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Acute kidney injury
Contrast media
Glomerular filtration rate
Consensus

Palabras clave (DeCS)
Lesión renal aguda
Medios de contraste
Tasa de filtración glomerular
Consenso

Consensus of the Asociación Colombiana de Nefrología e Hipertensión Arterial (Asocolnef) and the Asociación Colombiana de Radiología (ACR) on evidence-based recommendations for acute kidney injury* associated with the use of iodinated contrast media (AKI-ICM)

Consenso de la Asociación Colombiana de Nefrología e Hipertensión Arterial (Asocolnef) y la Asociación Colombiana de Radiología (ACR) sobre recomendaciones basadas en la evidencia de la lesión[1*] renal aguda asociada al uso de medios de contraste yodados (LRA-MCI)

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Summary

Introduction: Acute kidney injury associated with the use of iodinated contrast media (AKI-ICM) is an iatrogenic disorder with potential implications in morbidity and mortality, a cause for concern in imaging services. The last few years have marked important changes in the conception of this entity, from a more precise definition and its true incidence to the real impact of some strategies for its prevention. Objective: To generate evidence-based recommendations for the use of iodinated contrast media in patients undergoing diagnostic and therapeutic radiological procedures, by means of an expert consensus. Methodology: Based on the formulation of research questions related to AKI-ICM, a search for evidence was carried out in PubMed, Embase and Scopus, between January 2013 and August 2022. The articles were selected by means of a systematic review and with the modified Delphi consensus methodology. The quality of the papers was assessed by applying paper evidence quality assessment instruments. Results: Twenty-two recommendations were formulated for the management of patients requiring administration of iodinated contrast medium. A panel of 11 experts, including 4 nephrologists, 4 radiologists and 1 pediatric nephrologist, participated in the development of the consensus in 5 virtual sessions and 15 hours of work. Conclusions: The term acute kidney injury associated with the use of iodinated contrast media (AKI-ICM) should ideally be used and other definitions that infer overt causality abandoned. Its incidence: recent data show that it is well below that traditionally considered. Only a low estimated glomerular filtration rate (eGFR) is considered an independent risk factor. Regarding its prevention, only hydration has shown a potential benefit as a nephroprotective measure.

Resumen

Introducción: La lesión renal aguda asociada con el uso de medios de contrastes yodados (LRA-MCI) es un trastorno iatrogénico con potenciales implicaciones en morbilidad y mortalidad, motivo

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*Aunque es común usar la expresión "injuria renal aguda", se trata de un error de traducción de "acute kidney injury". Lo correcto en este contexto —como lo explica el reconocido traductor médico Fernando Navarro en su *Diccionario de dudas y dificultades de traducción del inglés médico*— es traducir *injury* por *lesión*. Por esta razón, en este Consenso se usa "lesión renal aguda", con su sigla, "LRA".

de preocupación en los servicios de imágenes. Los últimos años han marcado cambios importantes en la concepción que se tiene sobre esta entidad, desde una definición más precisa y su verdadera incidencia hasta el impacto real de algunas estrategias para su prevención. ***Objetivo:*** Generar recomendaciones basadas en la evidencia para el uso de medios de contraste yodados e n pacientes sometidos a procedimientos radiológicos terapéuticos y de diagnóstico, mediante un consenso de expertos. ***Metodología:*** A partir de la formulación de preguntas de investigación relacionadas con la LRA-MCI se realizó la búsqueda de evidencia en PubMed, Embase y Scopus, entre enero de 2013 y agosto de 2022. Los artículos se seleccionaron por medio de una revisión sistemática y con la metodología de consenso Delphi modificado. La calidad de los documentos se valoró aplicando instrumentos de evaluación de calidad de la evidencia de los documentos. ***Resultados:*** Se formularon 22 recomendaciones para el manejo de pacientes que requieren administración de medio de contraste yodado. Un panel de 11 expertos, entre los que se contó con 4 nefrólogos, 4 radiólogos y 1 nefrólogo pediatra, participaron en la elaboración del consenso en 5 sesiones virtuales y 15 horas de trabajo. ***Conclusiones:*** El término lesión renal aguda asociada al uso de medios de contraste yodados (LRA-MCI) debe usarse idealmente y abandonar otras definiciones que infieren una causalidad manifiesta. Su incidencia: los datos recientes demuestran que se ubica muy por debajo de lo tradicionalmente considerado. Solo una baja tasa de filtración glomerular estimada (TFGe) se considera factor de riesgo independiente. Respecto a su prevención, únicamente la hidratación ha mostrado un potencial beneficio como medida nefroprotectora.

Abbreviations

- **CKD:** chronic kidney disease
- **IA:** intra-arterial
- **PCI:** percutaneous coronary intervention
- **IV:** intravenous
- **AKI:** acute kidney injury
- **AKI-ICM:** acute kidney injury associated with the use of iodinated contrast agents
- **ICM:** iodinated contrast media
- **NAC:** n-acetylcysteine
- **CIN:** contrast media induced nephropathy
- **NSS:** normal saline solution (0.9%)
- **eGFR:** estimated glomerular filtration rate

Introduction

Acute kidney injury (AKI) that develops due to exposure to iodinated contrast medium (ICM) is an iatrogenic disorder of great clinical relevance that stands as the potential complication that generates the greatest fear among health care personnel involved in the practice of medical imaging for diagnostic and therapeutic purposes. Over time, different terms have been used to define it, without uniformity, mostly assuming an unprovable causal relationship and without excluding with certainty other probable causes of acute kidney injury (AKI). This has led to the current preference to use terms that do not imply causality and that take into account all concomitant conditions, such as the term Acute kidney injury associated with the use of iodinated contrast media (AKI-ICM).

Another fundamental aspect that has undergone profound changes over time is the determination of the real frequency of this entity. The first studies placed contrast media as the third cause of AKI in the in-hospital context, only surpassed by hypovolemia and major surgery; however, these did not have methodological designs that allowed adequate control of biases, so it was not possible to establish conclusions derived from their results. For this reason, and with the purpose of controlling confounding variables, propensity score studies have been developed that allow greater control of these variables and obtain data that are more in line with reality. Similarly, although multiple risk factors for the development of AKI-ICM have been cited, only the reduction in estimated glomerular filtration rate (eGFR) has been shown to be an independent risk factor.

Many pharmacological strategies have been used with the aim of preventing the development of AKI in patients undergoing radiological procedures with ICM. Most of these therapies have been derived from knowledge of pathophysiological mechanisms, uncontrolled clinical trials and studies with small populations; in new trials with greater methodological rigor and a larger sample size, some strategies that showed some benefit in previous studies may show none and even, paradoxically, deleterious effects on renal function.

This document, product of the consensus between the Colombian Association of Nephrology and Arterial Hypertension (Asocolnef) and the Colombian Association of Radiology (ACR) on evidence-based recommendations for AKI-ICM, is the first in the history of Colombia to bring together these two scientific associations, with the purpose of guiding all healthcare personnel involved in the management of patients who require the use of ICM in diagnostic and/or therapeutic procedures, providing guidelines and recommendations to be implemented before, during and after the application of ICM, in order to reduce the risk of AKI-ICM.

1. Scope and Objectives

1.1. Objective

To generate evidence-based recommendations for the use of ICM in patients undergoing diagnostic and therapeutic radiological procedures, through an expert consensus.

1.2. Population included

Patients undergoing diagnostic or therapeutic procedures requiring the use of ICM, regardless of age.

1.3. Population not included

The document does not include pregnant or lactating women.

1.4. Clinical aspects

Recommendations regarding the definition, epidemiology and risk factors for the development of AKI-ICM. Renal protection strategies and risk scales that can be used in clinical practice are evaluated.

1.5. Users

General practitioners, specialists in internal medicine, nephrology, radiology, among others, and health professionals involved in the care of patients requiring the use of contrast media.

2. Methodology

The questions of interest were elaborated by the coordinating group formed by the presidents of the associations, a leader developer of the guide and two epidemiologists expert in the methodology; they were selected according to the needs based on the experience of the professionals expert in the subject, supported by the literature review carried out by the experts.

2.1. Development group

The coordinating group, formed by the president of the Asocolnef, the president of the ACR, a nephrologist-epidemiologist and two methodologists (clinical epidemiologists), developed the questions of interest. Ten specialists (five nephrologists, four radiologists and one pediatric nephrologist) were called, taking into account their clinical experience and academic trajectory; nine specialists (four nephrologists, four radiologists and one pediatric nephrologist) responded to the call and completed the review process. The participation of the different regions of Colombia was sought: Eje Cafetero, Eastern Region, Caribbean, Pacific and Central. All participants declared that they had no conflicts of interest.

2.2. Clinical questions

They were posed by the research group taking into account the disparity of concepts detected in the experience, the clinical relevance, the implications for patient safety, the existence of barriers to access to interventions or procedures and the optimization of health system resources. The questions with a summary of the answers given in the consensus are described in Annex A.

2.3. Search for evidence

An evaluation was made of reviews obtained from different search bases, such as PubMed, Scopus and Embase. The main keyword or word included in the title ("Kidney Diseases" [Mesh]) AND "Contrast Media" [Mesh] was used as the main keyword and the following filters were used: Full text, Meta- Analysis, Practice Guideline, Systematic Review, in the last 5 years, Humans, Adult: 19+ years. For Scopus, Embase and Scielo the following search strategy was used: TITLE ("Contrast-Induced Nephropathy") AND (LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013)) AND (LIMIT-TO (DOCTYPE , "review article") OR DOCTYPE "Research article" OR DOCTYPE ("Practice guidelines").

2.4. Screening and selection of the evidence

A total of 114 articles were identified and evaluated by title and abstract, independently, by two reviewers: one clinical and one methodological expert. Seventy articles were discarded because they did not meet the inclusion criteria for the review of reviews based on the AMSTAR-2 for systematic literature reviews, 7 were repeated between databases. Finally, 36 articles (Figure 1) were distributed among the reviewers. The articles reviewed are presented in Annex B.

2.5. Preliminary recommendations

With the articles collected and oriented by the research questions, a narrative synthesis was made for each question, making recommendations based on the conditions of clinical practice according to the experience of each clinical specialist.

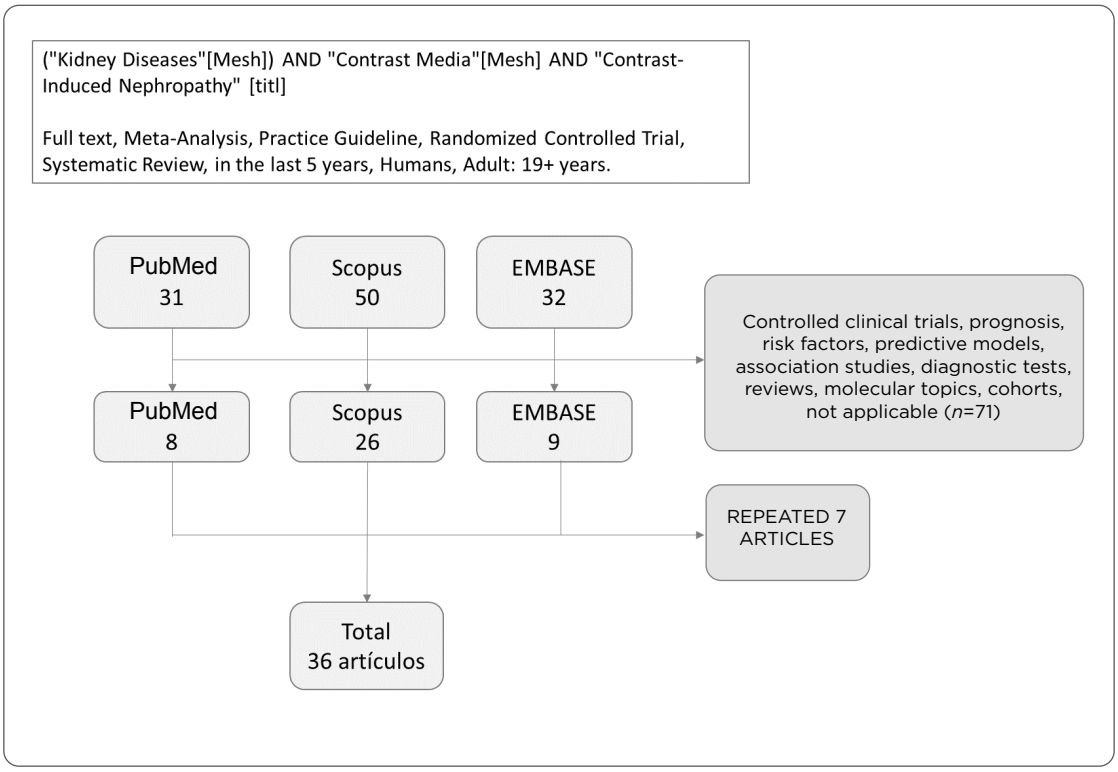
2.6 Formal expert consensus

The 36 articles were distributed among eight reviewers. Four articles with thematic relevance were identified and evaluated by all reviewers; the remaining 32 articles were distributed randomly. Once all the responses were received, the coordinating committee unified the responses by means of a narrative synthesis, which was initially delivered via e-mail to all the reviewers and subsequently meetings were held by means of video calls to make corrections and revisions to the document. Once the document was approved by all the specialists, a version was drafted and submitted for grammatical and stylistic correction; it was then reviewed by the consensus participants and, after taking into account the comments of the participants, the final revision of the document was made (Figure 2).

2.7. Grading of recommendations

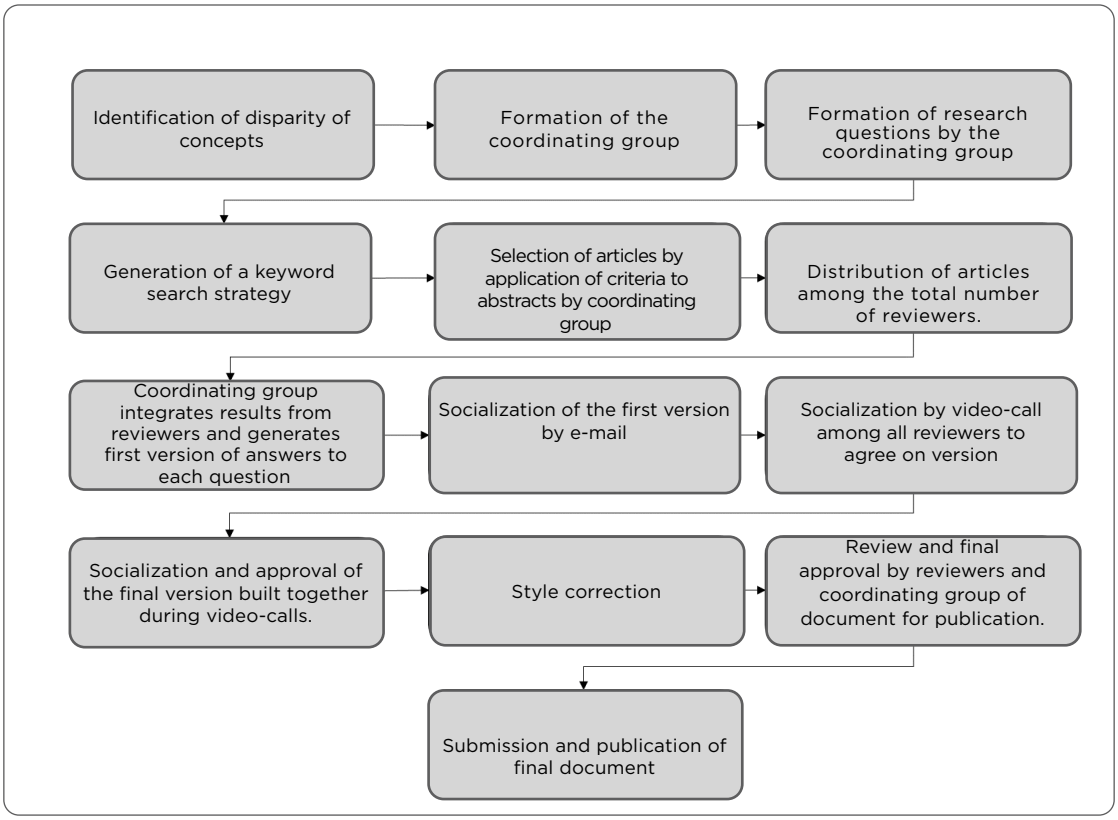
The coordinating group recorded the degree of acceptance of the specialists for each of the questions during the Delphy group discussions. The percentage of agreement among all participants was evaluated and recorded, which was 100% at the end of the discussions for each question.

Figure 1. Article selection process



Source: Authors' elaboration.

Figure 2. Document elaboration process



Source: Authors' elaboration.

3. Results

1. What is the definition of iodinated contrast media-induced nephropathy (ICN)?

Acute kidney injury (AKI) in patients exposed to iodinated contrast media (ICM) allowed us to infer a causal relationship: contrast media-development of AKI. Because of this, the term "contrast media-induced nephropathy" (CIN) was coined; however, this causality was not proven, so this definition was not in accordance with reality. Over time, different terms (based on multiple clinical and laboratory criteria) have been used to define renal injury that develops after the use of iodinated contrast media (ICM), absolute or relative (percentage) creatinine values and in some cases clinical variables such as changes in urinary volume, as well as a non-uniform timeline. On the other hand, in many cases the exclusion of another cause of AKI was required, which in clinical practice is unlikely.

The most relevant definitions include:

- Mehran et al. in 2004 defined it as an increase in serum creatinine (CrS) ≥ 0.5 mg/dL or ≥ 25 % within 48 h [1].
- The European Society of Urogenital Radiology (ESUR) in 2004 defined it as an increase in CrS > 0.5 mg/dL or > 25 % within 72 h [2].
- The Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2) in 2012 as an increase in CrS ≥ 0.5 mg/dL [3].
- The Improving Global Outcomes (KDIGO) - Clinical practice guideline for acute kidney injury, in 2021, as a low-grade, but steady increase in CrS over the course of several days (> 1.5 times baseline within 7 days), a sudden increase in CrS in the period immediately following exposure to iodinated ICM contrast medium (> 0.3 mg/dL within 48 h), and the development of oliguria (urine volume <0.5 mL/kg/h for ≥ 6 h) [4].

This heterogeneity in definitions is reflected in the very dissimilar results in clinical studies in fundamental aspects such as frequency of presentation, risk estimation, and contrast media-associated mortality.

Conclusion: The use of the term "iodinated contrast media-induced nephropathy" should be restricted only to those cases in which any other risk factor that may be involved in the development of acute kidney injury is exhaustively excluded, a fact that in clinical practice is not easily achievable, so its use is limited.

2. What is the definition of acute kidney injury associated with the use of iodinated contrast media (AKI-ICM)?

Acute kidney injury following ICM exposure, in patients in whom there are coexisting factors to which the development of AKI could be independently attributed: patient-related (age, chronic kidney disease [CKD], diabetes mellitus, and left ventricular dysfunction [LVdF], among others) and procedure-related factors (e.g., embolization of atheromatous material from the aorta during catheter manipulation, hypotension, and bleeding) [5].

The term association refers to the relationship between contrast medium exposure and the development of acute kidney injury, without necessarily implying causality. This term could be applied to those situations in which other causes of AKI cannot be conclusively excluded.

Conclusion: This Consensus recommends using the term "Acute kidney injury associated with the use of iodinated contrast media (AKI-ICM)" in those clinical scenarios in which any other risk factor that may be involved in the development of AKI coexists (Table 1).

3. What is the frequency of presentation of AKI-ICM?

The incidence of acute kidney injury following exposure to contrast media is difficult to determine. Heterogeneity in their definitions, the different physicochemical characteristics of ICM, the presence of multiple concomitant factors with nephrotoxic potential and the different routes of administration of ICM to patients explain the great variability in these results.

Early studies placed contrast media as the third cause of AKI in the in-hospital setting, surpassed only by hypovolemia and major surgery. These data were derived from hospital centers using hyperosmolar contrast media (no longer used today), did not take into account concomitant pathologies that trigger AKI, and the arterial route was the most commonly used [7]. Paradoxically, some studies found a lower risk of AKI with contrast medium compared to scans without contrast medium use, reflecting selection bias rather than any nephrotoxic effect derived from the contrast medium [8]. Making it even more difficult to determine the true frequency of AKI associated with the use of iodinated contrast media is the fact that more than a quarter of hospitalized patients may have serum creatinine elevations without exposure to ICM [9]. Bruce et al. in a study showed a high incidence of AKI among control subjects undergoing non-contrast computed tomography (CT). The incidence of serum creatinine elevation in this group was statistically similar to that of the group receiving isoosmolal contrast medium [10]. Another aspect that may explain the wide spectrum in the incidence data of AKI associated with ICM is the fact that patients who receive contrast media are generally sicker than those who do not; conversely, patients with decreased eGFR or who are perceived by their physicians to be at increased risk of AKI (elderly, baseline CKD or diabetes mellitus) may be less likely to undergo studies with iodinated contrast media [11]. In the largest study to date (5,922,537 patients), Wilhelm-Lee et al. evaluated the incidence of AKI post-administration of iodinated contrast media: patients who did and did not receive ICM developed AKI in 5.5 % vs. 5.6 %, respectively. This is associated with ICM administration with an OR for AKI of 0.93 (95 % CI, [0.88 to 0.97]) [12]. In this study, it is highly unlikely to conclude that ICM "protects" ICM-exposed patients from developing AKI. Rather, this

paradox could be explained by the fact that those patients whose physicians consider them to be at the greatest risk of AKI are treated in such a way as to minimize the perceived risk.

Rao and Newhouse [11], using the keywords contrast medium and renal failure, predetermining as a time limit the years 1996 to 2004, evaluated 3,081 articles, of which two facts were striking: only 40 (1.3%) included patients who received intravenous contrast media, while only two had control groups of patients who did not receive contrast media and were relatively small [13, 14], so that the data obtained from these were not derived from sources with a rigorous methodological design.

For ethical reasons, it is difficult to perform randomized clinical trials that allow establishing a causal relationship between exposure or intervention and outcome. Therefore, in order to control for confounding variables, propensity score studies have been developed. Propensity scores are a statistical tool to manage confounding bias, which will inevitably arise in observational epidemiological studies and, therefore, make it possible to obtain an identification of causal effects approximating (but not equal to) that achieved with randomized clinical trials (RCTs) [15]. It should be remembered that these studies only include known biases and covariates obtained from a database, which differentiates them from RCTs, in which unknown biases and confounding factors are taken into account. However, such studies have failed to demonstrate a conclusive causal relationship between the contrast medium and the development of AKI. Similarly, they also fail to demonstrate a higher incidence of AKI in patients exposed to contrast media compared to those who are not [8, 16].

All this evidence supports the fact that the causal relationship between ICM exposure and the development of AKI has not been consistently demonstrated, and that the perception of this risk has been overestimated for decades. Based on these findings, the American College of Radiology (ACR) and the National Kidney Foundation (NKF) in 2020 lowered the recommended level of caution for intravenous (IV) administration of ICM to patients with pre-existing CKD (eGFR < 30 mL/min/1.73 m^2) [17, 18].

Conclusion: The risk of AKI following ICM administration has been overestimated in the literature and exaggeratedly perceived by health care personnel, since the data derive from small, uncontrolled, non-randomized studies that did not take into account other confounding variables (ICM characteristics, comorbidities, baseline creatinine fluctuations, etc.). Additionally, a large number of well-controlled retrospective trials and meta-analyses involving a large number of individuals, in selected and unselected populations, have not found an independent association between the administration of intravenous (IV) ICM and the development of AKI-ICM, even in patients with advanced CKD (eGFR < 30 mL/min/1.73 m^2) and AKI in critically ill patients.

Table 1. Definition of terms

Term	Definition	Comment
Contrast-induced nephropathy (CIN)	Increase in absolute (> 0.5 mg/dL) or relative (> 25 %) serum creatinine (SCr) from baseline, after exposure to contrast medium [1].	Term coined in ancient literature. It implies unproven causality and non-uniform temporality (24-72 h).
Acute kidney injury (AKI)	Increased SCr ≥ 50% within 7 days or a sudden increase in SCr (> 0.3 mg/dL within 48 h), and the development of oliguria (urine volume < 0.5 mL/kg/h for ≥ 6 h) [4].	Global definition of acute kidney injury.
Post-contrast acute kidney injury	Acute kidney injury following exposure to iodinated contrast media [6].	It refers to chronology, not to a cause-effect relationship.
Contrast-induced acute kidney injury	Acute kidney injury following a contrast medium study to which the development of renal damage could be attributed. It is defined as a low-grade but steady increase in SCr over several days (> 1.5 times baseline within 7 days), a sudden increase in SCr in the immediate period following ICM exposure (> 0.3 mg/dL within 48 h), and the development of oliguria (urine volume < 0.5 mL/kg/h for ≥ 6 h). [4].	It is assumed that the contrast medium caused the renal injury without a proven causal relationship. To establish a causal link between contrast medium exposure and AKI, a detailed evaluation is necessary to rule out other potential causes of AKI. However, the failure to find an alternative etiology to ICM exposure in the development of AKI does not unequivocally establish causality.
Acute kidney injury associated with the use of contrast media (AKI-ICM)	Acute kidney injury following ICM exposure in patients with coexisting factors to which the development of AKI could be independently attributed: patient-related (age, chronic kidney disease [CKD], diabetes mellitus, and left ventricular dysfunction, among others) and procedure-related factors (e.g., embolization of atheromatous material from the aorta during catheter manipulation, hypotension, and bleeding) [5].	The term association refers to the relationship between exposure to iodinated contrast medium and the development of AKI without necessarily implying causality. This term could be applied to those situations in which other causes of AKI cannot be conclusively excluded.

Source: Authors' elaboration.

4. *Is there evidence to support the use of the absolute creatinine value as an isolated datum to define the use of an iodinated contrast medium?*

Creatinine is derived from creatine metabolism in skeletal muscle and dietary intake of meat and is released into the circulation at a relatively constant rate. Mean serum creatinine values differ between men and women, obese, low muscle mass or limb amputees (due to differences in muscle mass and thus creatinine generation) [19].

These factors lead to a large variability in creatinine values without them being directly related to glomerular filtration rate (GFR). Therefore, GFR estimation equations should be used from serum creatinine, rather than relying on the serum creatinine value. GFR estimation equations are more accurate and precise than the assessment of GFR from the exclusive measurement of creatinine. They also obviate the need for 24-hour urine creatinine clearance measurements. Serum creatinine should be obtained using a specific enzyme assay with calibration traceable to international standard reference materials and minimal bias compared to isotope dilution mass spectrometry (IDMS) reference methodology [20].

Conclusion: Serum creatinine as isolated data should not be used as a reference to determine the compromise of renal function; it is only one variable of the equation to estimate the glomerular filtration rate and based on the latter, the degree of compromise of renal function will be determined. This Consensus does not recommend the measurement of creatinine clearance in 24-hour urine.

5. *Which equation should be used to calculate the estimated glomerular filtration rate (eGFR) to determine a patient's risk of developing ARCI prior to injection?*

The Cockcroft-Gault equation was published in 1976 and has been traditionally used, especially to adjust drug dosage. To obtain this equation, a regression analysis was performed in which the serum concentration of creatinine, age and weight were included as variables. Its disadvantage is the laboratory method used for creatinine determination (Jaffé), which is greatly influenced by the extreme values of the weight and age variables, the assignment of an arbitrary value as a constant for the female sex, not taking into account body composition and overestimation of glomerular filtration rate (GFR) for values lower than 15 mL/min/ 1.73m2 [21].

The MDRD equation is the result of a retrospective analysis of the Modification of diet in renal disease study, whose purpose was to improve the Cockcroft-Gault formula by estimating the glomerular filtration rate (GFR) and not the clearance of able is r. The sample included adult patients, of both sexes, predominantly white, with baseline chronic kidney disease (CKD); 125I-iothalamate clearance was used as a measure of GFR. Six variables were analyzed: serum urea, creatinine and albumin concentrations, age, sex and ethnicity (MDRD-6) and included a multiple regression analysis [22]. The abbreviated version of four variables (MDRD-4) eliminated the need to use serum urea and albumin concentration, maintaining the same diagnostic efficacy as the original formula, but easier to apply [23]. Some of its limitations include: higher percentage of white individuals, without diabetes mellitus and with a glomerular filtration rate of less than 60 mL/min/1.73 m2. Its accuracy decreases linearly with increasing glomerular filtration rate, so it overestimates the prevalence of CKD, increasing the number of false positives [24].

The 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was developed using pooled data from 10 studies, subsequently validated with data derived from 16 additional studies, in which the gold standard was the direct measurement of glomerular filtration rate (GFR) using external filtration markers: iothalamate. The able population sample included individuals with and without kidney disease with large GFR heterogeneity. The 2009 CKDEPI equation was as accurate as the MDRD study equation among individuals with GFR less than 60 mL/min /1.73 m2 and somewhat more accurate in those with higher GFR [25].

The National Kidney Foundation (NKF) and the American Society of Nephrology (ASN) Task Force on Reevaluating the Inclusion of Race in the Diagnosis of Renal Disease have published their final report, which describes a new race-free approach to diagnosing kidney disease. In the report, the NKF-ASN Task Force recommends immediate adoption of the new creatinine eGFR 2021 CKD EPI creatinine equation that estimates renal function without a race variable [26].

Conclusion: This Consensus recommends able is the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021** equation, which does not include a race variable, to calculate estimated glomerular filtration rate (eGFR) for the population over 18 years of age. Taking into account that eGFR is the best general index of renal function, in the absence of a specific calculator for this equation, an alternative formula (CKD-EPI 2009, MDRD or C&G) can be used, since its results are more highly correlated with glomerular filtration rate than a creatinine value in isolation.

6. *What are the patient-related risk factors for developing AKI-ICM?*

Estimating the risk of developing AKI-ICM is critical to determine which patients are susceptible to preventable deterioration of renal function after ICM exposure.

Baseline renal function before ICM administration is the strongest predictor of GFR deterioration after ICM administration. In this regard, the presence of advanced CKD (eGFR <30 mL/min/1.73 m2) and AKI are the most relevant risk factors. Patient characteristics such as age, comorbidities such as diabetes, hypertension, hyperuricemia, low renal perfucion (reduced left ventricular ejection fraction, hypovolemia, diuretic use, dehydration), single kidney or renal transplantation have not been shown to be independent risk factors for eGFR [27].

**https://www.kidney.org/professionals/kdoqi/gfr_calculator

A propensity score study demonstrated that AKI following administration of low-osmolality intravenous ICM generally does not occur in patients with a GFR ≥ 45 mL/min/1.73 m2. Whereas in those with eGFR of 30 to 44 mL/min/1.73 m2 it occurred in 16 % of those who underwent CT with contrast, compared to 15 % of those who underwent CT without contrast (OR 1.22; 95 % CI [0.88-1.71]; p = 0.24). The picture changes dramatically in patients with eGFR <30 mL/min/1.73 m2, in whom ARL developed after CM in 35% of cases undergoing contrast-enhanced CT compared to 14% in those without ICM (OR 3.96; 95 % CI [1.29-12.21]; p = 0.016) [28]. These findings are similar to that evidenced by Davenport et al. who demonstrated an increased risk of AKI when stratified by eGFR (especially when eGFR ≤30 mL/min/1.73 m2) [16].

Conclusion: reduced baseline renal function, determined through an equation for calculating eGFR before ICM administration, is the only independent risk factor for the development of AKI-ICM. An eGFR <30 mL/min/1.73 m2 (high-risk patients) is the strongest predictor of development of AKI-ICM in patients undergoing intravascular studies with ICM.

7. What is the time range within which serum creatinine should be performed to be considered a valid and valid variable for eGFR calculation prior to ICM administration?

- **Ambulatory**

  For patients without a history of renal impairment or without intercurrent conditions that may modify eGFR (vomiting, diarrhea, fever, etc.), a creatinine performed within the last six weeks is considered acceptable. However, if there is a history of renal impairment and/or intercurrent conditions, then it would be more appropriate to reduce the interval to 72 hours, after resolution of the intercurrent condition.

- **Hospitalized**

  Creatinine processed within 24 hours prior to contrast exposure for updated eGFR calculation. However, if during hospitalization the patient presents with a potentially fatal condition, contrast study should not be delayed pending a serum creatinine; it should be performed immediately.

- **Emergencies**

  In this scenario, potentially fatal conditions are encountered, so studies or interventions should be performed immediately, regardless of the creatinine level. If the situation is not immediately life-threatening and allows creatinine measurement for eGFR determination, this could be done. However, a low eGFR should not be a limitation to perform the procedure, if the clinical condition indicates it.

- **Acute kidney injury**

  In patients with AKI, to determine the use of an IV or IA ICM, a strict analysis of the potential benefit/risk balance should be performed: if the benefit of an able diagnostic imaging or therapeutic intervention that limits or reverses a potentially fatal condition outweighs the risk of worsening AKI or of AKI developing into permanent or irreversible renal damage, the use of ICM is fully justified. Ehmann et al. designed an able to determine the association between IV ICM administration and persistent AKI in patients with pre-existing AKI. They performed a propensity-weighted, entropy-balanced, retrospective observational cohort analysis of hospitalized patients ≥ 18 years of age who met Kidney Disease Improving Global Outcomes (KDIGO) creatinine-based criteria for AKI on admission to one of three emergency departments between July 1, 2017 and June 30, 2021 who did or did not receive IV ICM. Outcomes included persistent AKI at hospital discharge and dialysis initiation within 180 days of index finding [19].
  Fourteen thousand four hundred forty-nine patients were included, of whom 12.8% were admitted to the intensive care unit (ICU). ICM was administered in 18.4 % of patients. AKI resolved before hospital discharge in 69.1 % of cases. No association was observed between IV ICM administration and persistent AKI afterwards. The unadjusted multivariable logistic regression model is (OR 1.0, 95 % CI [0.89-1.11]), propensity weighted (OR 0.93, 95 % CI [0.83-1.05]) and entropy balanced (OR 0.94, 95 % CI [0.83-1.05). Subgroup analysis in those admitted to the ICU yielded similar results. No association was observed between ICM administration and an increased risk of dialysis within 180 days (5.4 % of able patients). Additionally, ICM administration was not associated with persistent AKI in patients with community-acquired AKI and severe renal failure (eGFR <30 mL/min/1.73 m2) at the time of ED arrival (38 % of the cohort).

Conclusion: From this study it can be concluded that among patients with pre-existing AKI, ICM administration is not associated with persistent AKI at hospital discharge nor with an increased risk of dialysis initiation within 180 days. These findings are consistent for ED patients and for those with low eGFR (eGFR <30 mL/min/1.73 m2) and for those admitted to the ICU.

8. Do all ICMs have the same risk of producing AKI-ICM?

The most important physicochemical properties of contrast media are: iodine concentration (on which radio-opacity depends), molecular structure, osmolality and ionization.

Molecular structure is determined by the number of benzene rings: monomeric = 1 or dimeric = 2; while ionization refers to the dissociation capacity, being ionic or non-ionic. In relation to their osmolality (mOsm/kg), the first ICMs called high osmolality (HOCM), such as iothalamate and diatrizoate, consisted of monomeric ionic preparations with extremely high osmolalities (800-2,500 mOsm/kg) with respect to plasma (290 mOsm/kg). Because they were associated with a high risk of renal injury after contrast medium administration, ionic dimeric ICMs (ioxaglate) or nonionic monomers (iopromide, iopamidol, iohexol, ioversol, iomeprol, etc.) were developed, whose osmolalities were higher than those of plasma.), whose osmolalities were below hyperosmolar (~400-800 mOsm/kg), which is why they were called low osmolality ICMs (LOICMs), even though their osmolality was higher than that of plasma. Third-generation CMs (iodixanol and iotrolan) actually have a lower osmolality than plasma, which is why electrolytes are added to the solution used clinically to achieve plasma osmolality, which is why they are called isoosmolar (ICBM) [29, 30] (Table 2).

Lautin et al. demonstrated a clear benefit with the use of lower osmolality agents in a study in which the low osmolality ionic agent, ioxaglate, was less nephrotoxic than ionic hyperosmolar agents [31]. To resolve the question about the greater nephrotoxic potential among iso-osmolar ICMs compared with low-osmolality ICMs, Eng et al, conducted a meta-analysis involving 25 randomized trials comparing iodixanol (isoosmolal) with a group of various low-osmolality agents (most patients with CKD or diabetes), which reported a slight reduction in the risk of AKI-ICM (relative risk [RR] 0.80; 95 % CI [0.65-0.99]) with iodixanol [32]. However, despite their minimal statistical significance, these findings did not translate into a clear clinical benefit or difference in terms of risk of need for renal replacement therapy (RRT), cardiovascular outcomes, or death between the two groups.

On the other hand, the viscosity of an ICM could be of underestimated importance for renal safety, because like osmolality, high viscosity has been implicated in the pathophysiology of AKI-ICM. Viscosity depends on several factors: solvent (which in ICMs is water), molecular weight and size, molar concentration and temperature; it has a direct relationship with molecular size (hence monomeric ICMs have a lower viscosity than dimeric ones), whereas the relationship with osmolality and temperature is inverse [33]. The increased viscosity of an ICM favors its concentration in tubules and medullary vessels (due to the hyperosmolar environment), compromising blood flow and oxygen supply to the renal medulla; furthermore, glomerular filtration decreases due to congestion of the highly viscous tubular fluid [34].

Conclusion: The current data do not support the theory that all iso-osmolar media offer better results than low-osmolality media in terms of the risk of AKI-ICM. This Consensus recommends using iso-osmolal or low-osmolality media regardless of the patient's condition. Given the role of viscosity in the pathophysiology of AKI-ICM, it is recommended that ICM (not gadolinium-based) be prewarmed prior to administration.

9. *Does the route of administration of the contrast medium (intravenous, intra-arterial or percutaneous) modify the risk of developing AKI-ICM?*

Based on an anatomical substrate - proximity to the renal arteries - and pharmacokinetic aspects such as the dilution that the ICM may undergo in the bloodstream prior to contact with the renal vasculature, renal exposure to ICM can be classified into three categories: first-pass, second-pass and percutaneous renal exposure [35].

- First-pass renal exposure. Refers to the arrival of ICM into the renal arteries in a relatively pure (undiluted) form, due to the short distance between the injection site and the renal arteries. Procedures involving injection of ICM into the left ventricle, thoracic aorta, abdominal aorta above the origin of the renal arteries, and selectively into the renal arteries are examples of this category.

Table 2. Characteristics of contrast media

Compound	Ionicity	Structure	Osmolality (mOsm/kg)	Viscosity 20-25 °C (mPa.S)	Viscosity 37 °C (mPa.S)
High osmolality					
Diatrizoate	Ionic	Monomeric	1500-2000	3.3-16.4	1.4-19.5
Metrizoate	Ionic	Monomeric	2100	5-9	2.8-5
Iotalamate	Ionic	Monomeric	600-2400	2-9	1.5-5.0
Low osmolality					
Ioxaglate	Ionic	Dimeric	600	12-15.7	6-7.5
Iohexol	Non-ionic	Monomeric	322-844	2.3-20.4	1.5-10.4
Ioversol	Non-ionic	Monomeric	350-792	4.6-14.3	3.0-9.0
Iopamidol	Non-ionic	Monomeric	300-832	2.3-20.9	1.5-9.5
Iopromide	Non-ionic	Monomeric	340-880	2.3-22	1.2-12.3
Iopentol	Non-ionic	Monomeric	310-810	2.7-26.6	1.7-12.0
Iomeprol	Non-ionic	Monomeric	301-730	1.9-27.5	1.4-12.6
Isoomolals					
Iodixanol	Non-ionic	Dimeric	290	12.7-26.6	6.3-11.8
Iotrolan	Non-ionic	Dimeric	270-320	6.8-16.4	3.9-8.1

Source: Authors' elaboration.

- Second-passage renal exposure. Refers to the arrival of ICM in the renal arteries after being diluted by the circulation: through the right heart, pulmonary circulation or a systemic capillary bed. Examples of this type of renal exposure to ICM are: IV administration, injection of CM into the right ventricle and pulmonary arteries; as well as direct injection of CM into the coronary, carotid, subclavian, brachial and mesenteric arteries, as well as the infrarenal aorta and the iliac, femoral and crural arteries.

- Percutaneous procedures. Refers to minimally invasive image-guided interventions, which allow injection of the ICM by means of a skin puncture. Through this route it is possible to access vascular structures, percutaneous transluminal angioplasty, percutaneous coronary interventions, percutaneous transluminal coronary angioplasty, the biliary tract (percutaneous transhepatic cholangiography), endoscopic retrograde pancreatography cholangiography, the urinary tract (percutaneous antegrade urography), the intrathecal space or subarachnoid space, intraperitoneal and intraarticular. It is considered a second-pass type of renal exposure.

First-pass renal exposure to ICM has been described in the literature as higher risk for the development of AKI-ICM [36]; however, controversies exist in this regard-especially because of multiple confounding factors derived from patients' baseline comorbidities. In the context of therapeutic coronary angiography (not in the case of diagnostic coronary angiography), especially for acute myocardial infarction, an increased risk of AKI-ICM has been reported; however, the greater volume of contrast medium used in this type of procedure and the hemodynamic instability associated with acute myocardial infarction could explain this increased risk [37]. In cases of venous administration of ICM for CT, most studies have suggested a fairly low risk of AKI-ICM, even in patients with baseline CKD [38].

Conclusion: The use of ICM with first-pass renal exposure may be associated with an increased risk of developing AKI-CKD. Given the morbidity and mortality implications of AKI, this Consensus considers it reasonable to establish a higher cut-off point (eGFR < 45 mL/min/1.73 m2) than that established for second-pass arterial and intravenous procedures (eGFR < 30 mL/min/1.73 m2) to classify patients as being at high risk of developing AKI following ICM exposure.

Similarly, in high-risk patients, the Consensus suggests using alternative methods that do not require first-pass renal exposure to contrast media (e.g., echocardiogram instead of ventriculogram to assess ventricular ejection fraction [FEV]), as well as limiting the anatomical segments to be evaluated to those strictly necessary (infrapopliteal circulation if there is no clinical evidence of proximal involvement) and exploring other segments with methods that do not require contrast, such as segmental recordings of pulse volume (plethysmography), Doppler ultrasound, magnetic resonance angiography or CO2 angiography.

10. Is the volume of ICM used during a contrast media procedure a risk factor for the development of AKI associated with the use of contrast media?

The volume of ICM infused has been directly related in some studies to the risk of renal injury and depends on the route of administration. There is insufficient evidence that the volume of contrast modifies the risk when the IV route is used.

In patients undergoing coronary angiography, with compromised eGFR, an infused volume < 25 mL was associated with a 2 % increase in the risk of developing AKI, while a voumen > 125 was associated with a 19 % increase (p = 0.009) [39]. Similarly, in primary percutaneous coronary intervention for ST-segment elevation myocardial infarction-STEMI, higher contrast volume is associated with increased rate of AKI-MI and mortality; however, further studies are needed to determine whether limiting contrast volume would improve patient outcome [40].

Conclusion: The diagnostic and therapeutic benefit of an adequately contrasted procedure cannot be minimized. Therefore, once the need to perform such a study is established, the volume of ICM to be used should be determined based on the patient's weight (1-2 mL/kg, with a maximum dose of 300 mL), and not through equations that include creatinine or eGFR as variables, which allows obtaining high quality images in CT, and would avoid repeating the procedure with contrast medium, which would imply a greater volume of ICM applied to the patient. In the case of endovascular interventional procedures, the patient's benefit with such intervention should be prioritized in order to avoid greater morbidity and mortality, above the potential risk of AKI-ICM, for example, an acute coronary event.

11. Should scales to estimate the risk of developing AKI-ICM be used in the clinical setting?

In order to improve patient stratification, efforts have been made to develop predictive tools or risk scales to identify patients most likely to develop AKI-ICM. The variables included in these models are derived from already known risk factors - related to the patient, the procedure or the contrast medium - and some of these factors are common to all the scales (Table 3).

The discriminative capacity of these scales, measured through the C statistic or the area under the curve -the closer the value is to 1, the better the model is at correctly classifying the results-, reveals that some scales have demonstrated their superiority, Hitinder (0.84), Liu (0.773), Tziakas (0.741), when compared with more widely known and extensively used scales such as Mehran (0.67) or Bartholomew (0.589). Another important aspect is that most of these models have superior predictive capacity for dialysis requirement than for estimating the development of AKI-ICM.

One of the main criticisms of some of these models is that they cannot be used before the procedure because they use variables from the procedure itself-for example, contrast volume-which is fundamental in a predictive model. In addition, the complexity of the mathematical algorithms of

some of these tools means that specialized software or computer tools are required. In addition, it should be borne in mind that the data used for these scales were derived from patients undergoing arterial procedures, so they cannot be extrapolated to the venous route. In addition, the Latino population was not included in these studies.

The ideal characteristics of a predictive scale for the development of AKI-ICM are: high discriminative capacity in terms of C statistic (eC) or area under the curve (AUC), clinical or laboratory variables that can be obtained prior to the procedure, can be performed at the patient's bedside, does not require specialized software or hardware, differentiates the venous from the arterial route in its variables and can be validated with the specific population in which it is to be used.

Conclusion: Taking into account that predictive scales have been developed for arterial procedures, coronary procedures, this Consensus does not recommend the use of this type of scales to estimate the risk of developing AKI-ICM in procedures with IV contrast medium injection. The use of the BMC2 PCI Risk Calculator*** is recommended to estimate the risk of developing AKI-ICM (additionally it determines the risk of death, need for blood transfusion and dialysis requirement) in the setting of hemodynamic studies. The Consensus recognizes that this scale requires more variables than the other predictive scales; however, it allows calculations to be made without having all the variables. Likewise, it is essential to remember that this type of tool is a guide; therefore, the clinical analysis of the patient's own characteristics, comorbidities, potentially fatal conditions, etc., and the environment (scheduled vs. urgent procedures) should take precedence when deciding whether or not to perform the procedure with contrast medium.

12. Should any type of medication be discontinued before or after an ICM procedure?

A large percentage of patients undergoing ICM studies suffer from multiple underlying pathologies that require them to take medications chronically and uninterruptedly. It is common to ask about the interruption or continuation of these drugs before ICM injection and about the impact that these may have on their pharmacokinetics and pharmacodynamics. In relation to this question, in order to reach a conclusion, the potential benefit of these drugs on the underlying diseases and the effect in terms of morbidity and mortality that could result in case of discontinuation should be taken into account. Among the different drugs, the inhibitors of the renin-angiotensin-aldosterone system (iSRA): ACE inhibitors/ARA II, metformin and diuretics deserve a special analysis. No other drug has evidence to support discontinuing them before or after ICM exposure.

- **Metformin**

The risk of developing metformin-related lactic acidosis (MRLA) has been reported in the literature for some years. This can occur by three mechanisms: impaired clearance of metformin (acute and chronic renal failure), impaired tissue oxygenation (sepsis and hypovolemic septic shock) and impaired lactate metabolism (liver failure and alcohol abuse). ICMs do not have a direct effect on the risk of ALRM, and it is the presence of an episode of AKI-ICM following IV administration of CM that can lead to accumulation of this biguanide [46].

The incidence of acidosis with hyperlactacidemia in patients treated with metformin has been described as very low (frequency

Table 3. Evidence of risk scales

Author	Population	Variables	Statistic C/ Area under the curve
Mehran et al., 2004 [1]	(n=5,571) Percutaneous coronary intervention (PCI).	Sex, age, hematocrit, contrast volume, diabetes, hypotension, intra-aortic balloon pump use, heart failure, and eGFR.	0,67
Bartholomew et al., 2004 [41]	(n=20,479) Percutaneous coronary intervention (PCI).	eGFR < 60 mL/min, intra-aortic balloon pump (IABP) use, urgent PCI, diabetes, heart failure, hypotension, peripheral vascular disease, and contrast volume > 260 mL.	0,589
Hitinder et al., 2013 [42]	(n=68,773) Percutaneous coronary intervention (PCI).	Form of presentation (indication for PCI, timing of PCI, form of presentation: ischemic heart disease, cardiogenic shock, heart failure in the last two weeks, LV ejection fraction before PCI), diabetes mellitus, patient characteristics (age, weight, height), laboratory parameters (CK-MB, creatinine, hemoglobin, troponin I, troponin T).	0,84
Gao et al., 2014 [43]	(n=3,945) Coronary angiography/percutaneous coronary intervention (PCI).	Age > 60 years, arterial hypertension, acute myocardial infarction, heart failure, IABP use, eGFR and contrast volume (>100 mL).	0,76
Tziakas et al., 2014 [44]	(n=52,882) Percutaneous coronary intervention (PCI).	Preexistence of renal insufficiency, metformin use, previous PCI performance, peripheral artery disease, and contrast volume > 300.	0,741
Lin et al., 2017 [45]	(n=692) Percutaneous coronary intervention (PCI).	Age > 75 years, baseline serum creatinine greater than 1.5 mg/dL, arterial hypotension, and IABP use.	0,773

Source: Authors' elaboration.

*** https://bmc2.org/quality-improvement/risk-calculators/bmc2-pci-risk-calculator-death-transfusion-and-cin

<1/10,000) and has been mostly related to acute renal impairment [47]. However, some authors report that this incidence may be higher (4.3 events per 100,000 patients per year), with a case fatality ranging from 30-50%, and the main risk factors are acute renal failure and chronic hypoxemic states [48]. Multiple studies and meta-analyses have shown that the risk of lactic acidosis is more related to the underlying disease and possible comorbidities than to the use of metformin [49]. It is important to note that metformin use in patients with eGFR 30-59 mL/min/1.73 m2 is considered safe if doses are appropriately reduced [50, 51].

Conclusion: This Consensus recommends not suspending metformin use and continuing its intake at the eGFR-adjusted dose and on the usual schedule in patients not classified as high risk (eGFR > 30 mL/min/1.73 m2) or without evidence of AKI receiving intravenous or intra-arterial ICM with second-pass renal exposure.

In patients with eGFR < 30 mL/min/1.73 m2 receiving IV or IA ICM with first- and second-pass renal exposure or in the presence of AKI, the Consensus recommends discontinuing metformin prior to ICM injection and restarting it after at least 48 hours, only if renal function remains stable (< 25% increase from baseline creatinine) and continuing its use if the clinical condition warrants.

- **Renin-angiotensin-aldosterone system inhibitors (RASI), angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor antagonists (ARA II).**

The iSRA, ACEI and ARA-II were the first drugs to demonstrate efficacy in reducing proteinuria and delaying the progression of CKD; therefore, the main clinical practice guidelines recommend the use of iSRA as a first-line pharmacological strategy for patients with CKD -regardless of its clinical stages- and range of proteinuria. However, its use is restricted in the real world in the setting of severely reduced renal function with or without diabetes, due to a potential increased risk of hyperkalemia and hemodynamic effects leading to AKI or exacerbation of baseline CKD [52].

Several observational studies investigated the role of continuing vs. discontinuing iSRA therapy in patients with advanced CKD already receiving iSRA inhibition, focusing on renal and cardiovascular outcomes [53]. Some authors have shown that discontinuation of an ACEI or an ARB-II in patients with advanced CKD was associated with an increased risk of mortality and end-stage renal disease (HR, 1.59; 95 % CI [1.48-1.71]) [54-56]. Similarly, continuous iSRA therapy has been shown to be significantly and independently associated with a lower incidence of unplanned dialysis initiation [57]. These data could be extrapolated to the CKD population undergoing ICM studies. In relation to iSRAs and ICM exposure, Whiting et al [58], in a systematic review and meta-analysis (n = 1663), three randomized controlled trials (RCTs) and three prospective cohort studies, analyzed the effect of discontinuing ACEI/ARA II before coronary angiography. This meta-analysis reported that discontinuation of ACEI/ARA II did not reduce the risk of AKI-ICM (RR 1.48, 95 % CI [0.84-2.60]). Current evidence suggests that there is no significant benefit of discontinuing ACEI/ARA II before contrast medium injection in CKD patient, so it is reasonable to use these agents in advanced CKD patients exposed to CM. Additionally, the advance of potassium-binding therapy has led to improved tolerability of renin-angiotensin-aldosterone system inhibition in the setting of advanced CKD.

Conclusion: This Consensus does not recommend discontinuation of ACEIs or ARBs before or after administration of an ICM for diagnostic and/or therapeutic procedures, if they are fully indicated for the patient's clinical condition.

- **Diuretics**

Patients who chronically require diuretics have basic difficulties in maintaining an adequate balance between fluid intake and output, which allows them to have an optimal euvolemic state. In this scenario, two sides of the coin are faced: on the one hand, volume depletion in patients receiving diuretics theoretically could make them more susceptible to develop AKI-ICM; on the other hand, there are obvious risks in discontinuing diuretics in patients who require them to maintain euvolemia, as fluid overload may be precipitated [59]. Although some studies have linked diuretic use as a risk factor for AKI-ICM [16], a causal relationship has not been clearly established.

Conclusion: This Consensus does not recommend discontinuing diuretics before or after ICM injection for diagnostic and/or therapeutic procedures regardless of the route (venous or arterial).

Their requirement should be determined and the dose should be guided, based on the patient's fluid intake and output, in order to achieve an optimal euvolemic state. Likewise, in view of other medications, this Consensus does not recommend discontinuing any other medication that a patient receives on a regular basis for the management of his or her underlying pathologies.

13. What is the definition of nephroprotection?

The experimental demonstration that angiotensin II blockade with ACE inhibitors slows the progressive loss of renal function - in a series of animal models of renal disease, including diabetic nephropathy - provided the opportunity, for the first time, to design a treatment strategy that was not limited to accompanying the patient; thus the concept of nephroprotection has emerged [60]. Evidence from both experimental studies and clinical trials suggests that, in clinical practice-at best-postponement of end-stage renal disease is achieved for a few years and not avoidance of dialysis for most patients during their lifetime [61].

The holistic definition of nephroprotection, ideally, should encompass the entire continuum of the clinical horizon of kidney disease: its precursor conditions -before its onset-, when it is fully established, when it is a candidate for renal replacement therapy (RRT) and even during complications and fatal outcomes. From this perspective, it is not only limited to applying strategies aimed at preventing the onset and progression of the disease, but is also oriented to the management of complications and the avoidance of death.

Conclusion: The term nephroprotection is defined as: "The set of collective and individual preventive and therapeutic interventions aimed at identifying individuals susceptible to some type of renal impairment, avoiding the onset of renal function deterioration in the population at risk, limiting renal damage and delaying its progression to established chronic kidney disease, increasing the time to renal replacement therapy (RRT) or reducing its need, avoiding possible complications and sequelae, and avoiding fatal outcomes".

14. What are the nephroprotective measures that can be used to reduce the risk of developing AKI associated with the use of contrast media in high-risk patients?

Given that the sine qua non condition for the development of IRAC-ICM is exposure to ICM, it would seem reasonable that the non-use of ICM in high-risk patients (eGFR < 30 mL/min/1.73 m2 by any route and eGFR < 45 mL/min/1.73 m2 for first-pass renal exposure to CM) would be the ideal measure to avoid acute kidney injury associated with the use of contrast media. Based on this premise, the first question to be answered is whether the performance of the study or intervention is strictly necessary or whether there is an alternative method that does not use ICM (gadolinium-based contrast media [GBCM]) or any other diagnostic modality that can be offered to patients.

Many pharmacologic strategies have been used with the goal of preventing AKI in patients undergoing radiologic procedures with ICM. Most of these therapies have been derived from laboratory-derived knowledge of pathophysiologic mechanisms.

- **Hydration**

  Hydration has been the most widely used prophylactic strategy in the prevention of AKI-ICM. This strategy theoretically has the ability to dilute high concentrations of toxic substances, which avoids prolonged contact of the ICM with the tubule epithelium and ensures adequate blood flow to the medulla. However, its role is questioned, as it has been evidenced that the nephroprotective effect may have been related to a reduction of hypotensive episodes with intravenous fluids rather than reflecting a direct protective role against AKI-ICM in all high-risk groups [37]. There is no robust evidence in favor of oral hydration, despite two studies suggesting some benefit with its use [62, 63]. Regarding the type of hydration (saline vs. bicarbonate), bicarbonate does not provide any additional benefit to saline; moreover, it needs to be prepared, is more expensive and has a higher risk of side effects [64]. Muller et al. found that AKI-ICM was significantly reduced with 0.9 % saline (0.7 %; 95 % CI [0.1-1.4]) versus 0.45 % saline (2.0 %; 95 % CI [0.0-3.1]) (p = 0.04). However, this benefit was not as evident in patients with significant eGFR compromise, precisely the group with the highest risk of AKI-ICM [65].

Conclusion: Current evidence shows no benefit of IV hydration compared to no hydration in patients with eGFR > 30 mL/min/1.73 m2. In this regard, this Consensus recommends hydration prior to ICM injection via IV or via IA with second-pass renal exposure in patients with eGFR ≤ 30 mL/ min/1.73 m2. For patients who are going to undergo procedures with first-pass renal exposure, the Consensus considers it reasonable to institute hydration with eGFR ≤ 45 mL/min/1.73 m2, despite not against conclusive evidence, given the potential benefit and low risk of complications.

This Consensus does not suggest specific formulas to determine the volume of fluids to be used, since the aim is to prevent the patient from being exposed to ICM under conditions of dehydration (without reaching overhydration) and this, in turn, depends on the conditions of each patient. For the hydration protocol, the use of normal saline is recommended.

A summary of the most relevant studies can be seen in Table 4.

- **N-acetylcysteine**

  Since reactive oxygen species and free radicals have been implicated in the pathophysiology of AKI-ICM, antioxidant agents with the ability to neutralize these molecules have been envisioned as a preventive option. N-acetylcysteine (NAC) has the ability to increase oxidonitric-synthetase activity, increase levels of S-nitrosothiol (a molecule that acts as a free radical acceptor), and buffer metabolites involved in metabolic pathways leading to cell death caused by ischemia and apoptosis [72].

  Numerous studies have been conducted with the aim of evaluating the efficacy of this drug, with initially promising results, which were diluted over time when studies with a more rigorous methodological design and a larger number of participants were performed. In fact, large trials (n > 500) have been more homogeneous and do not show a benefit of NAC in the prevention of AKI-ICM [73].

  Meta-analyses show contradictory results on the theoretical benefit of NAC in the prevention of AKI-ICM. Similarly, the marked heterogeneity among the studies included in those, publication biases and small study effects do not allow conclusions to be drawn [30, 74-76]. Additionally, there are reports that NAC may artificially reduce measured serum creatinine without actually reflecting an improvement in renal function. This phenomenon would be directly related to its potential ability to interfere with the in vitro measurement technique [77]. Such a phenomenon would have a profound effect on clinical outcomes, especially in the AKI-ICM trials, in which the potential benefit of NAC as a preventive measure was measured based on a change in creatinine as an outcome, and not on clinical outcomes such as the need for dialysis or death. McCudden et al. evidenced that very high concentrations (>400 µg/mL) of NAC result in a significant negative bias (>10%) for the enzymatic method in creatinine measurement. No interference is observed with the Jaffe method, nor with other measures of renal function such as cystatin-C and trace protein beta [78]. Another aspect to consider regarding this molecule is that it can be associated with serious adverse events, such as anaphylactoid reactions, when used by IV [79]. Weisbord et al. conducted the largest randomized controlled study with the largest number of patients to date, in which they compared oral N-acetylcysteine vs. placebo: they found similar rates of AKI-ICM: 9.1 vs. 8.7 % (OR 1.06; 95 % CI [0.87-1.28]; p = 0.58); need for dialysis at 90 days: 1.2 vs. 1.2 (OR 0.97; 95 % CI [0.58-1.60]; p = 0.90) or persistent renal failure at 90 days: 1.0 % vs. 1.1 % (OR 0.96; 95 % CI [0.56-1.66]; p = 0.89) and death: 2.7 % vs. 2.4 % (OR 1.10; 95 % CI

[0.78-1.57]; p = 0.59). They concluded that among patients at high risk for renal complications who underwent angiography there was no benefit of oral N-acetylcysteine over placebo for the prevention of death, need for dialysis or persistent decline in renal function at 90 days or for the prevention of AKI-ICM [64]. Magner et al. produced a meta-analysis of 101 randomized clinical trials, showing that NAC was associated with prevention of AKI-ICM when all studies were considered together, using either a fixed-effects regression model or a random-effects analysis; however, substantial statistical heterogeneity and publication bias existed, undermining the validity of these pooled estimates. When we restricted the analysis to trials with a larger sample size-i.e., trials with a sample size greater than 500 or event rates greater than 100-or analyzed trials with clinical, not biochemical, outcomes, these problems were reduced and a null effect on the prevention of AKI-ICM was achieved [73].

Table 4. Summary of articles on nephroprotection measures

Study	Study Design	Results	Analysis
Solomon et al. (1994) [66]	*n* = 78. Patients with baseline CKD undergoing coronary angiography who received 0.45% saline vs. 0.45% saline + furosemide vs. 0.45% saline + mannitol.	Higher incidence of nephropathy in those who received mannitol and furosemide with respect to those who received hydration alone (28 %, 40 % and 11 %; *p* = 0.05).	No control group.
Mueller et al. (2002) [65]	*n* = 1.620. Patients undergoing angiography + stenting, who received normal saline (0.9 %) vs. hypotonic saline (0.45 %) + glucose 5 %, infused at a rate of 1 cm3/kg/hour for 24 hours prior to the procedure.	*Lower elevation of creatinine levels at 48 hours in the group that received normal saline (0.7 % vs. 2.0 %; p* = 0,04).	Very similar mean creatinine concentration in the two groups (0.92 mg/dL 0.9 % vs. 0.93 mg/dL 0.45 %); moreover, considering the low-risk population included in the study, the impact of the two therapies could not be adequately assessed.
Merten et al. (2004) [67]	*n* = 119. Patients scheduled for radiological procedures with iopamidol (mean creatinine 1.8 mg/dL), in two groups to receive 154 mEq/l bicarbonate vs. 0.9% saline (NSS) at 3 mL/kg one hour prior to media application and 1 mL/kg/hr for six hours post-media	Increased serum creatinine above 25 % (1.7 % vs. 13.6 %) bicarbonate group vs. NSS 0.9 % (OR 0.88; 95 % CI [0.79-0.97]) in the normal saline group (*p* = 0.02).	They concluded that hydration with sodium bicarbonate is more effective than hydration with normal saline. However, some aspects of the methodological design of the study and its early termination do not allow recommendations to be obtained in this regard.
Hiremath et al. (2013) [68]	n = 513. Included six studies, systematic review and meta-analysis of randomized trials with stratified analysis and meta-regression. Comparison of oral vs. intravenous volume	Summary OR was 1.19 (95 % CI [0.46-3.10]; *p* = 0.73), suggesting no difference between the two routes of volume expansion.	The oral route may be as effective as the intravenous route for volume expansion for the prevention of contrast-induced acute kidney injury.
Nijssen et al. (AMACING, 2017) [69]	*n* = 660. Patients with eGFR of 30-59 mL per minute/1.73 m2, aged 18 years or older, undergoing an elective procedure requiring administration of intra-arterial or venous iodinated contrast material, were randomized (1:1) to receive NaCl 0.9 % or no prophylaxis..	Contrast-induced nephropathy was recorded in eight (2.6 %) of 307 non-hydrated patients and in eight (2.7 %) of 296 hydrated patients (95 % CI [-2.25 to 2.06]; *p* = 0.4710).	No differences were found between hydration and non-hydration. The population was not at high risk for AKI-ICM (eGFR > 30 mL/min), only 48 % of the procedures involved intra-arterial contrast administration, and 65 % had only mild chronic kidney disease.
Weisbord et al. (PRESERVE, 2018) [64]	*n* = 4.993. Patients at high risk for renal complications scheduled for angiography to receive intravenous sodium bicarbonate 1.26 % or intravenous sodium chloride 0.9 %.	The primary endpoint occurred in 110 of 2,511 patients (4.4 %) in the sodium bicarbonate group compared with 116 of 2,482 (4.7 %) in the sodium chloride group (OR, 0.93; 95 % CI [0.72-1.22]; *p* = 0.62).	There was no significant difference between groups in rates of contrast-associated acute kidney injury: bicarbonate not superior to saline.
Liu et al. (2019) [70]	*n* =1074. Three moderate-quality trials comparing hydration vs. no hydration were included.	Intravenous hydration significantly reduced the incidence of CIN by 42 % (RR 0.58, 95 % CI [0.45-0.74]; *p* < 0.001). The estimated effects on all-cause mortality (RR 0.56; 95 % CI [0.30-1.02]; p = 0.057) and need for dialysis (RR 0.52; 95 % CI [0.14-1.88]; *p* = 0.462) were not statistically significant.	Intravenous hydration is likely to reduce the incidence of CIN in patients with STEMI (segmental elevation myocardial infarction) undergoing primary PCI. However, for key clinical outcomes such as mortality, heart failure, and dialysis, the effect estimates were imprecise.
Timal et al. (KOMPAS, 2020) [71]	n = 523. Pacientes con ERC en estadio 3 fueron aleatorizados en una proporción de 1:1 para no recibir prehidratación o prehidratación con 250 mL de bicarbonato de sodio al 1,4 % administrado en una perfusión, 1 hora antes de someterse a una TAC electiva con medio de contraste.	Postcontrast acute kidney injury occurred in 11 patients (2.1 %), including 7 of 262 (2.7 %) in the nonprehydration group and 4 of 261 (1.5 %) in the prehydration group, resulting in a relative risk of 1.7 (95 % CI [0.5- 5.9]; p = 0.36).	Like Nijssen et al. in 2017, they support nonhydration in patients with eGFR>30 mL/min.

Source: Authors' elaboration.

Conclusion: There is no evidence to support the use of Nacetylcysteine as a prophylactic measure for the prevention of AKI-ICM, so this Consensus does not recommend its use.

- **Statins**

  There is no clear mechanism to explain the potential nephroprotective role of statins in the prevention of AKI-ICM. The current evidence is inconclusive and in some cases even contradictory. Trials demonstrating a probable role in reducing renal injury following exposure to contrast medium have been performed in patients undergoing coronary angiography, who are at high cardiovascular risk and statins are commonly part of their baseline pharmacological management [80-82]. Similarly, other authors such as Toso et al. evidenced that a short-term administration of high-dose atorvastatin before and after contrast medium exposure, in addition to standard intravenous hydration and oral N-acetylcysteine, does not decrease the occurrence of AKI-ICM in patients with pre-existing CKD [83]. These findings are consistent with those found in a meta-analysis of eight studies (n = 5,024) conducted by Subramanian et al. in which no conclusive benefit of administering statins plus intravenous saline compared with saline alone was established (RR 0.68; CI [0.39-1.20]) [84].

Conclusion: This Consensus does not recommend the use of statin as a preventive measure for the development of AKI-ICM.

- **Other drugs**

  Multiple drugs have been postulated and evaluated in studies as potential molecules with the ability to prevent AKI-ICM; although some of these trials report a small benefit, these included small numbers of participants and unclear benefit in clinical outcomes. Unless randomized clinical trials (RCTs) are developed that include representative samples and show some clinical benefit, the use of these agents for the prevention of AKI-ICM will not have a strong level of evidence to recommend them for routine use in clinical settings. These molecules could include: theophylline [85], ascorbic acid[86], trimetazidine [87], allopurinol [88], prostaglandin E1 [89], phenoldopam [90], alpha tocopherol [91], nicorandil [92], natriuretic peptides [81], mannitol or diuretics [66, 93] or dopamine [94].

Conclusion: Current evidence does not support the use of the following drugs as a preventive measure for the development of AKI-ICM: theophylline, ascorbic acid, trimetazidine, allopurinol, prostaglandin E1, fenoldopam, alpha-tocopherol, nicorandil, natriuretic peptides, mannitol, diuretics or dopamine. This Consensus does not recommend their use as a preventive measure for the development of AKI-ICM.

15. Is there evidence for the role of herbal medicine or the use of medicinal plants in the prevention of AKI-CKD?

Based on the significant role of oxidative stress in the pathophysiology of AKI-IBM, different traditional herbal antioxidants (polyphenols and carotenoids are the largest groups of herbal antioxidant compounds) have been used for the prevention of AKI-IBM in different in vitro studies, animal models and humans. Well-known medicinal plants, such as ginger (Zingiber officinale) [95], tea (Camellia sinensis) [96], Asian red sage (Salvia miltiorrhiza)[97], silymarin [98], turmeric or turmeric (Curcuma longa) [99], resveratrol [100] and thymoquinone [101], have been examined. However, the scarce representation of these works in humans, their in vitro design and in animal models, do not provide sufficient evidence to recommend their use.

Conclusion: There is currently no evidence to support the use of herbal preparations as a preventive measure for the development of AKI-CML.

16. Does postcontrast injection RRT have any benefit as a preventive measure to reduce the risk of developing AKI-ICM?

Extracorporeal clearance techniques, such as hemodialysis (HD) and hemofiltration (HF), have been evaluated as preventive measures for the development of AKI-ICM. ICMs have a relatively small size, which, together with their lack of protein binding, make them amenable to removal from the circulation with these techniques. The use of TRR for the prevention of AKI-ICM, from a theoretical point of view, is based precisely on this ability to remove MC from the circulation and thus avoid their interaction with the kidney. However, it is unlikely that these techniques avoid such contact with the renal parenchyma, since few cardiac cycles are required for the MC to be distributed throughout the organism, once they are injected into the bloodstream. Another theoretical reason why RRT might provide a benefit in the prevention of AKI-ICM is related to the potential volume burden associated with CMs. However, some studies demonstrate that the increase in extracellular volume after a typical contrast load is minimal [102].

One of the objectives of instituting nephroprotective measures in patients at high risk of developing AKI-ICM is precisely to avoid the need for RRT, so it is not consistent to use this type of procedure as a preventive measure. In addition, these extracorporeal therapies reduce serum creatinine levels, a variable that is evaluated in most trials as an outcome to determine the impact of a nephroprotection strategy, so it could provide data on a false benefit. Finally, RRT is not free of complications (bleeding, hemodynamic instability, infections, etc.), so the risk outweighs the benefit.

To evaluate the efficacy of prophylactic RRT after contrast medium exposure, Cruz et al. in a systematic review and meta-analysis pooled the results of nine randomized controlled studies (RCTs) and two non-RCTs (n = 1,010). Eight studies used standard HD, while three studies used continuous modalities. The authors found no significant difference in the incidence of AKI-ICM between patients who underwent HD and HF vs. those with standard medical therapy (RR 1.02, 95 % CI [0.54-1.93]). Furthermore, HD did not offer significant advantages over standard treatment in terms of long-term dialysis requirements and mortality [103]. Regarding automated peritoneal dialysis (APD)

and continuous ambulatory peritoneal dialysis (CAPD), although they have been shown to be effective in removing contrast medium (with lower efficiency than HD), their use has no impact on the development of AKI-ICM [104].

Finally, a clear benefit of HD immediately after ICM injection could not be demonstrated, since, despite the fact that the concentration of CM can be effectively reduced by HD, HD offers no protection for the development of AKI-ICM [105].

Conclusion: This Consensus does not recommend the use of HD-type RRT or continuous slow therapies or peritoneal dialysis in any of its modalities (APD or CAPD), as a strategy for the prevention of the development of AKI-ICM. Additionally, in patients with baseline CKD who are enrolled in a program of chronic intermittent HD or continuous ambulatory peritoneal dialysis, the use of HD immediately after the injection of CM is not supported by current evidence, so the scheduled times for HD sessions or previously established peritoneal fluid exchanges should not be modified, except in those patients with volume overload at the time of contrast medium administration.

17. Does the presence of residual renal function (RRF) in patients with stage 5 CKD on RRT modify nephroprotective strategies?

Historically, it has been estimated that ICM could reduce the RRF available to some patients on HD type RRT or peritoneal dialysis (PD). This fact is of radical importance, since in this population (mainly in HD) RRF has been considered an important factor for the effective elimination of small and medium molecules, fluid management and optimization of nutritional status, including phosphorus and potassium management -independent of GFR which is already below 15 mL/min-. Additionally, it has been associated in some studies with improved patient survival and quality of life [106-108]. This has traditionally led to the use of residual urine volume (urine output > 100 mL/24 h) as a criterion for non-use -if RRF is present- or use -if RRF is absent- of ICM in this group of patients.

In a systematic review (nine studies) and meta-analysis (seven studies) including 434 patients by Oloko et al [109], analyzing as the main outcome the change in RRF in dialysis patients who have been administered an intravascular ICM, they found a weighted difference in means of -0.16 mL/min/1.73 m2 (95 % CI [-0.66-0.34 mL/min]; p = 0.53), suggesting a small reduction in RRF after administration of a contrast medium. They concluded that IV-administered ICMs may not result in a significant reduction in residual function in dialysis patients. However, significant heterogeneity was observed in the data, with a Cochran Q of 35.83 and an I2 of 83.25 ($p < 0.0001$), which does not allow us to make any conclusions based on these results.

When ICM is chosen in patients with stage 5 CKD, it is because a situation is faced in which there is no diagnostic or therapeutic alternative other than that requiring ICM (for example, coronary angiography); or there is an imminent fatal risk, so its use would be fully justified. In other scenarios, where procedures are scheduled and the pathological condition is not immediately life-threatening, the importance of RRF should be taken into account and other diagnostic alternatives that do not use ICM should be considered, with good diagnostic performance that allows adequate interpretation of the results.

Conclusion: Preservation of residual renal function (RRF: urine volume > 100 mL /24 h) is an objective that should be taken into account in patients with HD or DFP type RRT, since it improves the results in terms of morbidity and mortality. Therefore, other diagnostic alternatives that do not use ICM, and that do not imply a risk of reducing RRF in this population-for example, ultrasound or MRI-should be considered. In case it is decided to use ICM, due to a potentially fatal condition or that there is no alternative diagnostic modality, the recommended doses should be used, in an attempt to avoid results with poor diagnostic capacity that do not allow therapeutic behaviors to be taken or that force the procedure to be repeated, leading to a higher dosage of ICM.

18. Does the administration of repeated doses of ICM in patients at high risk of developing AKI-ICM require a minimum time interval between the first and subsequent procedures?

Considering that the risk of AKI following ICM exposure is directly related to the presence of ICM in the bloodstream, it follows that repeat studies confer an increased risk of developing AKI-ICM. Two studies have demonstrated its occurrence in patients who received a second dose of ICM for contrast media imaging.

Abujudeh et al [110] performed 328 contrast media CT scans (two in each patient), with an average interval of 11.4 hours. Of these, 21 (12.8 %) developed AKI-ICM. When comparing patients with and without AKI-ICM, the only statistically significant risk factor was an increase in serum creatinine between the first and second CT, with an OR 18 ($p < 0.0005$). Subsequently, Trivedi et al [111] subjected 28 subjects to a second CT scan with contrast medium after a mean interval of 20 ± 13 days. A significant increase in serum creatinine before vs. after ICM application (0.86 ± 0.15 vs. 0.93 ± 0.14 mg/dL, $p = 0.027$); and a decrease in eGFR (89.8 ± 13 vs. eGFR 83.9 ± 13.5 mL/min/1.73 m2, $p = 0.028$) was evident. Four subjects (14.3 %) developed AKI-ICM, suggesting an increased risk with repeated studies. None of these studies specifically evaluated whether the risk of AKI-ICM was increased in relation to having had a single contrast exposure or none at all.

Conclusion: This Consensus considers it reasonable to avoid repeated exposures to contrast media for less than 48 hours for elective procedures in patients at high risk for AKI-ICM (eGFR ≤ 30, AKI or IV administration of high volumes of ICM). Repeat doses should not be limited in lower-risk patients (eGFR ≥ 30, no AKI or IV route) when there is a justified need for a repeat procedure. Similarly, in the face of potentially fatal disease, a repeat dose of ICM is fully justified regardless of the time elapsed between one procedure and another, in order to establish a diagnosis and therapeutic conduct.

19. Is the use of ICM contraindicated in renal transplant patients?

Lee et al [112] evaluated 641 renal transplant recipients and found an incidence of AKI following the use of contrast media of 2.8% vs. 0.9 % in patients without kidney transplantation (p = <0.01); additionally, baseline warfarin use with an OR 4.73 [(1.62-13.8]; p = 0.03) and poor allograft function (eGFR < 60 mL/min) with an OR 4.04 (95 % CI [1.12-14.5]; p = < 0.01) were significantly associated with an increased risk of AKI-ICM. Based on propensity scores, they concluded that they found no increased risk of developing AKI-ICM in renal transplant recipients undergoing peripheral vascular interventions compared to patients without kidney transplantation, moreover, the incidence was very low (2.8 %) and with no impact on survival.

Conclusion: ICMs can be used in the renal transplant patient at doses recommended for non-transplanted individuals, given that the risk of AKI-ICM in renal transplant recipients does not differ significantly from the general population. eGFR continues to be the most important risk factor for the development of AKI-CKD in this population group.

20. Do patients at high risk for the development of AKI-ICM undergoing contrast media studies require any type of follow-up after the injection of the medium?

There are no studies evaluating the need for follow-up of patients exposed to ICM, so any recommendation on respect is derived from current knowledge of the kinetic behavior of creatinine and the clinical horizon of AKI-ICM. To issue any recommendation on serum creatinine measurement it is imperative to take into account that serum creatinine elevation occurs within 24-48 hours after ICM exposure and that peak creatinine occurs within 3-5 days after ICM application [113].

Conclusion: Given that patients with eGFR <30 mL/ min/1.73 m2 or AKI are considered at high risk for developing AKI-ICM, this Consensus recommends performing a follow-up serum creatinine measurement 24 hours after ICM injection, regardless of the route of administration (IV or IA). This same recommendation applies for patients undergoing first-pass renal exposure to ICM with eGFR < 45 mL/min/1.73 m2.

Since patients with eGFR >30 mL/min/1.73 m2 are at low risk of developing AKI-ICM, the Consensus does not recommend measurement of a follow-up serum creatinine in this group. However, all patients who have been exposed to an ICM-regardless of their eGFR-for diagnostic or therapeutic interventions by any route should be instructed to consult the emergency department in case of any signs or symptoms suggestive of AKI development in the days following injection of the CM: decrease in the volume of urine excreted, change in urine color, fluid retention causing edema in the legs, ankles or feet, or dyspnea.

21. Which group of patients requires assessment by nephrology, before and after ICM injection?

In the presence of life-threatening disease, when the diagnostic or therapeutic procedure with contrast medium is the only option, it should be performed regardless of the underlying renal condition or the risk of subsequent renal damage and does not require prior assessment by nephrology.

In the context of scheduled contrast media procedures, the first question to be resolved is whether there is an alternative that does not use ICM without affecting the potential benefit of imaging with an iodine-based contrast medium. In cases of scheduled diagnostic or therapeutic procedures that require the use of ICM as the only alternative-even in high-risk settings (e.g., with eGFR <30 mL/min/1.73 m2), comorbidities, or other associated conditions that increase the risk of AKI-ICM, nephrology assessment before and after contrast injection should be considered.

Conclusion: In the case of a potentially fatal clinical condition, when a procedure involving the use of ICM is mandatory to establish a diagnosis and/or a therapeutic conduct that can safeguard the patient's life, its performance should not be delayed pending concepts by any particular medical specialty.

This Consensus recommends assessment by nephrology before and after the procedure with contrast medium -with serum creatinine performed 24 hours after ICM injection- and in high-risk patients (eGFR <30 mL/min/1.73 m2) regardless of the ICM injection route -IV or IA- and in those patients undergoing first-pass renal exposure to ICM whose eGFR is <45 mL/min/1.73 m2, scheduled for non-urgent procedures.

22. What differential aspects related to AKI-ICM should be considered in the pediatric population for the use of ICM?

Because pediatric patients and especially newborns are more prone to water-electrolyte imbalance, in this age group it is recommended to use low osmolality, non-ionic contrast media at a dose not exceeding 2 mL/kg. In neonates, the maximum dose is 4-6 mL/kg body weight, particularly in cardiac imaging.

In the absence of known renal insufficiency, neonates do not appear to be at increased risk of developing renal toxicity from IV administration of iodine-based contrast material [114].

AKI-ICM is a known pathology in adult patients, but little information is available on the incidence, risk factors, and prognostic impact in the pediatric population.

Although further studies are needed in the pediatric setting, data from this Consensus suggest that clinicians should maintain a high degree of suspicion toward this complication among pediatric patients[115].

The osmolality of contrast media is of particular importance in neonates and the pediatric population because they are especially susceptible to fluid shifts and have a lower tolerance to intravascular osmotic loads when compared to adults[116]. If a large volume of fluid is received, heart failure and pulmonary edema may occur. Children with significant pre-existing cardiac dysfunction may be at increased risk [117].

Viscosity is a physical property of ICMs especially important for pediatric patients because of the use of small caliber angiocatheters in small blood vessels. The viscosity of the contrast medium and the size of the angiocatheter are important factors in determining maximum injection rates. If the viscosity of the medium is high, two problems may arise: first, the desired injection flow rate may not be achieved and second, the high pressure may lead to catheter failure and/or vessel injury [118].

In some cases, a slower injection rate-compared to that used in older children and adults-may be helpful in prolonging intravascular enhancement. Second, small-gauge angiocatheters-for example, 24-gauge-placed in small peripheral veins-for example, in the hand or foot-are commonly used in neonates and infants; when access is thought to be tenuous, manual injection of contrast medium should be strongly considered to minimize the risk of vessel injury and extravasation [119].

- Kidney injury associated with the use of contrast media in children.
- The effects of contrast media on the kidneys are similar between children and adults.
- Measurement of renal function in children

Serum creatinine concentration reflects the balance between creatinine production and excretion. Creatinine is a breakdown product of skeletal muscle and its rate of production is proportional to muscle mass. Muscle mass depends on a variety of factors, including the patient's age, sex, and level of physical activity.

Creatinine concentrations, therefore, are quite variable in pediatric patients, even in kidney preserved; therefore, normal creatinine concentrations in adults cannot be applied to the pediatric population. Normal pediatric serum creatinine concentrations increase with age.

increase with age. Glomerular filtration rate is the method used to define renal function prior to contrast media administration, using the modified Schwartz formula [120].

Modified Bedside Schwartz formula

Glomerular filtration rate (mL/min/1.73 m2) = (0.413 × height) / serum creatinine.

Height in cm and serum creatinine in mg/dL [121].

Table 5. Normal ranges for GFR in pediatric population

Age (months)	Mean GFR ± SD (mL/ min/1.73 m2)
≤ 1,2	52 ± 9
1,2 - 3,6	61,7 ± 14,3
3,6 ± 7,9	71,7 ± 13,9
7,9 - 12,8	82,6 ± 17,3
12 - 18	91,5 ± 17,8
18 - 24, 9	94,5 ± 18,1
>24	104,4 ± 19,9

Conclusión: No existe evidencia concluyente de que la población pediátrica tenga un mayor riesgo de desarrollar LRA-MCI con respecto a la población adulta. La osmolalidad de los medios de contraste es de particular importancia en recién nacidos y en población pediátrica, debido a que son especialmente susceptibles a los cambios de fluidos y tienen una menor tolerancia a las cargas osmóticas intravasculares cuando se compara con los adultos, por lo que este Consenso recomienda utilizar medios de contraste de baja osmolalidad, no iónicos, e una dosis que no exceda 2 mL/kg. En los recién nacidos, la dosis máxima es de 4-6 mL/kg de peso corporal, particularmente en imágenes cardiacas. Adicionalmente, el uso de angiocatéteres de calibre pequeño, obliga a considerar la viscosidad y la velocidad de infusión como factores por tener en cuenta en la población pediátrica. Finalmente, la tasa de filtración glomerular es el método usado para definir la función renal previa a la administración de medios de contraste, utilizando la fórmula de Schwartz modificada.

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Conflicts of Interest

When choosing the panel of experts, no conflicts of interest were taken into account.

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Appendix A. Clinical questions developed

#	Question	Recommendation/Conclusion
1	What is the definition of iodinated contrast media-induced nephropathy (CIN)?	The use of the term "iodinated contrast media-induced nephropathy" should be restricted only to those cases in which any other risk factor that may be involved in the development of acute kidney injury is exhaustively excluded, a fact that in clinical practice is not easily achievable, so its use is limited.
2	What is the definition of acute kidney injury associated with the use of iodinated contrast media (AKI-ICM)?	We recommend using the term "Acute kidney injury associated with the use of iodinated contrast media (AKI-ICM)" in those clinical scenarios in which any other risk factor that may be involved in the development of acute kidney injury coexists.
3	What is the frequency of presentation of acute kidney injury associated with iodinated contrast media (AKI-ICM)?	The risk of acute kidney injury (AKI) following the administration of iodinated contrast media has been overestimated in the literature and exaggeratedly perceived by health care personnel, since the data derive from small uncontrolled and non-randomized studies, which did not take into account other confounding variables (ICM characteristics, comorbidities, baseline creatinine fluctuations, etc.). Additionally, a large number of well-controlled retrospective trials and meta-analyses involving a large number of individuals, in selected and unselected populations, did not find an independent association between the administration of intravenous (IV) iodinated contrast media (IVCC) and the development of AKI-ICM; even in patients with advanced chronic kidney disease (eGFR < 30 mL/min/1.73 m2) and AKI in critically ill patients.
4	Is there evidence to support the use of the absolute value of serum creatinine as an isolated data, to define the use of an iodinated contrast medium?	Serum creatinine as isolated data should not be used as a reference to determine compromise of renal function; it is only one variable of the equation to estimate the glomerular filtration rate and based on the latter, the degree of compromise of renal function will be determined. The measurement of creatinine clearance in 24-hour urine is not recommended.
5	Which equation should be used to calculate the estimated glomerular filtration rate (eGFR) to determine the risk of a patient developing AKI associated with the use of iodinated contrast media prior to injection?	We recommend using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021* equation, which does not include a race variable to calculate the estimated glomerular filtration rate (eGFR) for the population over 18 years of age. Considering that the estimated glomerular filtration rate is the best general index of renal function, in the absence of a specific calculator for this equation, an alternative formula (CKD-EPI 2009, MDRD or C&G) can be used, as its results correlate better with glomerular filtration rate than a creatinine value in isolation. https://www.kidney.org/professionals/kdoqi/gfr_calculator * https://www.kidney.org/professionals/kdoqi/gfr_calculator
6	What are the patient-related risk factors for developing AKI associated with the use of iodinated contrast media?	Reduced baseline renal function, determined using an equation for calculating eGFR prior to administration of iodinated contrast media (ICM), is the only independent risk factor for the development of contrast media-associated AKI. An eGFR < 30 mL/min/1.73 m2 (high-risk patients) is the strongest predictor for the development of AKI-ICM in patients undergoing intravascular studies with iodinated contrast media.
7	What is the time range within which serum creatinine should be measured to be considered a valid and valid variable for the calculation of eGFR prior to ICM administration?	**Ambulatory** For patients with no history of any type of renal involvement or without intercurrent conditions that may modify eGFR (vomiting, diarrhea, fever, etc.), a creatinine performed within the last six weeks is considered acceptable. However, if there is a history of any renal impairment and/or intercurrent conditions, then it would be more appropriate to reduce the interval to 72 hours (after resolution of the intercurrent condition). **Hospitalized** Creatinine processed within 24 hours prior to contrast exposure for updated eGFR calculation. However, if during hospitalization the patient presents with a potentially fatal condition, the contrast study should not be delayed pending a creatinine; it should be performed immediately. **Emergencies** In this scenario, potentially fatal conditions are faced, so studies or interventions should be performed immediately, regardless of whether or not creatinine is available. If the situation is not immediately life-threatening and allows creatinine measurement for eGFR determination, this could be done. However, a low eGFR should not be a limitation to perform the procedure, if the clinical condition indicates it. **Acute kidney injury (AKI)** In patients with AKI, to determine the use of intravenous or intra-arterial ICM, a strict analysis of the potential benefit/risk balance should be performed: if the benefit of better diagnostic imaging or therapeutic intervention that limits or reverses a potentially fatal condition outweighs the risk of worsening AKI or of AKI developing into permanent or irreversible renal damage, then the use of CM is fully justified. Current evidence indicates that among patients with pre-existing AKI, ICM administration is not associated with persistent AKI at hospital discharge or an increased risk of dialysis initiation within 180 days.

#	Question	Recomendación/Conclusión
8	Do all ICMs have the same risk of producing AKI-ICM?	Current data do not support the theory that all isoosmolar media offer better outcomes than low-osmolality media in terms of AKI-ICM risk. It is recommended that iso-osmolal or low-osmolality media be used regardless of the patient's condition. Given the role of viscosity in the pathophysiology of AKI-ICM, it is recommended to pre-warm ICMs (not gadolinium-based ones), prior to administration.
9	Does the route of ICM administration (intravenous [IV], intra-arterial [IA] or percutaneous) modify the risk of developing AKI-ICM?	The use of ICM with first-pass renal exposure could be associated with an increased risk of developing AKI-ICM. Given the morbidity and mortality implications of AKI, it is considered reasonable to establish a higher cut-off point (eGFR < 45 mL/min/1.73 m2) than that established for second-pass arterial and intravenous procedures (eGFR < 30 mL/min/1.73 m2) to classify patients as being at high risk of developing AKI following ICM exposure. Similarly, in high-risk patients it is suggested to use alternative methods that do not require first-pass renal exposure to contrast media (e.g., echocardiogram instead of ventriculogram to assess ventricular ejection fraction [VEF]), as well as limiting the anatomical segments to evaluate those strictly necessary (infrapopliteal circulation if there is no clinical proximal involvement) and exploring other segments with methods that do not warrant contrast, such as segmental recordings of pulse volume (plethysmography), Doppler ultrasound, magnetic resonance angiography or CO2 angiography.
10	Is the volume of contrast medium used during a procedure a risk factor for the development of AKI-ICM?	The diagnostic and therapeutic benefit of an adequately contrasted procedure cannot be minimized. Therefore, once the need for such a study is established, the volume of ICM to be used should be determined based on the patient's weight (1-2 mL/kg, with a maximum dose of 300 mL), and not with equations that include creatinine or eGFR as variables. This makes it possible to obtain high-quality computed axial tomography (CT) images, which could avoid repeating the procedure with contrast medium, which would ultimately involve the application of a larger volume of ICM to the patient. In the case of endovascular interventional procedures, the patient's benefit from such intervention should be prioritized in order to avoid greater morbidity and mortality, above the potential risk of AKI-ICM, for example, an acute coronary event.
11	Should scales to estimate the risk of developing AKI-ICM be used in the clinical setting?	Taking into account that predictive scales have been developed for arterial procedures -coronary procedures-, this Consensus does not recommend the use of these scales to estimate the risk of developing AKI-ICM in procedures with IV contrast injection. The Consensus recommends the use of the BMC2 PCI Risk Calculator* to estimate the risk of developing AKI-ICM (additionally it determines the risk of death, need for blood transfusion and dialysis requirement) in the setting of hemodynamic studies. This scale requires more variables than the other predictive scales; however, it allows calculations to be made without having all the variables. Likewise, it is essential to remember that these tools are a guide; therefore, the clinical analysis of the patient's own characteristics, comorbidities, potentially fatal conditions, etc. and of the environment (scheduled vs. urgent procedures) should take precedence when making the decision to perform or not the procedure with contrast medium. *https://bmc2.org/quality-improvement/risk-calculators/bmc2-pci-risk-calculator-death-transfusion-and-cin
12	Should any medications be discontinued before or after the performance of an ICM procedure?	**Metformin** It is recommended not to discontinue metformin and to continue its intake at the eGFR-adjusted dose and on the usual schedule in patients not classified as high risk (eGFR > 30 mL/min/1.73 m2), without evidence of AKI, receiving IV or IA ICM with second-pass renal exposure. In patients with eGFR < 30 mL/min/1.73 m2 receiving IV or IA ICM with first- and second-pass renal exposure or in AKI, it is recommended that metformin be discontinued prior to ICM injection and restarted at a minimum after 48 hours, only if renal function remains stable (<25% increase from baseline creatinine) and continued use if the clinical condition warrants. **Renin angiotensin-aldosterone renin system (RAS) inhibitors: ACE/ARA II** This Consensus does not recommend discontinuing angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists (ARA II), before or after administration of an ICM for diagnostic and/or therapeutic procedures, if fully indicated for the patient's clinical condition. **Diuretics** The consensus does not recommend suspending diuretics before or after ICM injection for diagnostic and/or therapeutic procedures regardless of the route (venous or arterial). Their requirement should be determined and the dose should e guided, based on the patient's fluid intake and output, in order to achieve an optimal euvolemic state.
13	What is the definition of nephroprotection?	The term nephroprotection is defined as the set of collective and individual preventive and therapeutic interventions aimed at identifying individuals susceptible to some type of renal impairment, preventing the onset of renal function deterioration in the population at risk, limiting renal damage and delaying its progression to established chronic kidney disease, increasing the time to renal replacement therapy (RRT) or reducing its need, avoiding possible complications, sequelae and fatal outcomes.

#	Question	Recomendación/Conclusión
14	What are the nephroprotective measures that can be used to reduce the risk of developing AKI-CKD in high-risk patients?	**Hydration** Current evidence does not show the benefit of intravenous (IV) hydration compared to no hydration in patients with eGFR > 30 mL/min/1.73 m2. In this regard, the Consensus recommends hydration prior to IV or IA ICM injection with second-pass renal exposure in patients with eGFR ≤ 30 mL/min/1.73 m2. For patients who will undergo procedures with first-pass renal exposure, it is considered reasonable to use hydration in patients with eGFR ≤ 45 mL/min/1.73 m2, despite inconclusive evidence, given the potential benefit and low risk of complications. This Consensus does not suggest specific formulas to determine the volume of fluids to be used since what is sought is to avoid the patient being exposed to ICM under conditions of dehydration (without overhydration), which, in turn, depends on each patient's conditions. For the hydration protocol, the Consensus recommends the use of normal saline solution. **N-Acetylcysteine** There is no evidence to support the use of N-acetylcysteine as a prophylactic measure for the prevention of AKI-ICM, so this Consensus does not recommend its use. **Statins** The use of statins as a preventive measure for the development of AKI-ICM is not recommended. **Other drugs** Current evidence does not support the use of the following drugs as a preventive measure for the development of AKI-ICM: theophylline, ascorbic acid, trimetazidine, allopurinol, prostaglandin E1, fenoldopam, alpha-tocopherol, nicorandil, natriuretic peptides, mannitol, diuretics, or dopamine. Therefore, this Consensus does not recommend their use as a preventive measure for the development of AKI-ICM.
15	Is there evidence for the role of herbal medicine or the use of medicinal plants in the prevention of AKI-ICM?	There is no evidence to support the use of herbal preparations as a preventive measure for the development of AKI-ICM.
16	Does RRT after contrast medium injection have any benefit as a preventive measure to reduce the risk of developing AKI-ICM?	This Consensus does not recommend the use of renal replacement therapies (RRT) such as hemodialysis (HD), continuous slow therapy (CST) or peritoneal dialysis (PD) in any of its modalities as a strategy for the prevention of the development of AKI-CKD. Additionally, in patients with baseline chronic kidney disease (CKD) who are enrolled in a chronic intermittent hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) program, the use of HD immediately after contrast medium study is not supported by current evidence, so the scheduled times for HD sessions or previously established peritoneal fluid exchanges should not be modified, except in those patients with volume overload at the time of contrast medium administration.
17	Does residual renal function in patients with stage 5 chronic kidney disease on RRT modify nephroprotection strategies?	Preservation of residual renal function (RRF: Urine volume > 100 mL/24 h) is a goal to be considered in patients with HD-type RRT or peritoneal dialysis (PFD), as it improves outcomes in terms of morbidity and mortality. Therefore, other diagnostic alternatives that do not use ICM, which do not imply a risk of reducing RRF in this population, should be considered (e.g., ultrasound or MRI). In case it is decided to use ICM due to a potentially fatal condition or because there is no alternative diagnostic modality, the recommended doses should be used, in an attempt to avoid results with poor diagnostic capacity, preventing therapeutic behaviors or forcing repetition of the procedure, which entails a higher dosage of ICM.
18	Does the administration of repeated doses of ICM in patients at high risk of developing AKI-ICM require a minimum time interval between the first and subsequent procedures?	Este consenso considera razonable evitar exposiciones repetidas al MC durante 48 horas para procedimientos electivos en pacientes de alto riesgo de LRA-MCI) (TFGe ≤30, LRA o administración intraarterial de altos volúmenes de MC. No se deben limitar las dosis repetidas en pacientes de menor riesgo (TFGe ≥ 30, sin LRA o vía intravenosa) cuando exista una necesidad justificada de repetir el procedimiento. De igual forma, ante una enfermedad potencialmente fatal puede ser necesaria la repetición de la dosis de MC independientemente del tiempo transcurrido entre un procedimiento y otro, para establecer un diagnóstico y una conducta terapéutica.
19	Is the use of ICM contraindicated in renal transplant patients?	ICMs can be used in the renal transplant patient at the recommended doses, since the risk of AKI-ICM in renal transplant recipients does not differ significantly from the general population. eGFR remains the most important risk factor for the development of AKI-CKD in this population group.
20	Do patients at high risk for the development of AKI-ICM undergoing CM studies require any follow-up after media injection?	Given that patients with eGFR < 30 mL/min/1.73 m2 or AKI are considered high risk for developing AKI-ICM, this Consensus recommends measuring follow-up serum creatinine 24 hours after ICM injection, regardless of the route of administration (IV or IA). This same recommendation applies for patients undergoing first-pass renal exposure to CM with eGFR < 45 mL/min/1.73 m2. Because patients with eGFR > 30 mL/min/1.73 m2 are at low risk of developing AKI, this Consensus does not recommend measurement of a follow-up serum creatinine in this group. However, all patients who have been exposed to a CM (regardless of their eGFR) for diagnostic or therapeutic interventions via any route should be instructed to consult the emergency department if they manifest any signs or symptoms suggestive of developing AKI in the days following ICM injection: decreased volume of urine excreted (diuresis), change in urine color, fluid retention causing edema in the legs, ankles or feet, or dyspnea.

#	Question	Recomendación/Conclusión
21	Which group of patients require nephrological assessment prior to and after ICM injection?	In the case of a potentially fatal clinical condition, in which a procedure involves the use of a mandatory ICM to establish a diagnosis and therapeutic conduct that can safeguard the patient's life, its performance should not be delayed pending the concepts of a particular medical specialty. This consensus recommends nephrology assessment before and after the ICM procedure (with serum creatinine 24 hours after ICM injection), in high-risk patients (eGFR < 30 mL/min/1.73 m2) regardless of the route of ICM administration (IV or IA) and in patients undergoing first-pass renal exposure to ICM with eGFR < 45 mL/min/1.73 m2, scheduled for non-urgent procedures.
22	What differential aspects related to AKI-ICM should be considered in the pediatric population for the use of ICM?	There is no conclusive evidence that the pediatric population has an increased risk of developing AKI-ICM compared to the adult population. The osmolality of CMs is of particular importance in neonates and in the pediatric population, because they are especially susceptible to fluid shifts and have a lower tolerance to intravascular osmotic loads when compared to adults, so this Consensus recommends using low-osmolality, nonionic CMs at a dose not to exceed 2 mL/kg. In neonates, the maximum dose is 4-6 mL/kg body weight, particularly in cardiac imaging. Additionally, the use of small caliber angiocatheters makes it necessary to consider viscosity and infusion rate as factors to be taken into account in the pediatric population. Finally, GFR is the method used to define renal function prior to CM administration using the modified Schwartz formula*. *Modified Bedside Schwartz formula: Glomerular filtration rate (mL/min/1.73 m2) = (0.413 × height) / serum creatinine + height in cm / serum creatinine in mg/dL.

Annex B. Search strategies

Consulted source	Search strategy
PubMed	("Kidney Diseases"[Mesh]) AND "Contrast Media"[Mesh] AND "Contrast-Induced Nephropathy" [titl]
Embase	TITLE ("Contrast-Induced Nephropathy") AND (LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013)) AND (LIMIT-TO (DOCTYPE , "reviewarticle")OR DOCTYPE,"Research article",OR DOCTYPE ("Practice guilines")
Scopus	Contrast-Induced Nephropathy TITLE ("Contrast-Induced Nephropathy") AND (LIMIT-TO (DOCTYPE , "re")) AND (LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017))

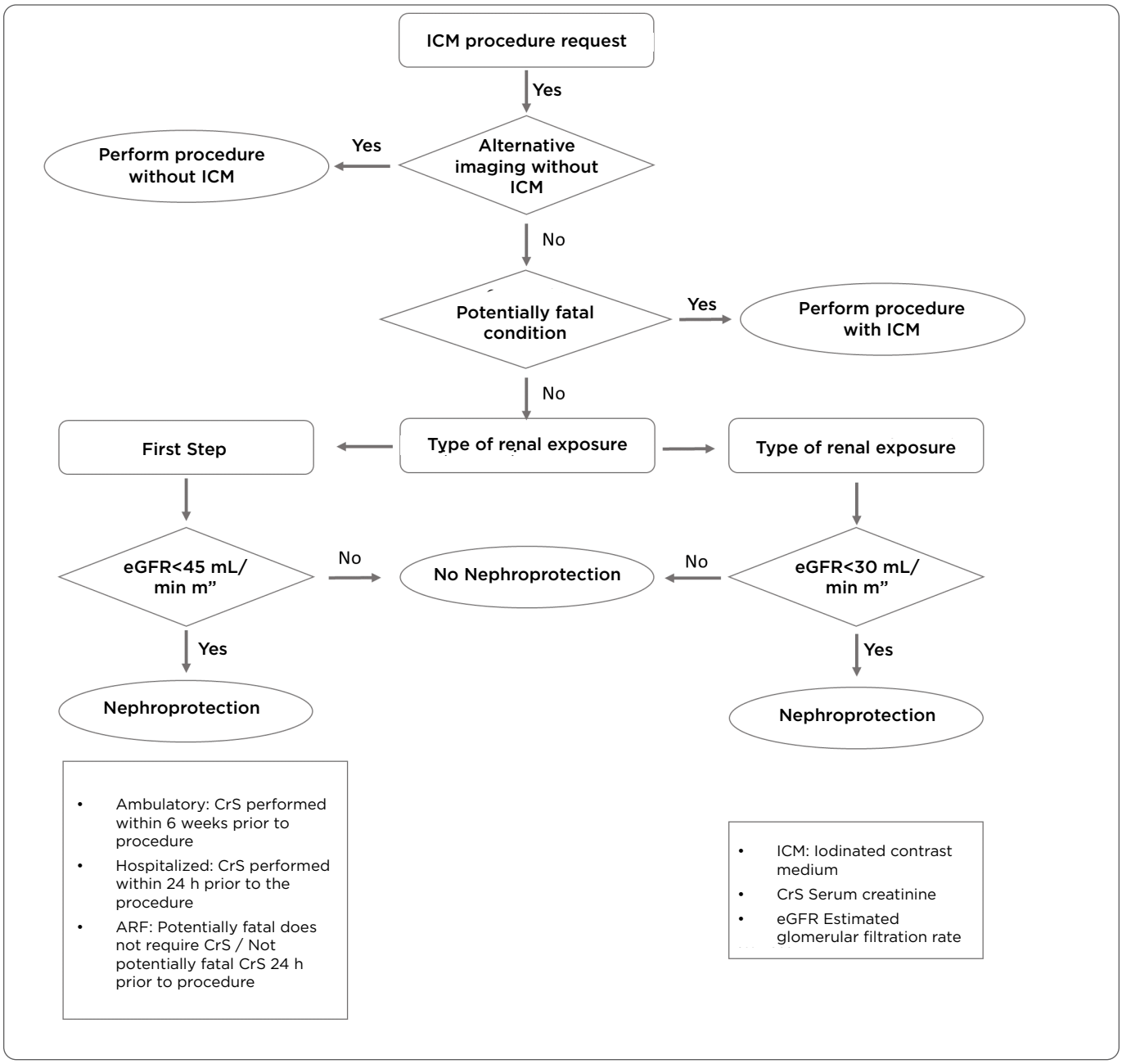
Annex C. Quality assessment

Title	Authors	Journal	Type of document	Quality of evidence. Risk of Bias
Efficacy of Alprostadil in Preventing Contrast-Induced Nephropathy: A Systematic Review and Meta-Analysis	Xu H, Wang H, Zhang C, Xiao J, Hua N, Tang X, Xie J, Zhang Z.	Angiology. 2021	Systematic Review and Meta-Analysis	High
Role of Hydration in Contrast-Induced Nephropathy in Patients Who Underwent Primary Percutaneous Coronary Intervention	Wang Z, Song Y, A G, Li Y.	Int Heart J. 2019	Systematic review and meta-analysis	High
Effects of intravenous hydration on risk of contrast induced nephropathy and in-hospital mortality in STEMI patients undergoing primary percutaneous coronary intervention: a systematic review and meta-analysis of randomized controlled trials	Liu Y, Hong D, Wang AY, Guo R, Smyth B, Liu J, Sun G, Chen S, Tan N, Jardine M, Brieger D	BMC Cardiovasc Disord. 2019	Systematic review and meta-analysis of randomized controlled studies.	High
A Bayesian network meta-analysis of preventive strategies for contrast-induced nephropathy after cardiac catheterization	Khan SU, Khan MU, Rahman H, Khan MS, Riaz H, Novak M, Opoku-Asare I, Kaluski E.	Cardiovasc Revasc Med. 2019	Bayesian network meta-analysis.	High
Effect of Alprostadil on the Prevention of Contrast-Induced Nephropathy: A Meta-Analysis of 36 Randomized Controlled Trials	Xie J, Jiang M, Lin Y, Deng H, Li L.	Angiology. 2019	Meta-analysis of randomized controlled studies.	High
Nicorandil for the prevention of contrast-induced nephropathy: A meta-analysis of randomized controlled trials	Ma X, Li X, Jiao Z, Zhang Y.	Cardiovasc Ther.2018	Meta-analysis of randomized controlled studies.	High

Title	Authors	Journal	Type of document	Quality of evidence. Risk of Bias
Latest Clinical Evidence About Effect of Acetylcysteine on Preventing Contrast-Induced Nephropathy in Patients Undergoing Angiography: A Meta-Analysis	Xie W, Liang X, Lin Z, Liu M, Ling Z.	Angiology. 2021	Meta-analysis	High
The effect of trimetazidine on contrast-induced nephropathy in patients undergoing coronary angiography and/or percutaneous coronary intervention – A systematic review and meta-analysis	Martha J.W, Pranata R, Wibowo A, Irvan I., Afrianti R, Akbar M.R.	Eur Rev Med Pharmacol Sci.2021	Systematic review and meta-analysis	High
Alpha-tocopherol and contrast-induced nephropathy: A meta-analysis of randomized controlled trials	Monami M, Cignarelli A, Pinto S, D'onofrio L, Milluzzo A, Miccoli R, Penno G, Mannucci E.	Int J Vitam Nutr Res. 2021	Meta-analysis of randomized controlled studies.	High
Contrast-induced nephropathy and oxidative stress: mechanistic insights for better interventional approaches	Kusirisin P, Chattipakorn SC, Chattipakorn N,	J Transl Med. 2020	Systematic review	High
Advances in the pathogenesis and prevention of contrast-induced nephropathy	Zhang F, Lu Z, Wang F.	Life Sci. 2020.	Systematic review	N/A
Biomarkers of Contrast-Induced Nephropathy: Which Ones are Clinically Important?	D'Amore C, Nuzzo S, Briguori C.	Interv Cardiol Clin. 2020	Systematic review	N/A
The efficacy of remote ischemic conditioning in preventing contrast-induced nephropathy among patients undergoing coronary angiography or intervention: An updated systematic review and meta-analysis	Zhan B, Zhu B, Hu J, Huang Q, Bao H, Huang X, Cheng X.	Ann Noninvasive Electrocardiol. 2020.	Systematic review and meta-analysis.	High
Carbon dioxide-angiography for patients with peripheral arterial disease at risk of contrast-induced nephropathy	Gupta A, Dosekun AK, Kumar V.	World J Cardiol. 2010	Narrative review	N/A
Intravenous fluids for the prevention of contrast-induced nephropathy in patients undergoing coronary angiography and cardiac catheterization	Hong WY, Kabach M, Feldman G, Jovin I.S.	Expert Rev Cardiovasc Ther. 2020	Narrative review	N/A
The Controversy of Contrast-Induced Nephropathy with Intravenous Contrast: What Is the Risk?	Rudnick MR, Leonberg-Yoo AK, Litt HI, Cohen RM, Hilton S, Reese PP.	Am J Kidney Dis. 2020	Narrative review	N/A
Predictive Value of Hepatorenal Status in Contrast-Induced Nephropathy Among Patients Receiving Coronary Angiography and/or Intervention: A Systematic Review and Meta-Analysis	Zhang E, Lu Y, Chen G, Huang L, Zhang J, Wang C, Qin Q.	Angiology. 2019	Systematic review and meta-analysis.	High
Pharmacology of contrast-induced nephropathy	Steffens L, Hayes L, Wiebe A.Z, Alexander E, Allen J.	AACN Adv Crit Care. 2019	Narrative review	N/A
Prevalence and Predictors of Contrast-Induced Nephropathy (CIN) in Patients with ST-Segment Elevation Myocardial Infarction (STEMI) Undergoing Percutaneous Coronary Intervention (PCI): A Meta-Analysis	He H, Chen X.-R, Chen YQ, Niu TS, Liao YM.	J Interv Cardiol. 2019	Meta-analysis	High
Baseline atrial fibrillation is associated with contrast-induced nephropathy after cardiac catheterization in coronary artery disease: Systemic review and meta-analysis	Prasitlumkum N, Kanitsoraphan C, Kittipibul V, Rattanawong P, Chongsathidkiet P, Cheungpasitporn W.	Clin Cardiol. 2018	Systematic review and meta-analysis.	High
Effect of Nicorandil Administration on Preventing Contrast-Induced Nephropathy: A Meta-Analysis	Zhan B, Huang X, Jiang L, Bao H, Cheng X.	Angiology. 2018	Meta-analysis	High
Comparative efficacy of pharmacological interventions for contrast-induced nephropathy prevention after coronary angiography: a network meta-analysis from randomized trials	Ma WQ, Zhao Y, Wang Y, Han XQ, Zhu Y, Liu NF.	Int Urol Nephrol. 2018	Network meta-analysis of clinical trials	High
Statins and contrast-induced nephropathy: A systematic review and meta-analysis	Briasoulis A, Pala M, Telila T, Merid O, Akintoye E, Vogiatzi G, Oikonomou E, Tousoulis D.	Curr Pharm Des. 2018	Systematic review and meta-analysis	High

Título	Autores	Revista	Tipo de documento	Calidad de evidencia. Riesgo de sesgo
Contrast-Induced Nephropathy: Update on the Use of Crystalloids and Pharmacological Measures	Patschan D, Buschmann I, Ritter O.	Int J Nephrol. 2018	Narrative review	N/A
Contrast-induced nephropathy: Basic concepts, pathophysiological implications and prevention strategies	Mamoulakis C, Tsarouhas K, Fragkiadoulaki I, Heretis I, Wilks MF, Spandidos DA, Tsitsimpikou C, Tsatsakis A.	Pharmacol Ther. 2017	Systematic review	High
Strategies preventing contrast-induced nephropathy after coronary angiography: A comprehensive meta-analysis and systematic review of 125 randomized controlled trials	Ali-Hassan-Sayegh S, Mirhosseini SJ, Ghodratipour Z, Sarrafan-Chaharsoughi Z, Rahimizadeh E, Karimi-Bondarabadi A.A, Haddad F, Shahidzadeh A, Mahdavi P, Dehghan AM, Tahernejad M, Shahidzadeh A, Dehghan H, Ghanei A, Lotfaliani M, Weymann A, Zeriouh M, Popov AF, Sabashnikov A.	Angiology. 2017	Systematic review and meta-analysis	High
Intravenous Contrast-Induced Nephropathy—The Rise and Fall of a Threatening Idea	Ye Z, Lu H, Su Q, Guo W, Dai W, Li H, Yang H, Li L.	Medicine (Baltimore). 2017	Literature Review and Meta-Analysis	High
Race and contrast-induced nephropathy in patients undergoing coronary angiography and cardiac catheterization	Chawla R, Turlington J, Arora P, Jovin I.S.	Int J Cardiol. 2017	Narrative review	N/A
Advances in the pathogenesis and prevention of contrast-induced nephropathy	Fangfei Zhang, Zeyuan Lu, Feng Wang	Life Sciences. 2020	Literature Review	Moderate
Contrast Media—Different Types of Contrast Media, Their History, Chemical Properties, and Relative Nephrotoxicity	Lohani S, Rudnick MR.	Interventional Cardiology Clinics. 2020	Literature Review and Meta-Analysis	High
Can Fundus Fluorescein Angiography be Performed for Diabetic Patients on Oral Metformin?	Junhui Du, Rong Li	Chinese Med Sci Journal. 2017	Literature review	Moderate
Nephrotoxicity of iodinated contrast media: From pathophysiology to prevention strategies	Anne-Laure Faucon, Guillermo Bobrie, olivier clement	European Journal of Radiology. 2019	Narrative review	N/A
Contrast-Induced Acute Kidney Injury—Definitions, Epidemiology, and Implications	Azzalini L, Kalra S.	Interventional Cardiology Clinics. 2020	Narrative review	N/A
Procedural Strategies to Reduce the Incidence of Contrast-Induced Acute Kidney Injury During Percutaneous Coronary Intervention	Almendarez M, Gurm HS, Mariani J Jr, Montorfano M, Brilakis ES, Mehran R, Azzalini L.	JACC: Cardiovascular Interventions. 2019	Narrative review	N/A
Current comments on contrast media administration in patients with renal insufficiency	Shin H, Taghavifar S, Salehi S, Joyce P, Gholamreza-nezhad A.	Clinical Imaging. 2020	Narrative review	N/A

Annex D. Decision algorithm for patients undergoing ICM studies.



Annex E. Voting results of the response consultation

Question	Percentage of agreement
1. What is the definition of ICM-induced nephropathy?	100 %
2. What is the definition of AKI-ICM?	100 %
3. What is the frequency of presentation of AKI-ICM?	100 %
4. Is there evidence to support the use of the absolute creatinine value as an isolated data to define the use of an ICM? 100 %?	100 %
5. By which equation should eGFR be calculated to determine a patient's risk of developing AKI-ICM prior to the injection of the medium?	100 %
6. What are the patient-related risk factors for developing AKI-ICM?	100 %
7. What is the time range within which a serum creatinine must be performed to be considered a valid and current variable for eGFR calculation prior to ICM administration?	100 %
8. Do all ICMs have the same risk of producing AKI-ICM?	100 %
9. Does the route of ICM administration (IV, IA or percutaneous) modify the risk of developing AKI-ICM?	100 %
10. Is the volume of CM used during a contrasted procedure a risk factor for the development of AKI-ICM?	100 %
11. Should scores or scales to estimate the risk of developing AKI-ICM be used in the clinical setting?	100 %
12. Should any type of medication be discontinued before or after performing a procedure with iodine-containing media?	100 %
13. What is the definition of nephroprotection?	100 %
14. What are the nephroprotective measures that can be used to reduce the risk of developing AKI-ICM?	100 %
15. Is there evidence of the role of herbal medicine or the use of medicinal plants in the prevention of AKI-CKD?	90 %
16. Does RRT after contrast medium injection have any benefit as a preventive measure to reduce the risk of developing AKI-ICM?	100 %
17. Does residual renal function in patients with stage 5 chronic kidney disease on RRT modify nephroprotective strategies?	100 %
18. Does the administration of repeated doses of ICM in patients at high risk of developing AKI-CKD require a minimum time interval between the first and subsequent procedures?	100 %
19. Is the use of ICM contraindicated in patients with renal transplantation?	100 %
20. Do patients at high risk for the development of AKI-ICM who have undergone contrasted studies require any type of follow-up after the injection of the medium?	100 %
21. Which group of patients requires nephrological assessment before and after ICM injection?	100 %
22. What differential aspects related to AKI-ICM should be taken into account in the pediatric population for the use of ICM?	90 %