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# Contrast media use in patients with chronic kidney disease undergoing coronary angiography: A systematic review and meta-analysis of randomized trials

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ABSTRACT

*Background:* Patients with chronic kidney disease (CKD) undergoing coronary angiography (CA), adequate hydration and minimizing volume of contrast media (CM) are class 1b recommendations for preventing contrast induced nephropathy (CIN). Current data are insufficient to justify specific recommendations about isoosmolar vs. low-osmolar contrast media by the ACCF/AHA/*SCA*I guidelines.
*Methods:* Randomized trials comparing IOCM to LOCM in CKD stage 3 and above patients undergoing CA, and reporting incidence of CIN (defined by a rise in creatinine of 25% from baseline) were included in the analysis. The secondary outcome of the study was the incidence of serum creatinine increase by >1 mg/dl.
*Results:* A total of 2839 patients were included in 10 trials, in which 1430 patients received IOCM and 1393 received LOCM. When compared to LOCM, IOCM was not associated with significant benefit in preventing CIN (OR = 0.72, [CI: 0.50–1.04], $P = 0.08$, I2 = 59%). Subgroup analysis revealed non-significant difference in incidence of CIN based on baseline use of *N*-acetylcystine (NAC), diabetes status, ejection fraction, and whether percutaneous coronary intervention vs coronary angiography alone was performed. The difference between IOCM and LOCM was further attenuated when restricted to studies with larger sample size (>250 patients) (OR = 0.93; [CI: 0.66–1.30]) or when compared with non-ionic LOCM (OR = 0.79, [CI: 0.52–1.21]).
*Conclusion:* In patients with CKD stage 3 and above undergoing coronary angiography, use of IOCM showed overall non-significant difference in incidence of CIN compared to LOCM. The difference was further attenuated when IOCM was compared with non-ionic LOCM.



## 1. Introduction

Contrast-induced nephropathy (CIN) is one of the most common cause of hospital acquired kidney injury, which accounts for increase in morbidity, mortality, length of stay and hospitalization cost [1,2]. Chronic kidney disease (CKD) patients have higher risk of developing cardiovascular disease requiring coronary interventions compared to general populations [3], placing them at higher risk of developing CIN [4]. Risk factors for CIN are type and amount of contrast media (CM), older age, intra-arterial administration of CM, dehydration and use of nephrotoxic agents [5–7]. Adequate hydration and minimizing volume of contrast media administered are class 1b recommendations for preventing CIN [8–11]. It is also well recognized that high osmolar contrast media (HOCM) are more nephrotoxic than low (LOCM) or isoosmolar contrast media (IOCM) [12–14]. Trial done by Netti et al. [15] showed a significant benefit of IOCM over LOCM but other trials have failed to show this [16–19]. Current data are insufficient to justify specific recommendations about IOCM and LOCM, and specific guidelines on use of different CM especially in patients with higher stages of CKD have been lacking [20].

The aim of the current meta-analysis is to compare the renal safety of IOCM to LOCM in patients with advanced CKD and to assess the incidence of CIN in patients undergoing coronary angiography. To our best knowledge this is the first meta-analysis reporting difference in CIN between two types of CM among advanced CKD patients undergoing coronary angiography.

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## 2. Methods

### 2.1. Data sources and search strategy

A literature review on published RCTs was performed using Pubmed, Medline (via OVID), Scopus, and Web of science up till January 2016 without any language restrictions. Search keywords included "contrast media", "contrast-induced nephropathy", "chronic kidney disease" and "coronary angiography" as MeSH and free text terms. Additionally, root variations of the mentioned keywords were used in an attempt to improve search outcomes. Abstracts from the annual meetings of the American Heart Association, American College of Cardiology and European Society of Cardiology were searched over the same time period in an attempt to retrieve more articles. With the intention to identify additional RCTs, the references of all articles were manually reviewed and identified. All searches were limited to studies in humans.

### 2.2. Study selection

Selected studies included prospective randomized controlled comparisons of CIN rates after coronary angiography in patients with CKD stage 3 or more (GFR < 60) using IOCM versus LOCM. Only full-text articles with at least two arms of parallel comparisons were selected. Non-randomized studies, studies assessing rates of CIN in procedures other than percutaneous coronary angiography, and those only published as conference abstracts were excluded.

### 2.3. Outcome measure

The primary outcome was the incidence of CIN in subjects receiving IOCM vs. LOCM. CIN is defined by an initial increase in serum creatinine (Cr) concentration of at least 0.5 mg/dl or by a relative increase of at least 25% from baseline within 36–72 h of exposure, which usually resolves within 10 days. The incidence of serum creatinine increase by >1 mg/dl in the two aforementioned groups was the secondary outcome of this study.

### 2.4. Study selection and data extraction

Two investigators (BP and JC) independently identified, reviewed, and screened studies based on their titles and abstracts. The authors performed a full-text review of the selected articles and used standardized sheets for data collection. Decisions of inclusion and exclusion were resolved by consensus among authors. The primary author addressed disagreements concerning study inclusion and discrepancies of data extraction. The PRISMA statement was used as guidance for selection of studies to be included in the meta-analysis and is depicted in Fig. 1. Quality and trial bias risk assessment of all RCTs were done per the Cochrane collaboration criteria, which emphasized on evaluating adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding for outcome assessment, incomplete outcome, selective outcome reporting, and other potential bias.

### 2.5. Statistical analysis

Preferred Reporting Items for Systematic Reviews and Meta analysis Protocols (PRISMA-P) (Table 2 Supplementary materiel) criteria was used for analysis [21,22]. The dichotomous endpoints from individual trials were analyzed using the odds ratio (OR) as a parameter of efficacy with its 95% Confidence Interval (CI). We assessed heterogeneity with both Chi-square and the $I^2$ statistic that describes the percentage of total variation across trials due to heterogeneity rather than chance. $I^2$ values lie between 0% (no heterogeneity) and 100% (maximal heterogeneity). Markers of significant heterogeneity were Chi-square *p*-values of <0.1 and $I^2$ values of >50% or 0.5. Considering higher heterogeneity between studies DerSimonian and Laird's random-effect model was used for analysis. Risk of bias was assessed using RevMan (Table 3 Supplementary materiel) and sensitivity analysis was deemed unnecessary due to the low risk of bias in the included studies. Binary outcomes from individual studies were combined and the summary estimators effect were calculated using random-effect method. A *P* value of ≤0.05 was regarded as significant. Publication bias was assessed by construction of funnel plot and confirmed by Egger's precision test. Subgroup and sensitivity analyses were planned in advance using the random effects model. Subgroup analysis was done based on study sample size (≤250 vs. >250), use of n-acetylcysteine (NAC) in the precatherization preparation, the inclusion of CKD patients from all causes vs. those only secondary to diabetes, left ventricular function (EF > 40 vs. EF < 40), ionic vs non-ionic LOCM and whether coronary intervention (PCI) was performed or not. All analyses were performed using Review Manager (RevMan) Version 5.3 for Windows (Oxford, England).

## 3. Results

### 3.1. Identification of studies

As shown in Fig. 1, initial search yielded 198 potential studies. Out of these 71 were excluded based on the titles. Remaining

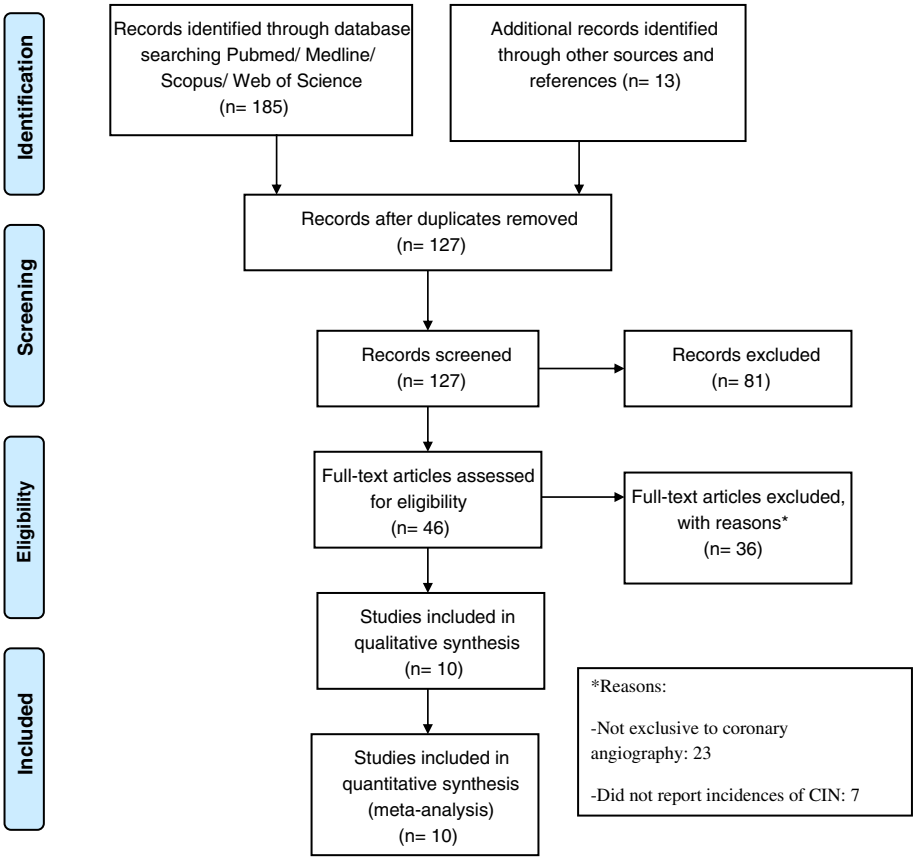


**Fig. 1.** PRISMA 2009 Flow Diagram for study selection.