The effectiveness of N-acetylcysteine in preventing contrast-induced nephropathy in patients undergoing contrast-enhanced computed tomography: A meta-analysis of randomized controlled trials
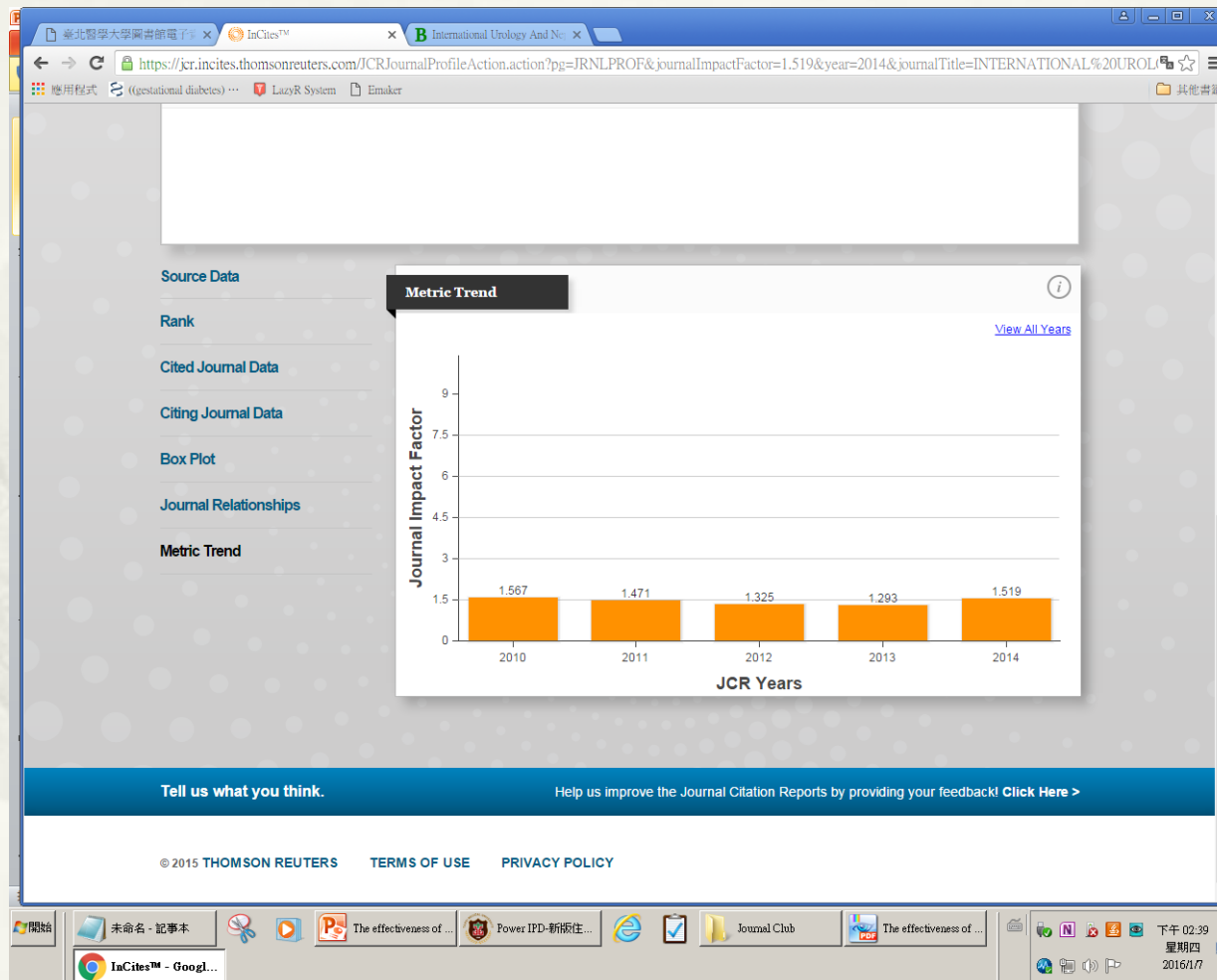
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Introduction

* Contrast-induced nephropathy (CIN) is a major complication of intravenous administration of an iodine contrast medium

* Defined an increase in serum creatinine greater than 25 % or 0.5 mg/dl within 3 days of iv contrast

Introduction

* CIN is uncommon in patients with normal renal function, ranging from 0 to 10 %. However, the incidence is perhaps as high as 50 % in patients with preexisting renal impairment or certain risk factors.

* Renal insufficiency, old age, diabetes mellitus, reduced left ventricular systolic function, advanced congestive heart failure, kidney transplantation, reduced effective arterial volume, and concurrent administration of nephrotoxic drugs.

* A large dose of intravenous contrast and using high-osmolar contrast agents in patients with renal impairment also increase the risk for CIN

Introduction

* Reduction in the incidence of CIN using adequate intravenous fluid hydration, low-osmolality contrast media instead of high-osmolar agents and iso-osmolar agents instead of low-osmolar agents.

Introduction

* Several randomized controlled trials (RCTs) and meta-analyses evaluating the anti-oxidative agent N-acetylcysteine (NAC) in preventing CIN in patients undergoing coronary angiography have yielded promising results.

* However, the effectiveness of NAC in preventing CIN in patients undergoing contrast-enhanced computed tomography (CT) is still controversial

Kelly AM, Dwamena B, Cronin P, Bernstein SJ, Carlos RC (2008). Ann Intern Med 148: 284–294.

步驟 1：系統性文獻回顧探討的問題為何？

* 研究族群 / 問題 (**Population/ Problem**)
  * patients undergoing contrast-enhanced computed tomography
* 介入措施 (**Intervention**)
  * acetylcysteine, administered orally or intravenously
* 比較 (**Comparison**)
  * control group with hydration alone
* 結果 (**Outcomes**)
  * requirement for dialysis
  * changes of serum creatinine

步驟 2：系統性文獻回顧的品質如何？（FAITH)

F – 研究是否找到 (Find) 所有的相關證據？

最好的狀況是？	我可以在哪裡找到這些資訊？
良好的文獻搜尋至少應包括二個主要的資料庫(如：Medline, Cochrane 考科藍實證醫學資料庫, EMBASE 等)，並且加上文獻引用檢索(參考文獻中相關研究、Web of Science, Scopus 或 Google Scholar)、試驗登錄資料等。文獻搜尋應不只限於英文，並且應同時使用 MeSH 字串及一般檢索詞彙 (text words)。	在文章的**方法(Methods)**章節，可以找到詳細搜尋策略的說明，包括使用的名詞，**結果(Results)**章節中可以找到本篇系統性文獻回顧評估的摘要及全文文獻數目、文獻納入與排除的數量及原因。資料可能會以圖表或 PRISMA 的流程圖呈現。

評讀結果：☑是　　口否　　口不清楚
說明：

F – 研究是否找到 (Find) 所有的相關證據？

Methods

Review protocol

We utilized the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement, explanation and elaboration document, and checklist to guide our methodology and reporting [9]. The systematic review described herein was accepted by the online PROSPERO international prospective register of systematic reviews of the National Institute for Health Research (CRD42012002094).
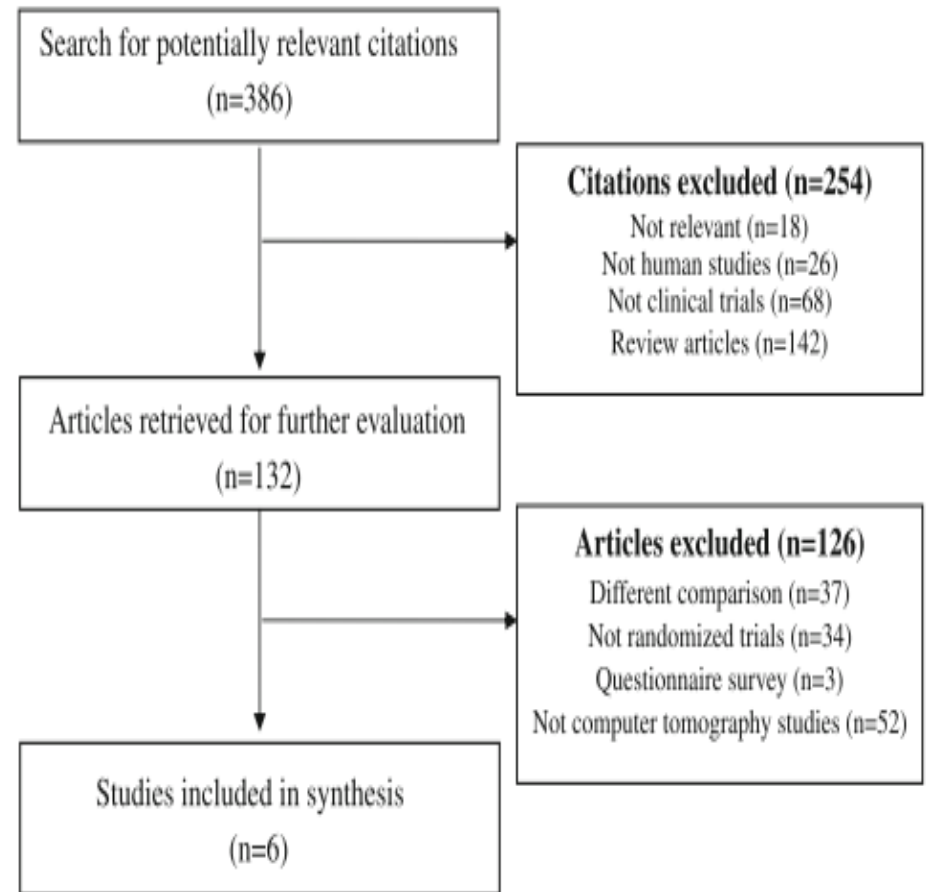
Search methods

The studies were identified by computerized searching in the PubMed, EMBASE, SCOPUS, and Cochrane databases. The following MeSH search headings were used: *acetylcysteine, radio induced or contrast induced, renal insufficiency or renal failure or kidney injury or nephropathy*, and *computed tomography*. These terms and their combinations were also searched as text words. All included studies were also entered into the PubMed 'related articles' function and the science citation index. In addition, we attempted to identify other studies by hand-searching the reference sections of these papers and by contacting known

Flowchart for the selection of the studies

Search for potentially relevant citations (n=386)

→ **Citations excluded (n=254)**
Not relevant (n=18)
Not human studies (n=26)
Not clinical trials (n=68)
Review articles (n=142)

↓

Articles retrieved for further evaluation (n=132)

→ **Articles excluded (n=126)**
Different comparison (n=37)
Not randomized trials (n=34)
Questionnaire survey (n=3)
Not computer tomography studies (n=52)

↓

Studies included in synthesis (n=6)

Finally, unpublished trials were sought in the ClinicalTrials.gov registry (http:// clinicaltrials.gov/). No language restrictions were applied. The final search was performed in October 2012.

A－文獻是否經過嚴格評讀 (Appraisal)？

A－文獻是否經過嚴格評讀 (Appraisal)？

最好的狀況是？	我可以在哪裡找到這些資訊？
應根據不同臨床問題的文章類型，選擇適合的評讀工具，並說明每篇研究的品質(如針對治療型的臨床問題，選用隨機分配、盲法、及完整追蹤的研究類型)。	在文章的**方法**章節，可以找到所使用的文獻品質評讀標準的描述，而**結果**章節則會列出每篇研究品質的評讀結果。

評讀結果：☑是　　□否　　□不清楚
說明：

Data extraction and quality assessment

Two reviewers (M.Y. Wu and K.W. Tam) independently extracted the following information from each study: study population characteristics, study design, inclusion and exclusion criteria, experimental drug administration, assessment of CIN, and complications. The individually recorded decisions of the two reviewers were compared, and any disagreements were resolved by a third reviewer (M.S. Yao). The authors of the studies were contacted for additional information when necessary.

The risk of bias in the included trials was assessed according to individual domains, reporting the following aspects: adequacy of randomization, allocation concealment, blinding, length of follow-up, number of drop-outs and whether intention-to-treat (ITT) analysis was conducted.

A – 文獻是否經過嚴格評讀 (Appraisal)？

Study selection

1. RCTs that have evaluated the efficacy of acetylcysteine, administered orally or intravenously, versus a control group with hydration alone.

Paper excluded:

1. Patients enrolled in the trials had undergone other contrast-enhanced diagnostic and therapeutic procedures concomitantly.
2. Trials compared NAC with another active treatment.

Table 1 Characteristics of studies fulfilling inclusion criteria in the meta-analysis

Study [references]	Inclusion criteria	No. of patient (% of male)	Age, years, mean ± SD	Baseline serum creatinine, mg/dl	Hydration/intervention	Contrast type, volume, ml
Burns et al. [11]	Serum creatinine >1.2 mg/dL or urine output <0,5 ml/kg over 4 h	A: 21 C: 21	NA	A: 1.15 ± 0.46 C: 1.34 ± 0.30	NS 12 h before and 24 h after CT A: 5 g IV post-randomization and 2 doses of 2.5 g at 6 h and 12 h after CT C: D5 W instead of NAC	NA
Kitzier et al. [16]	Serum creatinine >1.25 mg/dL for males and 1.09 mg/dL for females	A: 10 (20) E: 10 (60) C: 10 (50)	A: 76.6 ± 9.5 E: 73.3 ± 11.9 C: 74 ± 8.5	A: 1.37 ± 0.51 E: 13.7 ± 0.2 C: 1.33 ± 0.12	0.45 % saline 1 ml/kg 12 h before and 12 h after CT A: Orally, 1,200 mg 12 and 6 h before and 6 and 12 h after CT E: 540 mg IV 12 and 6 h before and 6 and 12 h after CT C: 0.45 % saline instead of NAC and vitamin E	Iopromide ultravisit 100 ml
Hsu et al. [15]	Patients received abdominal or chest CT in the emergency department	A: 106 (74) C: 103 (76)	A: 79.7 ± 8.5 C: 79.3 ± 11.1	A: 1.59 ± 0.56 C: 1.61 ± 0.63	A: 600 mg IV in 3 ml/kg NS 1 h before CT and NS 1 ml/kg 6 h after CT C: only hydration	Iohexol or iopromide or iobitridol
Poletti et al. [12]	Patients with serum creatinine >1.2 mg/dL admitted to emergency department	A: 44 (59) C: 43 (67)	A: 66 ± 11 C: 65 ± 15	A: 1.65 ± 0.40 C: 1.67 ± 0.41	0.45 % saline 5 ml/kg 1 h before and 1 ml/kg 12 h after CT A: 900 mg IV diluted in 50 ml D5 W 1 h before and in 0.45 % saline 1 ml/kg 12 h after CT C: 50 ml of NS instead of NAC	Iopromide ultravisit 100 ml
Sar et al. [13]	Diabetic patients with serum creatinine <1.2 mg/dL or creatinine clearance >60 ml/min	A: 25 (52) C: 20 (55)	A: 60 ± 11.3 C: 53.5 ± 9.9	A: 0.83 ± 0.15 C: 0.81 ± 0.17	NS 12 h before and 24 h after CT A: Orally, 1,200 mg before and 2 days after CT C: Only hydration	Iohexol 100 ml
Tepel et al. [14]	Serum creatinine >1.2 mg/dL or creatinine clearance <50 ml/min	A: 41 (58.5) C: 42 (54.8)	A: 66 ± 11 C: 65 ± 15	A: 2.5 ± 1.3 C: 2.4 ± 1.3	0.45 % saline 1 ml/kg 12 h before and 12 h after CT A: Orally, 600 mg BID on the day before and on the day of CT C: Only hydration	Iopromide ultravisit 75 ml

A N-acetylcysteine, *C* control, *CT* computer tomography, *E* vitamine E, *NA* not available, *NS* normal saline

I - 是否只納入 (included) 具良好效度的文章？

The risk of bias in the included trials was assessed according to individual domains, reporting the following aspects: adequacy of randomization, allocation concealment, blinding, length of follow-up, number of drop-outs and whether intention-to-treat (ITT) analysis was conducted.

I – 是否只納入 (included) 具良好效度的文章？

Table 2 Methodological quality assessment of included trials

Study [references]	Allocation generation	Allocation concealment	Double blinding	Data analysis	Duration of follow-up	Loss to follow-up (%)	Other bias
Burns et al. [11]	Random number table	Unclear	Unclear	PP	5 days post-contrast	0	Stopped early due to slow recruitment
Kitzier et al. [16]	Block randomization scheme	Unclear	Adequate	PP	48 h post-contrast	0	Low risk
Hsu et al. [15]	Computer-generated	Adequate	Unclear	PP	72 h post-contrast	13 %	Significant differences in body weight, amount of contrast material administered, and the presence of CKD between groups
Poletti et al. [12]	Serial enrollment	Unclear	Adequate	PP	4 days post-contrast	2.1 at day 2 4.6 at day 4	9 patients died before final measurement
Sar et al. [13]	Unclear	Open-label	Inadequate	ITT	72 h post-contrast	0	No real amount of volume infusion provided
Tepel et al. [14]	Unclear	Unclear	Unclear	ITT	48 h post-contrast	0	Low risk

CKD chronic kidney disease, *ITT* intention-to-treat, *PP* per protocol

T – 作者是否以表格和圖表「總結」(total up) 試驗結果？

最好的狀況是？	我可以在哪裡找到這些資訊？
應該用至少 1 個摘要表格呈現所納入的試驗結果，若結果相近，可針對結果進行統合分析(meta-analysis)，並以「森林圖」(forest plot)呈現研究結果，最好再加上異質性分析（見後文）。	在文章的**結果**章節，可以找到摘要的圖表，以及作者對系統性文獻回顧結果的解釋。

評讀結果：☑是　　□否　　□不清楚

說明：

T – 作者是否以表格和圖表「總結」(total up) 試驗結果？
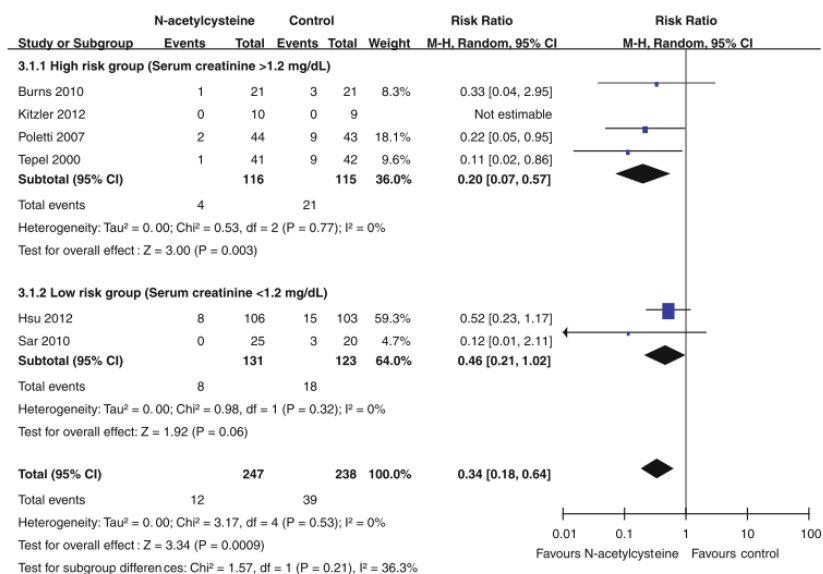
Fig. 2 Forest plot of comparison: *N*-acetylcysteine with hydration versus hydration. Outcome: the incidence of contrast-induced nephropathy
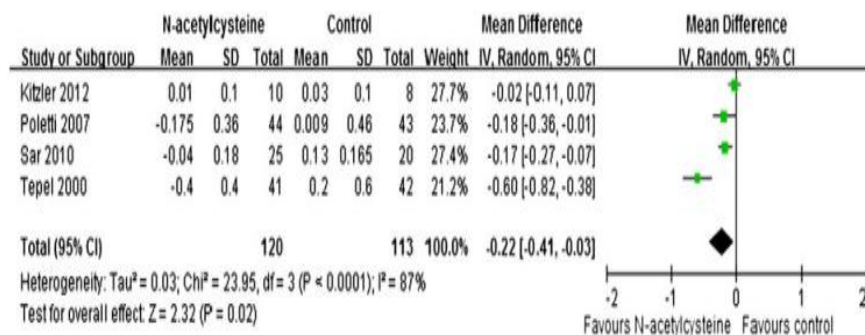
Fig. 3 Forest plot of comparison: *N*-acetylcysteine with hydration versus hydration. Outcome: change of serum creatinine

H – 試驗的結果是否相近 – 異質性(Heterogeneity) ?

H – 試驗的結果是否相近 – 異質性 (Heterogeneity) ?

最好的狀況是？	我可以在哪裡找到這些資訊？
在理想情況下，各個試驗的結果應相近或具同質性，若具有異質性，作者應評估差異是否顯著(卡方檢定)。根據每篇個別研究中不同的 PICO 及研究方法，探討造成異質性的原因。	在文章的**結果**章節，可以找到研究結果是否具異質性，及造成異質性可能的原因探討。森林圖中可以找到異質性的卡方檢定結果。

評讀結果：☑是　　口否　　口不清楚
說明：

H – 試驗的結果是否相近 – 異質性 (Heterogeneity)？

The incidence of CIN

The definition of CIN varied considerably across trials. The incidence of CIN was proportional to the number of patients in whom nephrotoxicity developed after CT, defined as an increase of 0.3–0.5 mg/dL and/or an increase of 20–25 % over baseline creatinine at 2–5 days after the administration of a contrast agent. We performed subgroup analysis on populations with serum creatinine above or below 1.2 mg/dL. In high-risk patients, our analysis revealed that a significant difference between the 2 treatment groups, with more patients in the control group experiencing greater incidence of CIN (RR = 0.20; 95 % CI 0.07–0.57). In low-risk patients, we found no significant difference between the 2 groups (RR = 0.46; 95 % CI 0.21–1.02), although the incidence of CIN was lower in the NAC group (Fig. 2). No significant heterogeneity was observed among these trials ($I^2 = 0$ %). The number of people needed to receive the treatment before 1 person would experience a beneficial outcome [number needed to treat (NNT)] was 8.73.

Sar et al. [13] cannot provide the real delivered amount of saline in each group, which could

Discussion

* N-Acetylcysteine with antioxidant and vasodilatory properties is of potential benefit in preventing CIN because it minimizes both vasoconstriction and oxygen-free radical generation after administering a radiocontrast agent.

* The most popular protocol involves an oral NAC, 600 mg, twice daily for 24 h the day before and on the day of the procedure.

Discussion
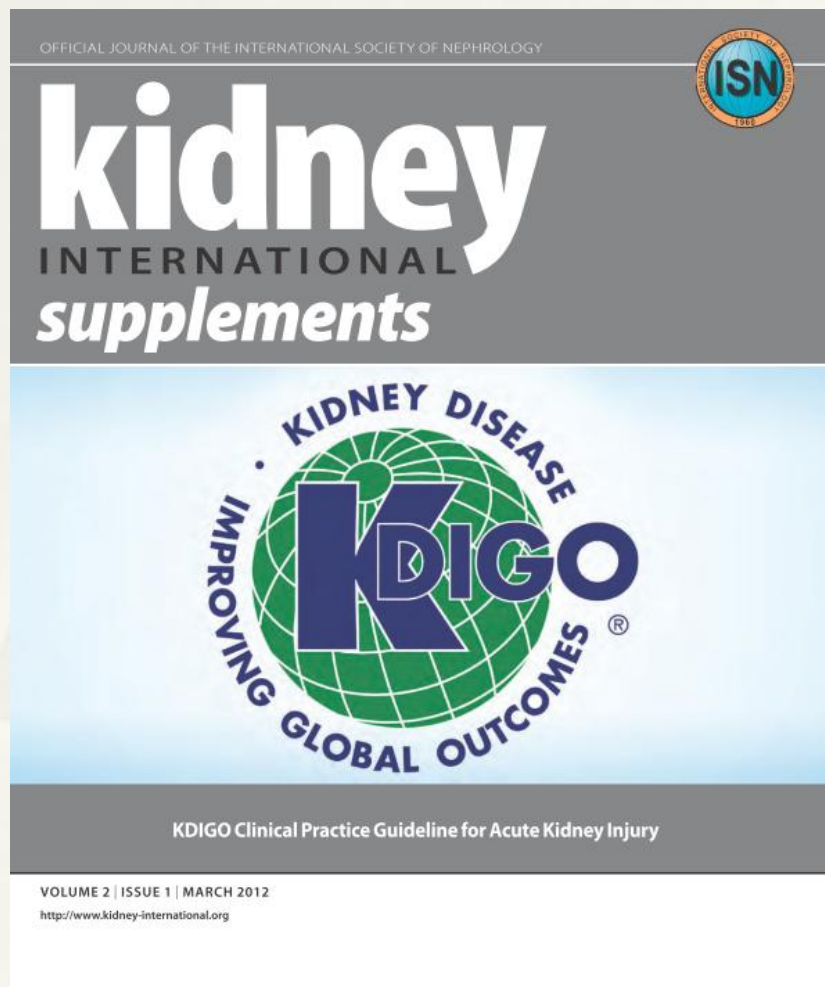
kidney
INTERNATIONAL

KDIGO Clinical Practice Guideline for Acute Kidney Injury

Discussion

ROLE OF NAC IN THE PREVENTION OF CI-AKI

4.4.3:   We suggest using oral NAC, together with i.v. iso-
           tonic crystalloids, in patients at increased risk of
           CI-AKI. (*2D*)

Discussion

1. 心導管前投藥已常規給予Acetin，以減少顯影劑對腎功能的影響。但尚未納入腎臟科新進人員訓練，也並不是排檢的常規。

2. Acetin的安全性高，相當贊成常規在CT前投與，後續提案至醫療科討論全院推展之可行性

3. 水分補充以0.9% normal saline為主，0.45% saline 或 Glucose water 對腎臟反而有負擔

4. 在這六篇RCT中確實有涵蓋IV Actein 作為介入措施，但本院並無使用針劑的經驗，對於需NPO 個案，建議以水分補充為主

Discussion

Except IV hydration (1.0-1.5 ml/kg/h) 12 h before and 12 h after CT.
Added PO N-acetylcysteine 200mg/ pk 2 PK TID as routine prescription in patient ongoing for CT examination

Thank You!