Patients without CIN* | *Patients with CIN* | *Difference* | *Patients without CIN* | *Patients with CIN* | *Difference* |
| 16 | 2005 | PCI | 7,230 | 25% or 0.5 mg/dl increase in SCr level | 4.7 | 1.9 | 2.8 | 2.3 | | |
| 25 | 2003 | PCI | 743 | 25% increase in SCr level | 9.6 | 4.9 | 4.7 | | 0.6 | 1.7 |
| | | | | **Mean (95% CI)** | 7.15 (2.3–12.0) | 3.4 (0.5–6.3) | 3.75 (1.9–5.6) | | | |

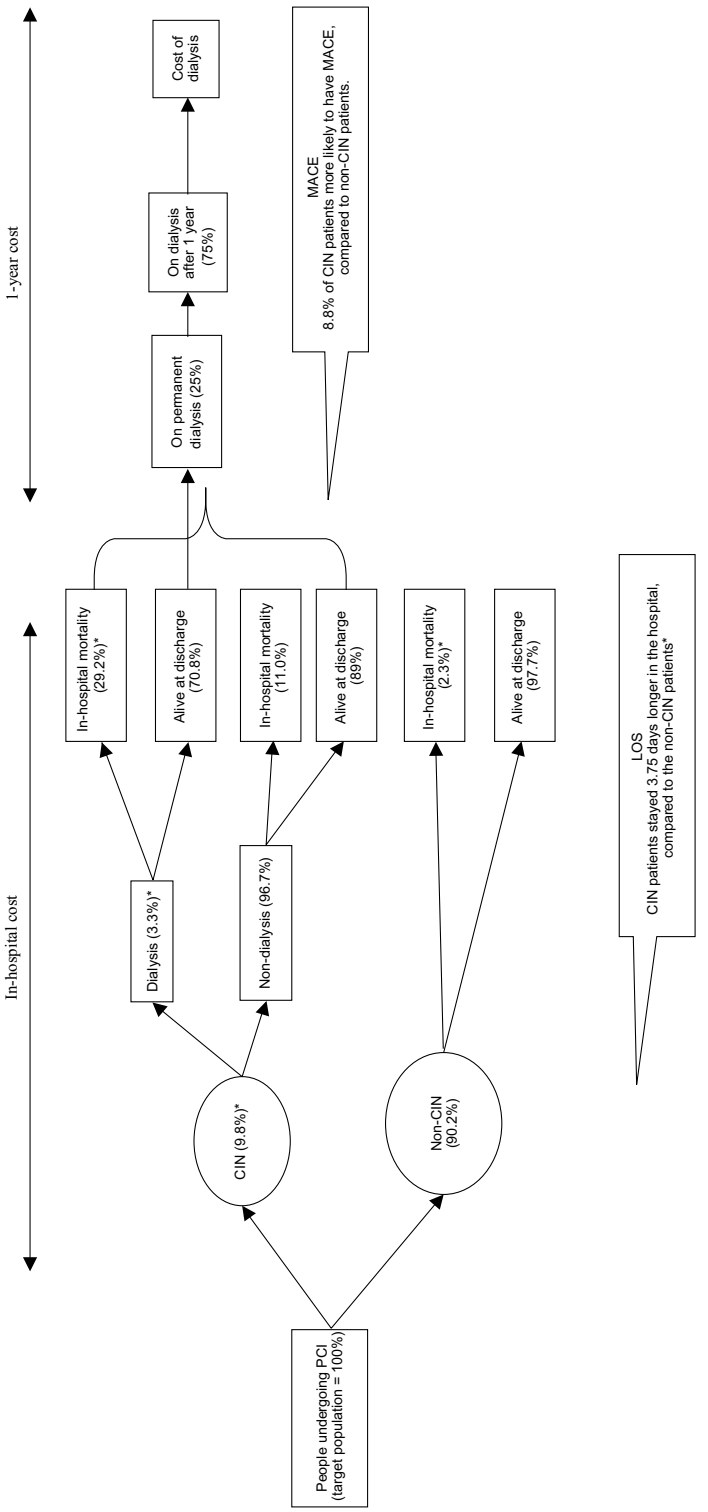
CIN, contrast-induced nephropathy; SCr, serum creatinine; ICU, intensive care unit.
A recent study by Bartholomew *et al*[12] found that patients with CIN were 15 times more likely to have an extended hospitalisation of more than 4 days (90 vs. 20%).
Source: RTI International.

## Economic burden of CIN

Based on the review of the short- and long-term sequelae of CIN, key healthcare resource impacts of CIN during hospitalisation and during 1-year follow-up were identified. Figure 1 provides a diagrammatic representation of the pathways and the incremental resource use related to CIN. The incremental in-hospital cost related to CIN was based on the length of stay differential (3.75 days) identified in the systematic review. Separate costs related to dialysis or other adverse events were not computed as it was assumed that the increase in length of stay was related to all adverse events experienced by patients with CIN. During the 1-year follow-up a small proportion of CIN patients will remain on permanent dialysis and, in addition, these patients will experience a higher incidence of MACEs (8.8% higher)[16] than patients without CIN. Using the incremental MACE and dialysis rate for CIN patients, the 1-year costs for dialysis and MACEs were computed. The total 1-year cost of CIN comprised of three costs: incremental in-hospital cost of CIN based on length of stay, 1-year cost of dialysis and 1-year incremental cost of MACEs.

Table 4 presents the unit cost parameters derived from the literature used to compute the cost estimates, and Table 5 provides the cost per patient with CIN and the cost per procedure. The average unit cost estimates were derived for 1 day of hospital and physician services from studies that estimated the cost related to PCI procedures[26,27]. The average or base hospital cost was derived from a recent study that specifically addressed cost related to treating complications of PCIs[26]. The cost of providing renal dialysis was derived from another recent study[28]. In addition to the base cost, higher and lower values were also identified from the literature to assess potential variation in the cost estimation[29]. The average in-hospital cost of CIN was $10,345 (range $5,032– 12,959) and the 1-year follow-up cost was $1,467 ($422 due to dialysis and $1,045 related to interventions for

**Figure 1. Decision analytic model to compute the economic burden of CIN.**




CIN, contrast-induced nephropathy; PCI, percutaneous coronary intervention; LOS, length of stay; MACE, major adverse cardiac event.

* These rates are based on RTI's systematic review of literature.

† These rates are based on information derived from Gruberg *et al* (2001)[23] and McCullough *et al* (1997)[4].

‡ These rates are based on information derived from Gruberg *et al* (2001)[23].

**Table 4. Cost data parameters to assess the economic burden of contrast-induced nephropathy.**

| *Measure* | *Estimate* | *Source* |
|---|---|---|
| Cost of 1 hospital day | | |
| Average | $2,654 | Kugelmass *et al* (2006)[26] |
| Low | $1,237 | Candrilli *et al* (2006)[29] |
| High | $3,351 | Kugelmass *et al* (2006)[26] |
| Physician cost for 1 day | $105 | Subramanian *et al* (2003)[27] |
| 1-year follow-up cost after PCI | $11,870 | Subramanian *et al* (2003)[27] |
| 1-year cost of haemodialysis | $72,189 | Shih *et al* (2005)[28] |

PCI, percutaneous coronary intervention.

MACEs). The average per patient 1-year cost due to CIN was $11,812 (range $6,499–14,426).

The cost per procedure based on different rates of CIN for the patient pool undergoing interventions that use contrast media is also presented. As shown in Table 5, the cost per procedure ranges from $1,158 to $1,417 (range $637–1,731 in the sensitivity analysis) based on the rate of CIN. Using the risk profile developed by Mehran *et al*[11], the cost per procedure for different levels of risk of developing CIN was estimated. The author's estimates are $886, $1,654, $3,083 and $6,768 for the low, moderate, high and very high risk groups, respectively. Using these risk profiles and cost estimates, they show the results from a simulation on potential future cost per procedure if there is a shift in the risk profile. In Figure 2, the costs per procedure for the baseline risk profile (based on the rate reported in Mehran *et al*[11]) and for a shift in the risk profiles by 1 (that is, an additional 1% of the patient pool moves into a higher risk category), 2, 3, 4, 5 and 10% are presented. The bolded top line represents the cost associated with the baseline rate of CIN and, as anticipated, this increases with the shift in the risk profiles. In addition to the baseline rate of CIN, the changes in the cost per procedure were also shown if interventions are implemented to reduce the risk of developing CIN. Interventions targeted at the very high or high-risk groups, even when there is a large proportion of high-risk patients (10% shift in risk profile), will only yield cost savings that are lower than the cost savings achieved when individuals at all risk levels are targeted.

# Discussion

In this study, a thorough review of the literature was performed to assess the clinical and economic consequences of CIN and to estimate the in-hospital and 1-year costs associated with CIN. Patients who develop the disease are more likely to experience adverse events, undergo prolonged dialysis, have longer hospital and ICU stays and have higher mortality rates. Patients with CIN have a 13% higher mortality rate at 1 year than those without CIN. In addition, approximately one-third of CIN patients requiring dialysis die during the initial hospitalisation.

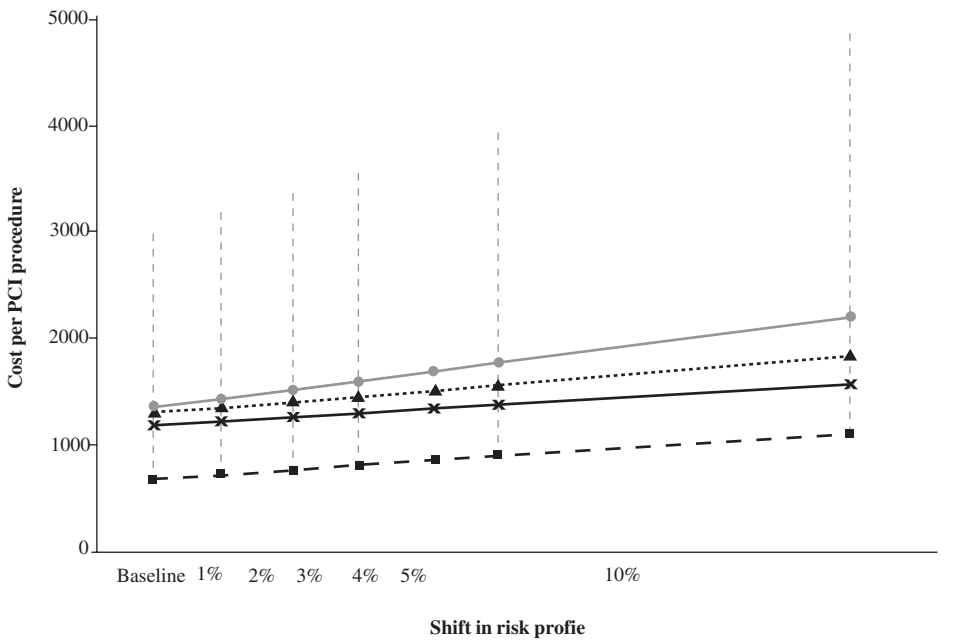
**Table 5. Economic burden of CIN.**

| | *Rate of CIN* | *Cost estimate ($)* | | |
|---|---|---|---|---|
| | | *Average* | *Sensitivity analysis* | |
| | | | *Low* | *High* |
| **Cost per patient with CIN** | | | | |
| In-hospital cost | – | 10,345 | 5,032 | 12,959 |
| Follow-up cost | – | 1,467 | – | – |
| Dialysis | – | 422 | – | – |
| MACE | – | 1,045 | – | – |
| In-hospital and 1-year cost | – | 11,812 | 6,499 | 14,426 |
| **Cost per procedure** | | | | |
| CIN rate for all cardiac procedures | 9.8 | 1,158 | 637 | 1,414 |
| CIN rate from risk score study* | 11.6 | 1,370 | 754 | 1,673 |
| CIN rate based on 25% increase in serum creatinine level | 12.0 | 1,417 | 780 | 1,731 |
| **Cost by risk of CIN*** | | | | |
| Low | 7.5 | 886 | 487 | 1,082 |
| Moderate | 14.0 | 1,654 | 910 | 2,020 |
| High | 26.1 | 3,083 | 1,696 | 3,765 |
| Very high | 57.3 | 6,768 | 3,724 | 8,266 |

CIN, contrast-induced nephropathy; MACE, major adverse cardiac event; PCI, percutaneous coronary intervention.

* Rate and classification based on information derived from Mehran *et al*[11].

**Figure 2. Cost of CIN stratified by risk profile and rate of CIN.**




CIN, contrast-induced nephropathy; PCI, percutaneous coronary intervention.

Overall, the economic burden associated with CIN is high. Based on the information currently available in the literature, it was estimated that the incremental cost of CIN per PCI procedure is approximately $1,000, and even our lowest possible estimate is over $500.

The largest cost driver is the increased length of stay associated with the initial hospitalisation. Approximately 4 million cardiac catheterisations are performed in the US and Europe and, therefore, billions of dollars are spent treating the sequelae of CIN. In addition, many cardiac catheterisation procedures are performed in the outpatient setting and for these patients no follow-up serum creatinine level is obtained and, therefore, the rate of CIN could be underestimated. As mentioned earlier, with the general aging of the population and growth in chronic conditions such as diabetes, an increase in the number of patients with risk factors for CIN is anticipated. Therefore, without targeted interventions to reduce the incidence of CIN, it's economic burden will continue to increase. Pre-hydration, prophylactic *N*-acetylcysteine administration and the use of an iso-osmolar, dimeric, non-ionic contrast medium are among the promising approaches to prevent CIN[28]. Interventions targeted at all patients, as well as those at high and low risk, will achieve the largest reduction in the economic burden associated with CIN.

There are several potential limitations to this study, including those resulting from attempts to develop estimates by pooling results across studies. The definition of CIN varies across studies and this can impact the incidence rate reported. For instance, it has been found that when using an absolute increase in serum creatinine as the definition, the incidence of CIN is higher compared with when a definition based on relative increase in serum creatinine level is used[31]. The patient population included in the studies may also have differed significantly and often not all the information necessary to identify systematic differences was available. The estimates used in the studies reviewed were often derived from databases and retrospective assessments that included only patients for whom serum creatinine levels were measured prior to and after the intervention (generally 48 h). There could be systematic differences between the patients included in these studies and those excluded because serum creatinine measurements were missing or unavailable. In addition, since patients with CIN have multiple comorbidities, there may be some confusion in the results presented and some of the costs attributed to CIN may be due to other causes. High and low values have been presented whenever possible to control for this potential bias. In addition, some of the estimates used in this study, including length of stay and long-term incidence of MACE, were based on only a limited number of studies that are currently available. The economic burden of CIN is presented from the US perspective and these results may not be applicable to other settings where the patterns of care may differ. In addition, microcosting may produce more accurate estimates of the healthcare costs associated with CIN.

Also, the estimate of the economic burden did not include indirect costs, in particular, cost associated with loss in productivity due to premature death. Patients with CIN have a much higher mortality rate than those without CIN and, therefore, the estimate provided in this study underestimates the total economic burden of CIN to society.

The author's believe this contains valuable information to understand the economic burden of CIN. Although this and other studies have added to the growing body of literature on the prevalence and consequences of CIN, several unanswered questions remain. First, the true incremental cost of CIN controlling for patient risk factors and other potentially systematic differences need to be understood between those with and without CIN. Second, the cost of treating adverse events related to CIN for those with and without multiple co-morbidities needs to be assessed. Third, the long-term resource use and cost associated with CIN needs to be systematically explored. Lastly, additional studies are required to assess the cost effectiveness of prevention strategies. Future studies, especially analysis of patient-level databases with long-term follow-up, can help address some of these issues. There are significant clinical and economic consequences associated with CIN and additional research is required to better understand the cost impacts and to identify targeted interventions to reduce the burden of CIN.

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