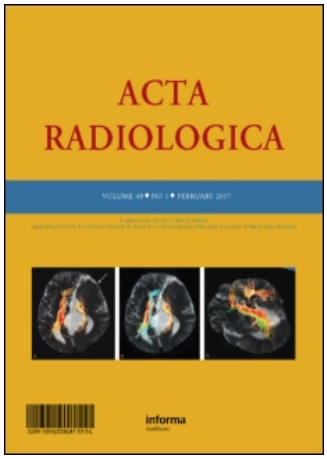

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Contrast Medium Dose-to-GFR Ratio: A Measure of Systemic Exposure to Predict Contrast-Induced Nephropathy after Percutaneous Coronary Intervention

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Contrast Medium Dose-to-GFR Ratio: A Measure of Systemic Exposure to Predict Contrast-Induced Nephropathy after Percutaneous Coronary Intervention

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Background: The contrast medium (CM) dose-to-eGFR (estimated glomerular filtration rate) ratio has recently been advocated to express systemic exposure to CM in assessing the risk of contrast medium-induced nephropathy (CIN).

Purpose: To evaluate how CIN risk might vary with decreasing eGFR at fixed CM-dose/eGFR ratios and other CIN risk factors, and to find a relatively safe CM-dose/eGFR ratio.

Material and Methods: 391 patients underwent primary coronary angioplasty for ST-segment elevation acute myocardial infarction. CM dose (grams iodine; g I), eGFR (ml/min), and preprocedural CIN risk factors were entered into a multiple logistic regression model. From the established statistical model, the probability of CIN ($\geq$44.2 μmol/l serum creatinine rise or oliguria/anuria) was calculated at various eGFR levels based on g-I/eGFR ratios of 1:2, 1:1, 2:1, and 3:1.

Results: At a g-I/eGFR ratio <1 the risk of CIN was 3%, while it was 25% at a g-I/eGFR ratio ≥ 1. Independent predictors of CIN were CM dose, eGFR, left ventricular ejection fraction (LVEF) and cardiogenic shock (ROC area = 0.87). An estimated CIN risk of 10% would for example occur at a g-I/eGFR ratio of 1.5:1 in patients with 50% LVEF without shock. At a 1:2, 1:1, 2:1, and 3:1 g-I/eGFR ratio with 50% LVEF without shock, the CIN risk was about 2, 6, 18, and 30%, respectively, over a wide range of eGFR values (30–90 ml/min). At a 1:1 g-I/eGFR ratio with 50% LVEF + shock, 25% LVEF without shock, or 25% LVEF + shock, the CIN risk was 20, 55, and 80%, respectively.

Conclusion: Relating CM dose to eGFR appears to be an attractive pharmacotoxic model to assess CIN risk. At fixed CM-dose/eGFR ratios, CIN risk increased marginally with decreasing eGFR. Limiting the CM dose in g I numerically to the eGFR value in ml/min or less may be relatively safe with regard to CIN, unless multiple risk factors are present.

Key words: contrast medium; coronary intervention; glomerular filtration rate; nephropathy; renal insufficiency

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Radiographic iodine contrast medium (CM) has been recognized as the third leading cause of hospital-acquired renal insufficiency or the most common cause among pharmaceutical agents (1). CM-induced nephropathy (CIN) has been associated with increased in-hospital morbidity and mortality as well as increased 1-year mortality, at least in connection with percutaneous coronary

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artery interventions (PCI) (2). Patients with ST-segment elevation acute myocardial infarction (STEMI) treated with primary PCI have a very high risk of developing CIN, despite the fact that most of them have apparently normal renal function at hospital presentation (3). Thus, reliable prediction of preprocedural renal function and risk of CIN, institution of adequate prophylactic regimens, and modification of the examination technique to reduce CM dose are crucial to reduce patient suffering and cost, since curative treatment is not available.

A wide spectrum of CIN risk factors, including high age, diabetes mellitus, decreased left ventricular ejection fraction (LVEF), and hemodynamic instability, has been thoroughly outlined in recent reviews (4, 5). The main non-modifiable risk factor is *preexisting renal impairment*, and the main modifiable risk factor is the offending agent itself, i.e., the *contrast medium* (5). It is well recognized that serum creatinine is a poor predictor of renal function (6), especially in the elderly with decreasing muscle mass, the major source of creatinine. Glomerular filtration rate (GFR) is regarded the best measure of renal function in health and disease (7). Consequently, newly developed CIN risk scores include estimated GFR (eGFR), using prediction equations taking into account not only serum creatinine but also anthropometric and/or demographic data (8, 9). This opens the possibility of combining CM dose and eGFR into a single continuous risk variable, i.e., the CM-dose/eGFR ratio, as first suggested by Altmann et al. (10). Such a ratio is a fundamental parameter in expressing systemic exposure to drugs, which in turn is regarded a critical link between dosing and clinical endpoints such as toxicity (11, 12). Based on mean values of CM dose, eGFR, and the frequency of CIN in published reports, Nyman et al. (13) found a gram-iodine (g-I)/eGFR ratio <1 to be a relatively safe cut-off to avoid CIN following PCI, coronary angiography, and computed tomography (CT). Based on individual data in 3179 unselected patients undergoing PCI, Laskey et al. (14) recently found that a CM-volume/eGFR ratio of <3.7 may be a useful tool in determining the amount of CM volume that is not likely to cause CIN. However, in both studies there was no stratification made for patients with or without additional CIN risk factors, and the risk of CIN was not evaluated as a function of decreasing eGFR at a fixed CM-dose/eGFR ratio. Hence, there is a further need to empirically test the feasibility of CM dose/eGFR ratio as a measure of the risk of CIN at a wide range of eGFR levels, and to examine how it may covariate with other risk factors.

The aim of the present study was 1) to evaluate how the risk of CIN might vary with decreasing eGFR if the CM dose is adapted to eGFR according to various fixed CM-dose/eGFR ratios, 2) to assess the effect of non-modifiable CIN risk factors other than renal function, and 3) to find a relatively safe CM-dose/eGFR ratio.

Material and Methods

Patients

The primary material and methods of 208 patients have been thoroughly described in a previous report (3). Briefly, patients admitted to the coronary care unit for STEMI with onset of symptoms ≤ 12 hours who were treated with primary PCI were included. The original material was then extended with a further 184 patients with the same history and treatment. Patients in chronic peritoneal or hemodialysis were not included. One patient was excluded (see results). Thus, the present analysis was based on 391 consecutive patients, including 77 women. Baseline characteristics and available preprocedural risk factors for patients with and without CIN are presented in Table 1. The study was approved by the institutional ethics committee, and informed consent was obtained for all patients. All procedures involving subjects and data were in agreement with the ethical principles for medical research involving human subjects established in the Helsinki Declaration of 1975.

Study protocol

Serum creatinine concentration was measured at hospital admission (just before PCI) and daily for the following 3 days. Estimated GFR was calculated as creatinine clearance by the Cockcroft-Gault equation (15). CIN was defined as a serum creatinine rise ≥ 44.2 μmol/l or oliguria/anuria within 72 hours post-PCI.

An echocardiographic evaluation was performed shortly (≤ 6 hours) after admission. LVEF was calculated by the Simpson rule (16). Cardiogenic shock was defined as prolonged hypotension (systolic blood pressure <85 mmHg), with evidence of decreased organ perfusion caused by severe left ventricular dysfunction, right ventricular infarction, or mechanical complications of infarction.

Intravenous hydration with 0.9% saline was instituted at a rate of 1 ml/kg body weight per hour, with the shortest possible delay before the procedure, and continued for 12 hours postprocedure.

Table 1. Baseline characteristics of study patients ($n=391$) and univariate analysis.

Variables	Median (2.5–97.5 percentile) or number (percent)		Univariate analyses
	CIN ($n=65$)	No CIN ($n=326$)	P value
Age, years	72 (45–83)	61 (40–81)	<0.001
Body weight, kg	72 (55–83)	72 (55–100)	>0.30
Serum creatinine, μmol/l	106 (75–197)	88 (64–140)	<0.001*
eGFR, ml/min	60 (26–100)	77 (36–136)	<0.001
Contrast medium volume, ml	340 (124–645)	248 (101–582)	<0.001*
Contrast medium dose, g I	119 (43–226)	87 (35–204)	<0.001
g-I/eGFR ratio	2.1 (0.7–4.8)	1.1 (0.5–3.1)	<0.001
Diabetes mellitus	8 (12%)	46 (14%)	>0.30
Hypertension	35 (54%)	149 (46%)	0.28
LVEF,% †	41 (20–61)	51 (35–68)	<0.001
LVEF <40%	26 (40.0%)	5 (1.5%)	
Cardiogenic shock	22 (34%)	13 (4%)	<0.001

CIN: contrast medium-induced nephropathy; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction.
*Not evaluated in the multivariate analyses: serum creatinine, since it is included in eGFR, and contrast medium volume, since the dose was expressed in grams iodine in the regression model.
†Data on left ventricular ejection fraction were missing for one patient with CIN and six patients without CIN.

The hydration rate was reduced in patients with decreased LVEF or overt heart failure. None of the patients were subjected to prophylactic hemofiltration or N-acetylcysteine.

Primary PCI using bare metallic stents was performed by a 24-hour on-call interventional team, according to standard clinical practice, using a femoral approach and a 7F guiding catheter. All procedures were performed with the nonionic low-osmolar CM iopentol (Imagopaque 350 mg I/ml; GE Healthcare, Milan, Italy).

Statistical analysis

All statistical analyses were conducted using SPSS (release 12.0.1; SPSS Inc., Chicago, Ill., USA). We regarded $P<0.05$ as statistically significant. Associations with CIN and the variables shown in Table 1 were tested in univariate analyses using the Mann-Whitney U test for continuous variables and Fisher's exact test for binary variables. In multivariate logistic regression analysis (17), we investigated the effect of age, body weight, eGFR, CM dose in grams iodine (g I), diabetes mellitus, hypertension, LVEF, and shock, and included them in the regression modeling if the P value was ≤ 0.30 in the univariate analyses. The full regression model was then simplified by excluding insignificant predictors one by one, starting with the variable with the highest P value, until only significant ($P<0.05$) predictors remained. Finally, the g-I/eGFR ratio was added to the model as a separate predictor to test for any unforeseen interaction between CM dose and eGFR. The fit of the final logistic regression model was assessed using the Hosmer-Lemeshow test (17) for goodness of fit. All continuous variables were entered log-transformed, using the natural logarithm (LN), in the regression model. Since the logistic regression model is exponential, using LN ensures that the risk of CIN approaches zero for very low CM doses. The area under the receiver operating characteristic (ROC) curve was used as an overall measure of CIN classification ability for the final regression model (18). We also used the area under the ROC curve to compare with classification ability if only CM dose and eGFR were used as predictors.

Gram-iodine/eGFR ratio

CM dose expressed in g I was numerically adapted to various levels of eGFR in ml/min according to a certain g-I/eGFR ratio and entered into the present regression model to evaluate how the risk of CIN varied over a wide range of eGFR levels. Thus, at a g-I/eGFR ratio of 1:1, the gram-iodine dose was numerically equal to each level of eGFR, e.g., 60 g of iodine at 60 ml/min, 30 g of iodine at 30 ml/min, etc. Subsequently, the gram-iodine dose was halved, doubled, and tripled at each level of eGFR, resulting in a g-I/eGFR ratio of 1:2, 2:1, and 3:1, respectively.

Results

Patient sample

CIN defined as a ≥ 44.2-μmol/l rise in serum creatinine occurred in 64 patients. Seven of these

patients developed severe CIN, i.e., oliguria/anuria requiring renal replacement therapy (RRT) in terms of hemofiltration or hemodialysis. Two patients without an established $\geq$44.2-μmol/l rise in serum creatinine started treatment with hemofiltration within 3 days of the PCI procedure because of acute pulmonary edema. One of these patients also simultaneously developed transient anuria and was therefore included in the CIN group. In the other patient, diuresis was maintained and, since hemofiltration cosmetically reduces creatinine levels, it was not possible to establish whether CIN had occurred or not. Therefore, the patient was excluded from further analysis. Thus, CIN occurred in 65 of 391 patients (17%; 57 males, eight females), of whom eight (12%) required RRT. Among the patients with CIN, three of 22 patients with shock (14%) and five of the remaining 43 patients without shock (12%) developed oliguria/anuria.

In patients with a g-I/eGFR ratio <1 the risk of CIN was 3% (0% of those with LVEF $\geq$50% and 8% for those with LVEF $<$50%), while at a ratio ≥ 1 the risk was 25%. The number of patients with severe CIN in the present material was too low to be investigated separately.

Logistic regression

Statistically significant predictors of CIN in the uni- and multivariate analyses are presented in Tables 1 and 2, respectively. The established regression model based on the independent predictors gram-iodine dose, eGFR, LVEF, and shock (no = 0, yes = 1) resulted in the following equation for the probability of CIN:

$$1/\{1 + \mathrm{EXP}[-16.7 - 1.67*\mathrm{LN}(\text{g-I}) + 2.16*\mathrm{LN}(\mathrm{eGFR}) + 4.49*\mathrm{LN}(\mathrm{LVEF}) - 1.24*\mathrm{shock}]\} \quad (1)$$

The Hosmer-Lemeshow test showed a satisfactory goodness of fit ($P = 0.71$) for this model. No significant interaction between CM dose and eGFR on CIN risk was detected ($P = 0.16$).

Separate analyses

Constructing a second model for the probability of CIN with exclusion of patients with shock ($n = 35$) yielded an equation similar to that in model 1, in which all three predictors (gram-iodine dose, eGFR, and LVEF) remained statistically significant ($P <$ 0.001 for all three):

$$1/\{1 + \mathrm{EXP}[-13.8 - 1.93*\mathrm{LN}(\text{g I}) + 2.25*\mathrm{LN}(\mathrm{eGFR}) + 3.94*\mathrm{LN}(\mathrm{LVEF})]\} \quad (2)$$

In an additional analysis based on all patients, it was found that age became an independent predictor of CIN ($P = 0.01$; model not presented) when serum creatinine was used as a measure of renal function instead of eGFR.

ROC curve (model 1)

The area under the ROC curve for model 1 was 0.87 (95% confidence interval 0.83–0.92) (Fig. 1). As an example, predicting patient outcome as CIN if the risk were estimated to be $\geq$10% yielded a sensitivity of 86% and specificity of 65%. An estimated CIN risk of 10% would for example occur at a g-I/eGFR ratio of about 1.5:1 in a patient with no shock and an LVEF of 50%. If only gram-iodine dose and eGFR are used to predict CIN risk, the area under the ROC curve decreases to 0.80, a significant difference ($P = 0.03$) compared to the full-scale model including the other risk factors.

Gram-iodine/eGFR ratio (model 1)

Knowing the eGFR, LVEF, and whether shock is present or not, various CM doses in g I may now be entered into model 1 together with the other parameters to estimate the percentage risk of CIN.

Table 2. Multivariate logistic regression analysis.

Variables*	Regression coefficient	Standard error	*P* value
Constant	16.7	4.01	<0.001
Estimated GFR, ml/min	−2.16	0.487	<0.001
Contrast medium dose, g I	1.67	0.422	<0.001
LVEF,%	−4.49	0.876	<0.001
Cardiogenic shock	1.24	0.474	0.009

GFR: glomerular filtration rate; LVEF: left ventricular ejection fraction.

*All continuous variables were entered log-transformed, using the natural logarithm based on complete data in 384/391 patients (LVEF missing in seven patients). The following variables with a *P* value $\leq$0.30 in the univariate analysis were not significant in the multivariate model and therefore excluded: age (*P* value at exclusion $>$0.30) and hypertension (*P* value at exclusion = 0.09). No significant interaction between gram-iodine dose and estimated GFR was detected ($P = 0.16$).

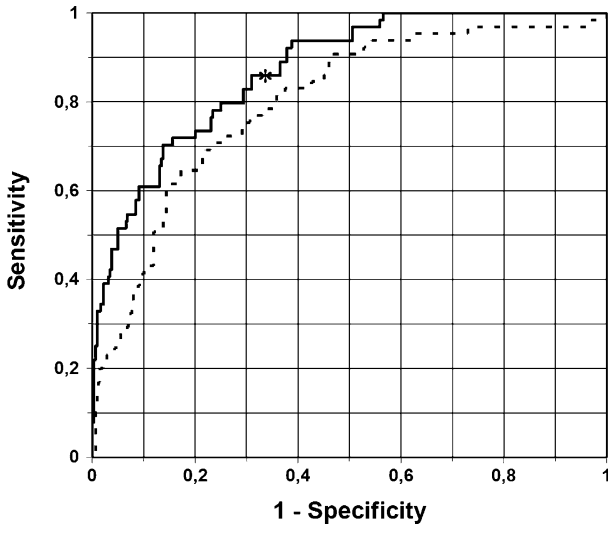

Fig. 1. The receiver operating characteristic curves for the risk of CIN for two different prediction models: 1) model 1 in the Results section based on gram-iodine dose, eGFR, left ventricular ejection fraction, and shock (solid line; area under the curve = 0.87); 2) a model based only on gram-iodine dose and eGFR (dotted line; area under the curve = 0.80). Predicting the patient outcome as CIN if the risk were estimated to be ≥10% with model 1 yielded 86% sensitivity and 65% specificity (asterisk). CIN: contrast medium-induced nephropathy; eGFR: glomerular filtration rate.

The predicted risk of CIN at various g-I/eGFR ratios in patients without and with shock when LVEF was set to 50 and 25%, respectively, is illustrated in Fig. 2. As evident from this figure, the risk of CIN changed only to a minor extent if the eGFR was set to any value between 30 and 90 ml/min. Fig. 3 illustrates the risk of CIN as a function of increasing g-I/eGFR ratios at various LVEF values (50 and 25%), and with and without shock when eGFR was fixed at 40 ml/min.

Discussion

AUC, systemic exposure, and toxicity

Radiographic contrast media are well-established exogenous markers for measuring GFR (19). Following intravascular injection of CM, multiple blood samples may be used to measure the plasma concentration of CM over time and calculate the *area under the plasma concentration–time curve* (AUC). Since the injected CM dose is known, GFR may be calculated from mathematical models in which GFR is directly proportional to CM dose divided by AUC. Consequently, AUC is directly proportional to the ratio between CM dose and GFR. AUC is a fundamental pharmacokinetic parameter used to estimate *systemic exposure* to drugs that are distributed and eliminated according to linear kinetics, such as contrast media (11, 12). The systemic exposure of such a drug is often well correlated with its *toxicity* and hence is generally held as an index for dose optimization (11). However, measuring GFR by using exogenous substances would be impractical in daily routine before injections of CM, particularly in emergency PCI. Instead, many organizations (20) recommend that GFR can be estimated with acceptable accuracy using dedicated prediction equations taking into account not only serum creatinine but also anthropometric and/or demographic data (20–22). Sherwin et al. (12) showed that, with eGFR calculated from the Cockcroft-Gault equation, the CM-dose/eGFR ratio correlated strongly ($r = 0.95$) with *measured* AUC. The clinical value of AUC as a predictor of nephrotoxicity has been shown for a variety of drugs (12). However, among the vast literature on CIN, there are only occasional reports that have explored the use of AUC as a nephrotoxic predictor (10, 13, 14).

Gram-iodine/eGFR ratio and the risk of CIN

The resulting area under the ROC curve in this study indicated that entering CM dose and eGFR along with traditional clinical risk factors into a logistic regression model yielded discrimination considered to be excellent (17) in predicting the risk of CIN in patients undergoing emergency PCI. This is a better classification than that of Laskey et al. (14), who only used CM-dose/eGFR ratio for CIN prediction, and reached an area under the ROC curve of 0.69. In addition, using only the CM-dose/eGFR ratio in the present study yielded a significantly smaller area under the ROC curve than when other significant risk factors also were included in the model. McCullough et al. (23) presented a similar model (Appendix) to ours and found that, assuming a constant dose of 250 ml CM ($\approx$90 g I at 350 mg I/ml) of mainly high-osmolar CM during elective PCI, the risk of acute renal failure requiring dialysis rose steeply and exponentially below an eGFR of 40 ml/min for diabetics and 30 ml/min for non-diabetics. However, if the CM dose was adapted to a 1:1 g-I/GFR ratio in McCullough's formula, there was no marked increase in the risk of severe CIN at GFR down to 20 ml/min in non-diabetics (13). This is in accordance with the present study, which also indicates that by keeping the gram-iodine dose constant relative to the numerical value of eGFR, the risk of CIN (serum creatinine rise ≥44.2 μmol/l) may be fairly constant over a wide range of eGFR values and increases only to a minor extent with decreasing eGFR.

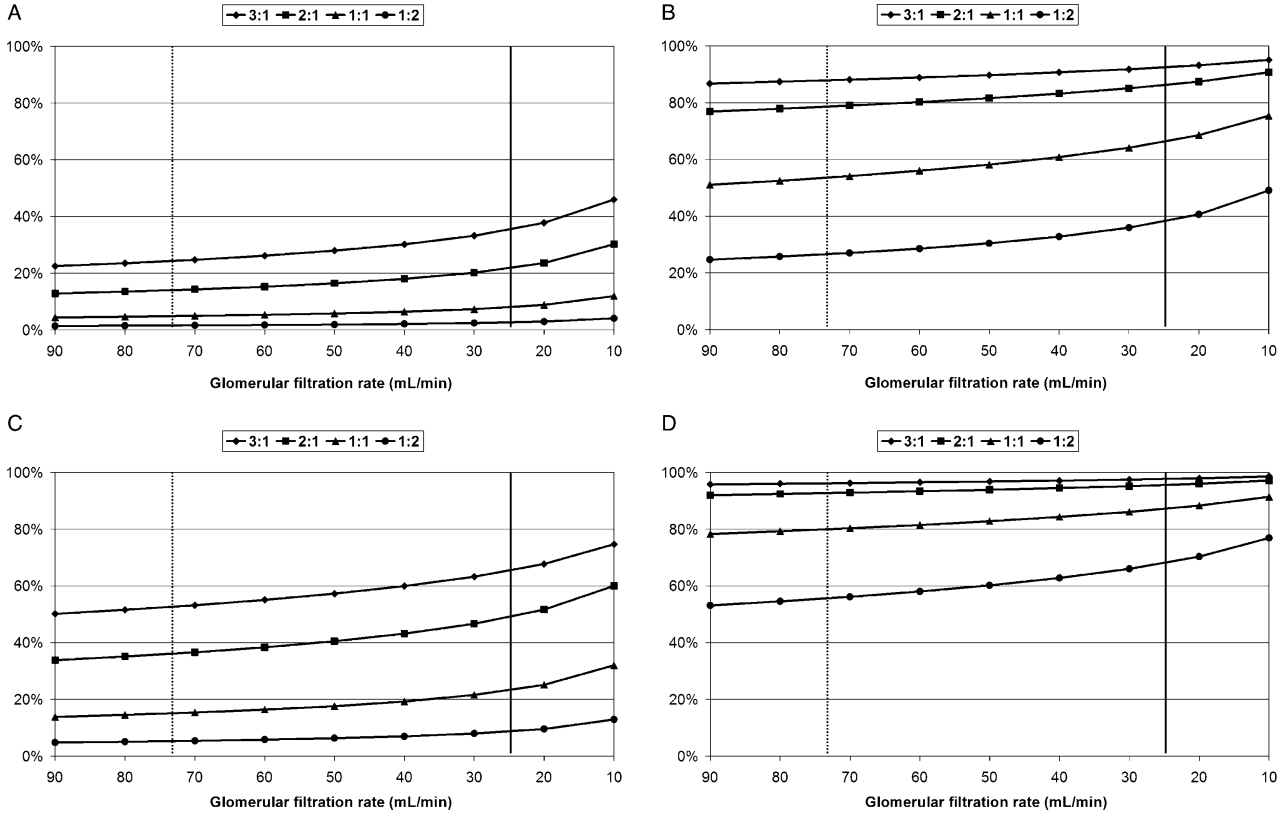

Fig. 2. Risk of contrast medium-induced nephropathy (according to model 1) as a function of the 1:2, 1:1, 2:1, and 3:1 ratio between contrast medium dose (grams iodine) and eGFR, with LVEF set to 50% and no shock (A), LVEF set to 25% and no shock (B), LVEF set to 50% and shock (C), and LVEF set to 25% and shock (D). Solid vertical line corresponds to the minimum eGFR (25 μmol/ml) and dashed vertical line to the median eGFR (73 μmol/ml) in the present study cohort. LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate.

At an AUC corresponding to a 1:1 g-I/GFR ratio in the present model and using low-osmolar CM, the risk of CIN only ranged between 4 and 7% over a wide range of eGFR values (30–90 ml/min) in patients with no other significant risk factors (LVEF at 50% and no shock), despite the fact

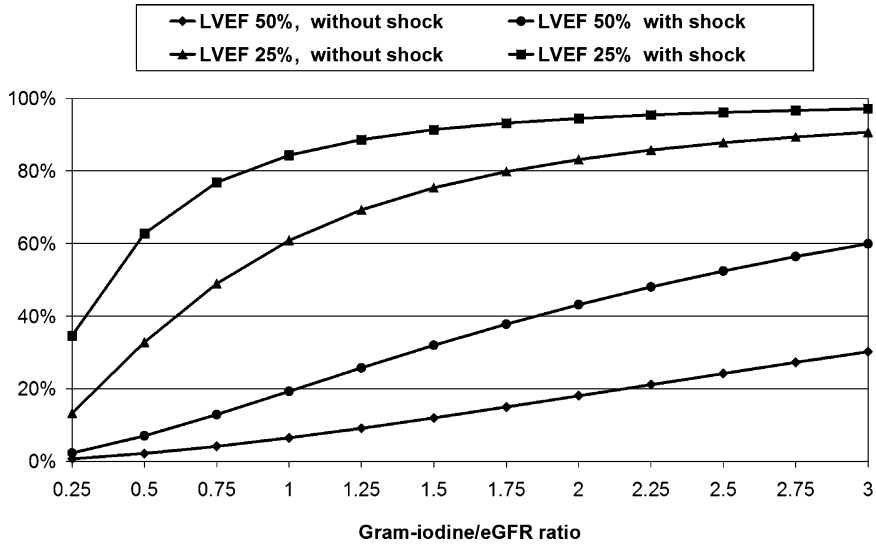

Fig. 3. Risk of contrast medium-induced nephropathy (according to model 1) at an eGFR of 40 ml/min and as a function of various ratios between contrast medium dose (grams iodine) and eGFR at 50% and 25% LVEF without and with shock. LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate.

emergent PCI was performed in patients with STEMI. This is close to the overall 10% risk of CIN (serum creatinine rise $\geq$44.2 μmol/l or $\geq$20–25%) at a 1:1 g-I/GFR ratio calculated from mean data reported in PCI, coronary angiography, and CT studies using low-osmolar CM (13). LASKEY et al. (14) found a CM-volume/eGFR ratio of 3.7 to be a fair discriminator for CIN (serum creatinine rise >44.2 μmol/l) in an unselected population undergoing PCI with high- (2%), low- (41%), and iso-osmolar (57%) CM. This would correspond to a g-I/eGFR ratio of 1.3 at a common approximate CM concentration of 350 mg I/ml for coronary studies. This is close to our 1:1 g-I/eGFR ratio, indicating a low risk of CIN in patients with no other significant risk factors apart from the fact that they all had STEMI, a risk factor per se (3, 5). There was no stratification for patients with and without risk factors in the studies reported by NYMAN et al. (13) and LASKEY et al. (14), meaning that data were based on populations with a certain mean number of CIN risk factors, which may explain the similar results compared to ours.

ALTMANN et al. (10) found a CM volume/eGFR ratio $\leq$6.0 (g-I/eGFR ratio of 2.1 at 350 mg I/ml) to be associated with only a 1% risk of more pronounced CIN (serum creatinine rise $\geq$1 mg/dl) in patients undergoing cardiac angiography or angioplasty, and using both high- (42%) and low-osmolar (58%) CM. Thus, their suggested safe g-I/GFR ratio was about twice that of the other studies, a difference that may be attributed to their more narrow definition of CIN. Letting the numerical value of eGFR serve as a guideline to maximize the CM dose in grams iodine (g-I/eGFR ratio = 1) results in substantially lower dose limits in elderly low-weight patients than those obtained with Cigarroa's formula (Appendix) or according to a consensus reported by the European Society of Urogenital Radiology (ESUR; Appendix) (13). This is not surprising, since the CM dose was related to serum creatinine in both Cigarroa's formula and the ESUR consensus report. Serum creatinine is notorious for underestimating renal function in this elderly category of patients (24).

Cardiogenic shock, LVEF, and CIN

Our results indicate that a 1:1 g-I/eGFR ratio predicts a low risk of CIN only if no other major CIN risk factors are present. When a 1:1 g-I/eGFR ratio was combined with shock and/or a low LVEF, CIN risk increased substantially. It may be argued that including patients with cardiogenic shock (1/3 of patients with CIN) and low LVEF (<40% in 40% of patients with CIN) may be suboptimal in studying CIN specifically. It is obvious that shock and congestive heart failure may per se cause acute renal failure. However, both shock and cardiac failure are commonly included among risk factors (4) and risk-score systems (8) for CIN, presumably since both may potentiate the toxic effect of contrast media. Furthermore, including shock and LVEF in a CIN risk-score system provides the examiner with a tool to assess the risk of post-PCI creatinine increase, even in patients with hemodynamic instability, and the possibility to plan the approach accordingly.

CM dose in volume or grams iodine

ALTMANN et al. (10) and Laskey et al. (14) expressed CM dose only in terms of volume in milliliters, presumably because the CM concentration used during coronary procedures usually varies within narrow ranges, i.e., 320–370 mg I/ml, and may thus be disregarded. We prefer to express CM dose in grams iodine, since commercially available and used concentrations range from 140 to 400 mg I/ml for a variety of radiological diagnostic and interventional procedures. Furthermore, common gram-iodine doses for radiography-based procedures (15–80 g I = 100–200 ml or 150–400 mg I/ml) are in the same numerical range as severely–moderately–mildly decreased GFR, i.e., 15–80 ml/min per 1.73 m^2 (7). Thus, forming a ratio between an expected gram-iodine dose and the patient's eGFR provides the examiner with a simple numerical relationship and an expedient way to predict the risk of CIN. Simply reporting CM volumes and not the concentration used may also make it difficult to expand the experience of CIN made from one type of examination or department to another if different concentrations are used. It should also be noted that the off-label use of gadolinium CM (primarily intended for magnetic resonance imaging) in patients with renal impairment has provided satisfactory results during coronary procedures (25, 26). The attenuation of 0.5–1.0 M gadolinium CM corresponds only to roughly 75–150 mg I/ml (27, 28), but they may actually be more nephrotoxic than iodine CM in equal attenuating doses (27, 29). This indicates that iodine CM may be used at lower concentrations than those conventionally used for coronary procedures to reduce the risk of CIN in patients with renal impairment and without the risk of inducing nephrogenic systemic fibrosis (30). This may be especially true in thin patients where a lowered X-ray tube kilovoltage increases the attenuation of iodine and partially compensates for

the lowered concentration. Thus, an individual adjustment of CM concentration in coronary procedures may also favor grams iodine instead of simply volume to express CM dose.

Study limitations

There are several limitations to the present study that may restrain the applicability of the risk model in more widespread populations undergoing CM-based examinations. The selection included only patients with STEMI undergoing primary PCI; diabetes mellitus, regarded to increase the risk of CIN in connection with renal impairment (4, 5), did not turn out to be a significant predictor, possibly due to the relatively few diabetics with decreased renal function (eGFR <60 ml/min; $n=15/391$, 3.8%); a number of risk factors such as dehydration, anemia, and nephrotoxic drugs were not available for evaluation; the low proportion of females (20%) in the patient sample may also hamper the generalizability of our risk model; the CIN prediction model was developed based on a patient cohort with a wide range of eGFR values, although no individuals had an eGFR below 25 ml/min, and the validity of the equation at such low eGFR levels is therefore uncertain; similarly, the model may not be applicable for very low doses of CM.

We are also well aware that it may be argued that there is not enough time to evaluate renal function prior to PCI in patients admitted with STEMI, and that CM dose has to be governed primarily by the complexity and number of lesions that need to be opened, and not renal function. Thus, the present result may be purely academic in patients with STEMI, but importantly reinforces preliminary experiences (13, 14) indicating that CM dose in grams iodine should not exceed the numerical value of eGFR in patients undergoing procedures, implying intravenous applications of CM relative to the kidneys, e.g., computed tomography and most catheter-based selective arteriographies including coronary artery injections. However, considering the highly vulnerable patients with STEMI, where time to reperfusion, renal function, and CM dose are critical for a successful outcome, a fast serum creatinine value would seem to be of highest priority. In fact, this may become a reality, with recently introduced bedside blood analyzers such as the Reflotron Plus (F. Hoffmann-La Roche Ltd., Basel, Switzerland) and the EZ Chem (E-Z-EM, Inc., Lake Success, N.Y., USA). Knowing the patient has a low eGFR may alert the operator to use a CM dose "as low as reasonably achievable" (ALARA), for example by using biplane equipment, limiting unnecessary projections or excessive "puffs," and decreasing CM concentration, especially in small individuals, as already discussed.

At first glance, the present equation for predicting CIN or translating gram-iodine doses into volumes dependent on the iodine concentration used may seem complicated. However, by establishing a model such as the one presented here in a Microsoft Excel spreadsheet, it may used to readily predict the approximate risk of CIN prior to PCI at various g-I/eGFR ratios by entering eGFR, LVEF, and shock (0 = no, 1 = yes). By entering the CM concentration used, the volume may be instantly calculated at each ratio (Fig. 4).

In conclusion, relating CM dose in grams iodine numerically to eGFR on a continuous scale and expressing the risk of CIN according to AUC (g-I/eGFR ratio) appears pharmacokinetically more correct than hitherto used models. It provides the examiner with a fast and simple relationship to prospectively calculate the volume of a certain CM concentration that may be given to minimize the

Primary coronary intervention in acute myocardial infarction

Prediction of the risk of contrast medium-induced nephropathy (CIN)

g-I = gram-iodine contrast medium dose	Parameters	g-I/GFR ratio	CM volume (ml)	CIN-RISK
CM concentration (mg iodine/mL)	350	0.5	64	5%
Estimated GFR (mL/min)	45	1.0	129	15%
Left ventricular ejection fraction (%)	40	2.0	257	36%
Shock (0=no; 1=yes)	0	3.0	386	53%

Fig. 4. A Microsoft Excel spreadsheet (available at URL: www.arwen.se/radiology) for calculating the risk of CIN using the present regression model 1 in the Results section. The following parameters are entered: contrast medium concentration used, estimated GFR, left ventricular ejection fraction, and shock (0 = no, 1 = yes). The resulting contrast medium volumes at various fixed g-I/GFR ratios are then calculated as well as the percentage risk of CIN. CM: contrast medium; GFR: glomerular filtration rate.

risk of CIN. So far, accumulated evidence suggests that the gram-iodine dose of modern CM should not exceed the numerical value of eGFR (g-I/eGFR ratio <1) to minimize the risk of CIN (serum creatinine rise ≥ 44.2 μmol/l or $\geq 25\%$) when additional risk factors are absent, or even less if multiple risk factors are present. Combining the g-I/eGFR ratio with other risk factors into one risk index on a continuous scale may improve risk assessment of CIN when building future risk-scoring systems for various types of radiographic examinations. A single risk score based on a g-I/eGFR index may also be added to the integer score of additional risk factors in available risk stratification algorithms (8, 9).

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Appendix A

Cigarroa's formula for a "safe" maximum contrast medium dose of high-osmolar agents (31)

5 ml of contrast medium (maximum 300 ml) x body weight (kg)/serum creatinine (mg/dl)

The formula is based on high-osmolar contrast media at a concentration of 370 mg I/ml.

"Safe" doses of low osmolar contrast media (300 mg I/ml) according to an ESUR consensus report (32)

The probability of CIN according to McCullough et al. (23)

Serum creatinine, μmol/l	Volume, ml	Dose, g I
<130	300–400	90–120
130–300	150	45
>300	100	30

$$1/\{1 + \mathrm{EXP}[0.06011 + 0.194*\mathrm{eGFR} - 1.6987*\mathrm{DM}\ (1/0) - 0.0076*\mathrm{CM\ volume}]\}$$

EXP: returns the base (e) of the natural logarithm raised to a certain number; eGFR: estimated glomerular filtration rate (ml/min); DM: diabetes mellitus; CM: contrast medium (volume in ml).

The weighted mean CM concentration was about 350 mg I/ml (13), so the formula can be rewritten as:

$$1/\{1 + \mathrm{EXP}[0.06011 + 0.194*\mathrm{eGFR} - 1.6987*\mathrm{DM}\ (1/0) - 0.0076*\mathrm{CM\ volume}*\mathrm{concentration}/350]\}$$

Note that, by mistake, there is a "minus sign" before the eGFR expression in the original publication (13, 23).

Probability of CIN according to the present models

Patients ($n = 391$) with shock included:

$$1/\{1 + \mathrm{EXP}[-16.7 - 1.67*\mathrm{LN(g\ I)} + 2.16*\mathrm{LN(eGFR)} + 4.49*\mathrm{LN(LVEF)} - 1.24*\mathrm{shock}]\}$$

g I: grams iodine; LN: natural logarithm; LVEF: left ventricular ejection fraction.

Patients ($n = 356$) with shock excluded ($n = 35$):

$$1/\{1 + \mathrm{EXP}[-13.8 - 1.93*\mathrm{LN(g - I)} + 2.25*\mathrm{LN(eGFR)} + 3.94*\mathrm{LN(LVEF)}]\}$$