# Beyond Contrast Volume: Patient-Related Determinants and Methodological Considerations in Contrast-Induced Nephropathy

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**Dear Editor,**

We read with great interest the article by Freitas et al. [1], entitled "*Impact of Contrast Volume Used After Percutaneous Coronary Procedures in Patients at Risk for Contrast-Induced Nephropathy*". By evaluating the interaction between contrast type and volume through a post hoc analysis, the authors addressed a clinically relevant question in a high-risk population managed with contemporary preventive strategies, providing a valuable contribution to the literature.[1]

Nevertheless, we believe that the interpretation of the findings could be strengthened by integrating methodological and pathophysiological considerations beyond contrast-related parameters alone. The statistically significant protective effect of statin use against contrast-induced nephropathy (CIN) is particularly noteworthy and supported by prior randomized evidence.[2,3] Notably, the PRATO-ACS trial[4] demonstrated that early high-dose rosuvastatin significantly reduced contrast-induced acute kidney injury through pleiotropic anti-inflammatory, antioxidant, and endothelial-stabilizing effects, largely independent of contrast volume. The coexistence of a neutral contrast effect with a meaningful pharmacological benefit supports the concept that CIN susceptibility may be driven predominantly by patient-related vascular, inflammatory, and oxygenation-related vulnerability rather than by the physicochemical properties of contrast agents.[5]

Within this framework, the absence of hemoglobin assessment represents a relevant limitation. Murakami et al.[6] identified anemia as an independent predictor of CIN, particularly in patients with impaired renal reserve, by exacerbating renal medullary hypoxia and ischemic susceptibility following contrast exposure. Failure to account for this oxygen-delivery component may therefore have attenuated or obscured potential associations between contrast parameters and CIN risk. These observations align with contemporary perspectives emphasizing the central role of systemic inflammation and metabolic stress in contrast-associated renal injury.

Similarly, evaluating oral hypoglycemic therapy as a single, homogeneous category substantially limits interpretability. Growing evidence indicates that sodium–glucose cotransporter-2 (SGLT-2) inhibitors exert distinct renal hemodynamic and metabolic effects, including reductions in tubular oxygen consumption and improvements in medullary oxygen balance, which may translate into lower CIN susceptibility.[7,8] Lack of stratification by antidiabetic drug class may thus have obscured clinically relevant metabolic and microvascular heterogeneity. In addition, the absence of data regarding peri-procedural management of agents such as metformin introduces further uncertainty, as altered lactate handling under hypoxic conditions may complicate creatinine-based renal assessment and reflect underlying metabolic vulnerability rather than drug-specific toxicit.[9]

Another important consideration is that post hoc stratification by absolute contrast volume may have compromised baseline comparability and introduced confounding by indication. Contemporary percutaneous coronary intervention data consistently show that contrast volume alone inadequately reflects nephrotoxic burden unless contextualized by baseline renal function.[10] In this regard, the higher baseline eGFR among patients receiving ≥150 mL of iodixanol likely reflects permissive allocation to those perceived to have greater renal reserve, whereas the higher prevalence of prior coronary artery bypass grafting in the same subgroup indicates increased procedural complexity necessitating greater contrast use. This bidirectional selection may have substantially diluted true associations between contrast parameters and CIN.[11]

Finally, the predominance of a geriatric population introduces fundamental limitations to creatinine-based renal assessment. Large population-based studies have consistently demonstrated that age-related declines in skeletal muscle mass lead to lower baseline serum creatinine levels, resulting in systematic underestimation of true renal dysfunction in older adults.[12] As a consequence, reliance on creatinine-based definitions may obscure subclinical kidney injury and underestimate the incidence of contrast-induced nephropathy, particularly in populations characterized by frailty or sarcopenia.[13] This limitation is further compounded by the physiological age-related decline in glomerular filtration, which may be misclassified as preserved renal function when creatinine alone is used, thereby attenuating the detection of contrast-associated renal injury in elderly cohorts.[14]

In this context, while the present study provides important data regarding contrast selection, future prospective investigations incorporating composite risk assessment frameworks—such as baseline eGFR, the Mehran risk score, anemia, and markers of biological frailty, including sarcopenia—may allow for a more pathophysiologically coherent and clinically relevant stratification of CIN risk.

## Keywords

Kidney Diseases; Contrast Media; Percutaneous Coronary Intervention

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## Reply

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**Dear Editor,**

We sincerely appreciate your careful reading and thoughtful consideration of our article "Impact of Contrast Volume Used After Percutaneous Coronary Procedures in Patients at Risk for Contrast-Induced Nephropathy," published in the *Arquivos Brasileiros de Cardiologia* in December 2025. We greatly value your comments, as they enrich the scientific debate and contribute to the continuous improvement of clinical research.[1]

We would like to clarify some relevant points that were addressed in the letter.

The randomized IDPC study is the first large-scale randomized study to compare the contrast agents iodixanol and ioxaglate in preventing contrast-induced nephropathy (CIN) after percutaneous coronary intervention or diagnostic catheterization. The main finding of this investigation is that there was no significant difference between the contrast agents iodixanol and ioxaglate in the development of CIN in a high-risk population after diagnostic or therapeutic procedures in a hemodynamics laboratory of a tertiary cardiology hospital center.[2] Similarly, in the post-hoc analysis, there was no association between the type of contrast agent and the occurrence of CIN, even among patients exposed to higher volumes of both contrast agents.[3]

Regarding the use of statins, we fully agree with the importance of their pleiotropic effects in preventing contrast-induced nephropathy (CIN), as evidenced in previous studies. In our cohort, 77% of patients were using statins, reflecting the contemporary practice of optimized cardiovascular prevention. This data was not published in this article, but can be found in full in the doctoral thesis (2021).[4] This high percentage may possibly contribute to the attenuation of additional differences related exclusively to contrast parameters.

Regarding anemia, we recognize its pathophysiological role in renal medullary hypoxia and vulnerability to acute kidney injury. However, we emphasize that most of our

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patients had hemoglobin levels within the normal range. Furthermore, this parameter was indirectly addressed through the incorporation of the Mehran score, which includes anemia as a risk variable, contributing to a validated clinical stratification. The Table 1 below shows the Mehran score and probability of survival according to the type of contrast agent.[4]

Regarding SGLT-2 inhibitors, we fully agree on their relevant hemodynamic and renal metabolic effects. However, during the period in which the procedures were performed in the hemodynamics service, this therapeutic class was not yet available in Brazil, which is why none of the patients were using these medications. Thus, there was no potential impact of this variable on the analysis.

Regarding data on the periprocedural management of agents such as metformin, it is worth noting that it is routine for the service to suspend the medication 48 hours before the procedure in order to reduce the risks and complications related to lactic acidosis.

Regarding the hydration protocol, all patients included in the study had their creatinine levels measured 48 to 96 hours after undergoing diagnostic or therapeutic catheterization.

It should be added that patients with a filtration rate ≤ 45 mL/min were admitted for intravenous hydration, as were those who had previously presented with CIN, even with a clearance > 45 mL/min.

Those patients with clearance ≤ 45 mL/min received intravenous hydration with ordinary saline solution (0.9%), at doses of 0.5 to 1.0 mL/kg/min according to the presence or absence of left ventricular dysfunction, previously known through transthoracic echocardiography, for at least 12 hours before the procedure, which was maintained during the examination and for 12 hours after its completion.

Patients with creatinine clearance between 45 and 60 mL/min were also hydrated intravenously pre-procedure, for 4 hours before the start of the procedure, during the procedure, and for at least 4 hours afterward.

Patients with creatinine clearance ≤ 45 mL/min remained hospitalized until the following day, when urea, creatinine, sodium, and potassium levels were measured before hospital discharge to check for any further changes in renal function parameters. If these parameters were elevated, the patient remained hospitalized for hydration, clinical evaluation, and monitoring of tests until partial or complete improvement. Those who did not show changes in creatinine were discharged and instructed to have their creatinine levels measured between 48 and 96 hours after the procedure, according to protocol.

Those with clearance > 45 up to 60 mL/min were discharged on the same day, with instructions and a laboratory request to collect creatinine between 48-96 hours after the contrast-enhanced procedure.

Regarding the study population, we highlight that the predominance of elderly patients reflects the daily reality of our hemodynamics service, with a high number of procedures per year. We know that many of these patients are underrepresented or even excluded from large randomized clinical trials. Our objective was precisely to offer a pragmatic analysis, centered on real clinical practice, seeking to elucidate a recurring issue in daily care: the real weight of the absolute volume of contrast in a contemporary prevention scenario and in a population of high clinical complexity.

We agree that future prospective models incorporating additional variables—such as more sensitive markers of renal function, biological frailty, and more refined metabolic stratifications—could further deepen the understanding of individual vulnerability to CIN. However, we believe that our findings contribute by demonstrating that, in a context of optimized prevention and consolidated risk assessment, the absolute volume of contrast may not be the predominant single determinant of renal outcome.

We reiterate our gratitude for the valuable observations and for encouraging constructive scientific debate.

**Table 1 – Mehran score and probability of survival according to type of contrast agent**

| Mehran Score | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Variable** | | | **≤ 5** | **6 – 10** | **11 – 15** | **> 15** | **p-value** |
| Type | Total | n (%) | 386 (20.6) | 885 (47.2) | 523 (27.9) | 81 (4,3) | |
| | Ioxaglate | n (%) | 195 (50.5) | 432 (48.8) | 264 (50.5) | 31 (38.3) | |
| | Iodixanol | n (%) | 191 (49.5) | 453 (51.2) | 259 (49.5) | 50 (61.7) | 0.209 |
| Probability of Survival Death | | (%) | 97.7% | 97.1% | 96.9% | 92.6% | 0.081 * |
| Probability of Survival Combined | | (%) | 97.2% | 96.8% | 95.4% | 87.8% | 0.006 * |

*p-value obtained by the Mann-Whitney U test. * p-value obtained from the log-rank test. Table extracted from the doctoral thesis.[4]*

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