Prophylactic hydration to protect renal function from intravascular iodinated contrast material in patients at high risk of contrast-induced nephropathy (AMACING): a prospective, randomised, phase 3, controlled, open-label, non-inferiority trial

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Summary

Background Intravenous saline is recommended in clinical practice guidelines as the cornerstone for preventing contrast-induced nephropathy in patients with compromised renal function. However, clinical-effectiveness and cost-effectiveness of this prophylactic hydration treatment in protecting renal function has not been adequately studied in the population targeted by the guidelines, against a group receiving no prophylaxis. This was the aim of the AMACING trial.

Methods AMACING is a prospective, randomised, phase 3, parallel-group, open-label, non-inferiority trial of patients at risk of contrast-induced nephropathy according to current guidelines. High-risk patients (with an estimated glomerular filtration rate [eGFR] of 30–59 mL per min/1·73 m²) aged 18 years and older, undergoing an elective procedure requiring iodinated contrast material administration at Maastricht University Medical Centre, the Netherlands, were randomly assigned (1:1) to receive intravenous 0·9% NaCl or no prophylaxis. We excluded patients with eGFR lower than 30 mL per min/1·73 m², previous dialysis, or no referral for intravenous hydration. Randomisation was stratified by predefined risk factors. The primary outcome was incidence of contrast-induced nephropathy, defined as an increase in serum creatinine from baseline of more than 25% or 44 µmol/L within 2–6 days of contrast exposure, and cost-effectiveness of no prophylaxis compared with intravenous hydration in the prevention of contrast-induced nephropathy. We measured serum creatinine immediately before, 2–6 days, and 26–35 days after contrast-material exposure. Laboratory personnel were masked to treatment allocation. Adverse events and use of resources were systematically recorded. The non-inferiority margin was set at 2·1%. Both intention-to-treat and per-protocol analyses were done. This trial is registered with ClinicalTrials.gov, number NCT02106234.

Findings Between June 17, 2014, and July 17, 2016, 660 consecutive patients were randomly assigned to receive no prophylaxis (n=332) or intravenous hydration (n=328). 2–6 day serum creatinine was available for 307 (92%) of 332 patients in the no prophylaxis group and 296 (90%) of 328 patients in the intravenous hydration group. Contrast-induced nephropathy was recorded in eight (2·6%) of 307 non-hydrated patients and in eight (2·7%) of 296 hydrated patients. The absolute difference (no hydration *vs* hydration) was –0·10% (one-sided 95% CI –2·25 to 2·06; one-tailed p=0·4710). No hydration was cost-saving relative to hydration. No haemodialysis or related deaths occurred within 35 days. 18 (5·5%) of 328 patients had complications associated with intravenous hydration.

Interpretation We found no prophylaxis to be non-inferior and cost-saving in preventing contrast-induced nephropathy compared with intravenous hydration according to current clinical practice guidelines.

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Introduction

Procedures with intravascular iodinated contrast material pose a risk for renal function, especially in patients whose renal function is already compromised.[1] Contrast-induced nephropathy or contrast-induced acute kidney injury was recognised more than 60 years ago,[2] and is the third most common cause of acute kidney injury in patients admitted to hospital.[2–5] Contrast-induced nephropathy is marked by a decline in renal function typically occurring between 2 and 5 days after intravenous or intra-arterial iodinated contrast administration. Although the disorder is associated with increased in-hospital morbidity and mortality, contrast-induced nephropathy usually resolves and leaves no lasting effects, and clinically relevant consequences are reported to occur in less than 1% of cases.[6–8]

No treatment exists for contrast-induced nephropathy; therefore, the focus lies on prevention. Prevention guidelines exist in most countries and are implemented in most hospitals. Generally, intravascular volume expansion with isotonic saline is recommended as prophylaxis.[9–12] This recommendation has far-reaching

Research in context

Evidence before this study

To find studies assessing prophylactic intravenous hydration in the prevention of contrast-induced nephropathy we searched PubMed on July 31, 2016, for studies published in all languages with the MeSH search term "contrast media" and the keyword "hydration". The resultant 529 papers were further filtered for the article type "Clinical trial". Of the 150 studies subsequently found, only three included a randomised group not receiving prophylaxis, and none, although all were recent, compared not giving prophylaxis with intravenous prophylactic hydration given according to current guidelines. The results of the three studies are not likely to be representative of the total population targeted by the guidelines (all patients deemed to be at risk of contrast-induced nephropathy because of chronic kidney disease combined with specified risk factors) because they were done in specific clinical settings.

The two most relevant studies were published in 2014 and 2015, and were done in ST-elevation myocardial infarction patients referred for percutaneous coronary intervention, most of whom had normal renal function. The studies compared no hydration with intravenous hydration according to the guidelines with normal saline (n=216 and n=408). Both studies reported a high incidence of contrast-induced nephropathy (11–35%), and noted that hydration was superior in the prevention of contrast-induced nephropathy. This result might be explained by other factors such as higher contrast volume, haemodynamic instability, and nephrotoxic treatments. The third study was published in 2014 and included a group receiving no prophylaxis, but compared this with prophylaxis different to that recommended in the guidelines. 130 patients suspected of having acute pulmonary embolism and referred for a contrast-enhanced CT were included, and no hydration was compared with 1 h pre-hydration with bicarbonate. The no hydration treatment was non-inferior to the hydration treatment.

Studies comparing intravenous hydration with oral prophylaxis generally reported oral prophylaxis to be non-inferior to the intravenous treatment.

Added value of this study

Despite being widely recommended in national and international guidelines, no randomised trial has prospectively compared periprocedural intravenous hydration with normal saline with a group receiving no prophylactic hydration in the high-risk population targeted by the guidelines. Clinical trials have focused mainly on comparing one form of prophylaxis with another, and have been done in specific populations in which other factors might affect renal function, receiving other, often nephrotoxic, treatments. Additionally, in the published studies various contrast media types were used. The AMACING study included all patients deemed at risk of contrast-induced nephropathy according to the guidelines with an estimated glomerular filtration rate (eGFR) higher than 29 mL per min/1·73 m^2. We did not influence contrast injection protocols, and all procedures included in the AMACING study were done using minimum volume pre-warmed, low-osmolar, monomer, non-ionic, contrast material Iopromide, at 300 mg iodine per mL.

Implications of all the available evidence

The incidence of contrast-induced nephropathy recorded in our study (2·6–2·7%) is at the low end of the range of incidences reported in the scientific literature (0 to >50%). In AMACING, no prophylaxis was non-inferior to intravenous hydration in the prevention of contrast-induced nephropathy, and cost-saving. Interaction p values were not significant, suggesting a consistency of effect across the subgroups with intravenous versus intra-arterial contrast administration, diabetic versus non-diabetic patients, and patients with eGFR below 45 mL per min/1·73 m^2 versus those with eGFR above 45 mL per min/1·73 m^2. Additionally, intravenous hydration was not without risk; 18 (5·5%) of 328 patients had complications associated with the hydration treatment.

Based on these findings and assuming optimum contrast media administration, prophylactic intravenous hydration might not be necessary in patients with eGFR higher than 29 mL per min/1·73 m^2, and the substantial health-care costs, patient burden, and logistical complications of this prophylaxis might henceforth be avoided while maintaining patient safety.

consequences for patients, hospital logistics, and health-care budgets because high-risk patients need to be admitted to hospital for 8–24 h to accommodate the peri-procedural prophylactic treatment. More than 75 million procedures with intravascular iodinated contrast material are done worldwide every year.[13] Taking into account chronic kidney disease prevalence of 8–16%,[14] an estimated 6–12 million procedures per year include high-risk patients for whom the guidelines propose prophylaxis.

The prophylaxis prescribed by the guidelines is based on expert consensus that it is beneficial.[9,10,15] Accreditation programmes on quality of health care use the percentage high-risk patients receiving prophylaxis to reflect quality and safety in the clinical setting. However, very little is known about its efficacy.[15]

The mechanism by which iodinated contrast material might induce contrast-induced nephropathy is unclear, as is the mechanism by which prophylactic hydration might protect renal function from injury by iodinated contrast material.[16–18] Prophylactic intravenous hydration is not without risk, and patients can have mild to serious complications ranging from phlebitis to pulmonary oedema.[18–21] Patients selected for risk of contrast-induced nephropathy according to the guidelines, with risk

factors including reduced renal function, age, diabetes, and cardiac disease, are especially sensitive to complications of intravenous hydration. The risk of intravenous hydration in this population has not yet been charted, and is not taken into account by guidelines.

The baseline incidence of contrast-induced nephropathy in an untreated population is unknown. Up to now, intravenous hydration with normal saline has not been compared with a group not receiving prophylaxis in the population targeted by the guidelines. The aim of A MAstricht Contrast-Induced Nephropathy Guideline (AMACING) trial was to establish the clinical-effectiveness and cost- effectiveness of current guidelines on the use of intravascular iodinated contrast material, notably of prophylactic hydration. We aimed to assess whether giving no prophylaxis is non-inferior to standard care prophylactic hydration, by comparing contrast-induced nephropathy incidence and costs of resources used in patients receiving prophylaxis with that of a group receiving no prophylaxis, taking into account complications of intravenous hydration.

Methods

Study design and participants

The AMACING study is a prospective, randomised, phase 3, parallel-group, open-label, non-inferiority trial designed to assess the safety and cost-effectiveness of current guidelines on the prevention of contrast-induced nephropathy. During recruitment all consecutive patients aged 18 years and older, referred for an elective procedure requiring intravascular iodinated contrast material at Maastricht University Medical Centre, and with known eGFR lower than 60 mL per min/1·73 m², were prospectively screened to establish whether they met the study criteria. Patients were eligible for inclusion if they had an estimated glomerular filtration rate (eGFR) between 45 and 59 mL per min/1·73 m² combined with either diabetes, or at least two predefined risk factors (age >75 years; anaemia defined as haematocrit values <0·39 L/L for men, and <0·36 L/L for women; cardiovascular disease; non-steroidal anti-inflammatory drug or diuretic nephrotoxic medication); or eGFR between 30 and 45 mL per min/1·73 m²; or multiple myeloma or lymphoplasmacytic lymphoma with small chain proteinuria. These criteria corresponded to the criteria for identifying high-risk patients according to current local (the Netherlands) and European guidelines.[9,10,15] We calculated the eGFR with serum creatinine concentrations and the Modification of Diet in Renal Disease (MDRD) study equation.

Exclusion criteria were inability to obtain informed consent, eGFR lower than 30 mL per min/1·73 m², renal replacement therapy, emergency procedures, intensive care patients, known inability to plan primary endpoint data collection, no referral for prophylactic hydration, participation in another randomised trial, and isolation (infection control).

We chose a non-inferiority design based on the assumption that although contrast-induced nephropathy might occur more often in the absence of prophylaxis, withholding intravenous hydration might have the advantage of reducing patient burden and health-care costs. Furthermore, although it might be associated with increased morbidity and mortality, we regarded a small increase in contrast-induced nephropathy as acceptable because it usually resolves within a few weeks, and clinically relevant consequences are reported to occur in less than 1% of cases.[6–8]

All participants provided signed informed consent. The Maastricht University Medical Centre research ethics committee approved the study before first inclusion. The independent Clinical Trials Centre Maastricht monitored the study. Additionally, a data safety monitoring board of three independent external specialists monitored patient safety.

Randomisation and masking

We randomly assigned (1:1) eligible and consenting patients to receive either prophylactic intravenous hydration (H+ group) or no prophylaxis (H– group). Randomisation was stratified by diabetes (yes *vs* no), eGFR (<45 *vs* ≥45 mL per min/1·73 m²), contrast administration route (intravenous *vs* intra-arterial), and procedure type (diagnostic *vs* interventional). Randomisation was computer generated using the ALEA screening and enrolment application software (version v3.0.2083.212r; Formsvision BV, Abcoude, the Netherlands). Minimisation with stratification factors was applied.[22]

Laboratory personnel processing samples for serum creatinine values were masked to treatment allocation, with samples being labelled with coded stickers only. Minimisation ensured that allocated treatment was unpredictable. Physicians doing the contrast procedures were not masked, but not specifically informed of the allocated treatment. Blinding patients or nursing and research staff was not feasible due to the obvious difference in treatment of hydrated and non-hydrated patients. Therefore an open label design was chosen.

Procedures

The following baseline characteristics were obtained from contrast procedure referral forms: sex, age, inpatient versus outpatient status, contrast-administration route, screening serum creatinine, and screening eGFR. Guideline risk factors were obtained from referral forms where possible. When insufficient data were present on referral forms, the research assistant added the appropriate data from the hospital electronic file. Patients were asked to bring all their medication to the interview just before start of treatment, during which the research assistant filled in a standard questionnaire recording use of nephrotoxic medication and presence of cardiovascular disease. A representation of the data collection timeline is given in appendix p 1.

See Online for appendix

Prophylactic hydration protocols used were according to current guidelines:[10] standard protocol intravenous 0·9% NaCl 3–4 mL/kg per h during 4 h before and 4 h after contrast administration; long protocol intravenous 0·9% NaCl 1 mL/kg per h during 12 h before and 12 h after contrast administration. When deemed necessary on medical grounds, the treating physician could deviate from standard hydration protocols. Time and flow were recorded at the beginning and end of every intravenous hydration session for each patient.

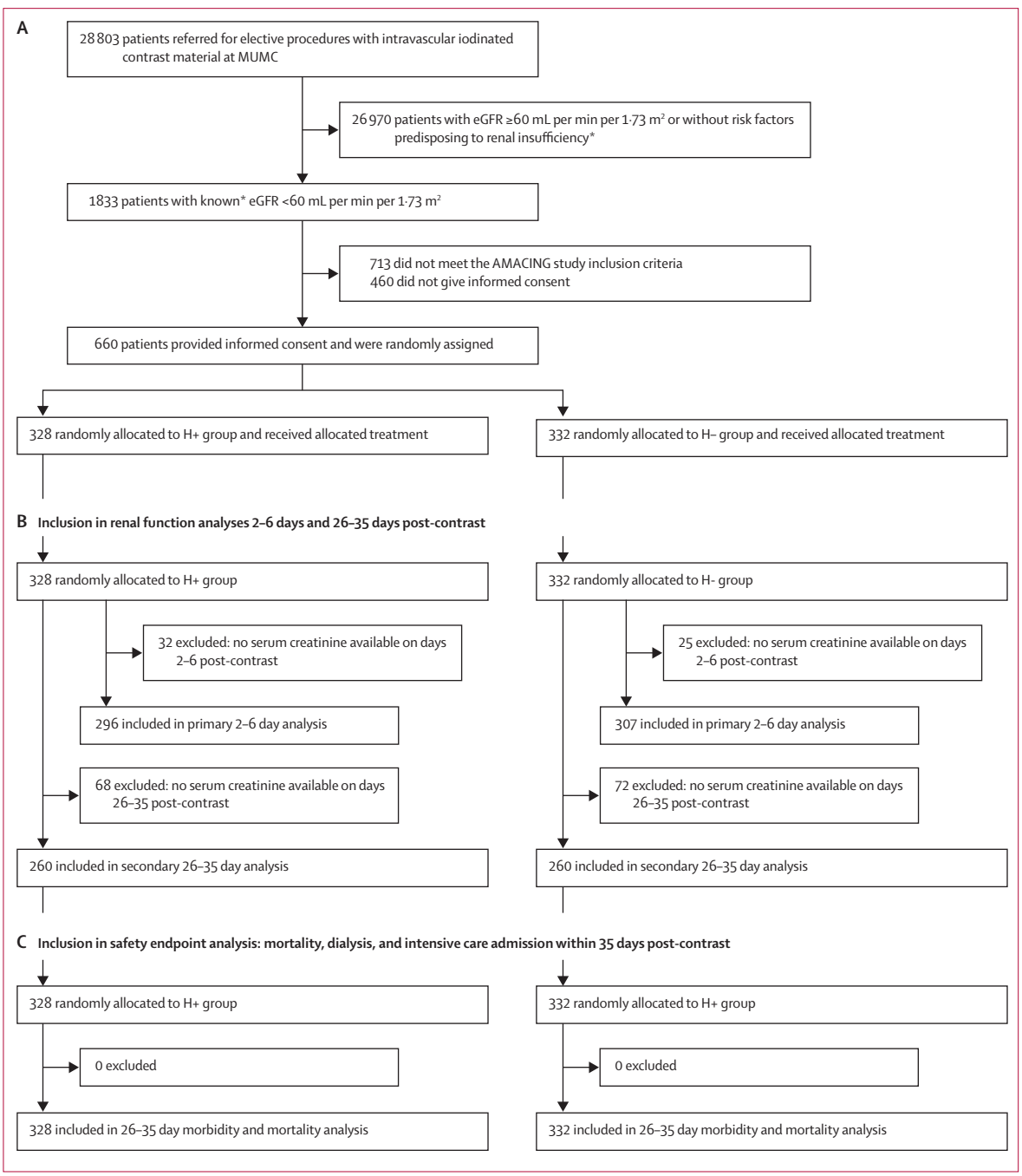

Figure 1: **Trial profile**
MUMC=Maastricht University Medical Centre. eGFR=estimated glomerular filtration rate. H+ group=received standard 0·9% NaCl prophylactic intravenous hydration. H– group=received no prophylaxis. *The MUMC follows the screening guidelines that propose renal function needs only be assessed if one of the following risk factors is present: age >60 years, diabetes, use of nephrotoxic medication, urological, or nephrological history, hypertension, peripheral vascular or cardiac disease, multiple myeloma or lymphoplasmacytic lymphoma.

Procedure details including time of contrast administration, contrast volume, contrast administration route, medication administered, and adverse events were recorded during the procedure. The contrast volume administered was measured in 1 mL increments with the total established from the dual-head power injector used during the procedure (CT power injectors: Stellant, MEDRAD, Pittsburgh, PA, USA; coronary power injector: Angiomat 903300D Angiomat Illumena injector system, Liebel-Flarsheim, Cincinnati, OH, USA; peripheral angiography and intervention injector: MEDRAD Mark 7 Arterion Injection system, MEDRAD, Pittsburgh, PA, USA).

All patients received pre-warmed (37°C) intravascular iopromide 300 mg iodine per mL (Ultravist, Bayer Healthcare, Berlin, Germany), which is a non-ionic, monomeric, low-osmolar iodinated contrast medium. Screening serum creatinine was obtained by the treating physician at the time of contrast procedure referral. We further measured serum creatinine concentrations immediately before start of treatment (baseline), at 2–6 days, and 26–35 days after contrast exposure. Patients could indicate availability for follow-up within the pre-specified timeframes. For incidence of contrast-induced nephropathy, 2–5 days was aimed for, but day 6 was allowed if no other option was available. Where a value immediately before start of treatment was unavailable, the most recent value in the hospital electronic file was used. Changes in use of medication, use of resources and presence or absence of major adverse events were systematically recorded at all the above timepoints (appendix p 1). The following uses of in-hospital resources were recorded directly: duration of hospitalisation, materials required for intravenous hydration, and treatment of any complications during hospitalisation. The following uses of resources related to adverse events following the procedure were recorded up to 35 days after contrast exposure based on standard questionnaires: consultation with general practitioner or specialist, hospitalisation, renal diagnostics or treatments, and loss in productivity due to absence from work.

	H+ group given standard prophylactic treatment (n=328)	H- group given no prophylactic treatment (n=332)
Men	194 (59%)	213 (64%)
Age at time of contrast administration	71·9 (9·3)	72·6 (9·3)
BMI (kg/m²)	28·64 (4·96)	28·73 (4·91)
Inpatient	30 (9%)	27 (8%)
Intra-arterial contrast	159 (48%)	160 (48%)
Referral for an interventional procedure	53 (16%)	50 (15%)
Baseline renal function		
eGFR (mL per min/1·73 m²)	47·30 (7·95)	47·59 (8·01)
Serum creatinine (μmol/L*)	118·78 (27·63)	117·71 (24·62)
Guideline risk groups		
eGFR 45–59 mL per min/ 1·73 m² and two risk factors	138 (42%)	151 (45%)
eGFR 45–59 mL per min/ 1·73 m² and diabetes	74 (23%)	65 (20%)
eGFR <45 mL per min/1·73 m²	114 (35%)	115 (35%)
Multiple myeloma or lymphoplasmacytic lymphoma	2 (1%)	1 (0%)
Guideline risk factors		
Diabetes	106 (32%)	109 (33%)
Age >75 years	140 (43%)	146 (44%)
Prescribed diuretic medication	152 (46%)	155 (47%)
Prescribed non-steroidal anti-inflammatory drug	157 (48%)	162 (49%)
Anaemia†	81 (25%)	103 (31%)
Cardiovascular disease	236 (72%)	257 (77%)
Administered volumes (mL)		
300 mg iodine per mL contrast	92 (41)	89 (41)
Intravenous 0·9% NaCl		
Pre-hydration	822 (486)	0
Post-hydration	809 (539)	0
Total	1637 (950)	0

Data are n (%) or mean (SD). eGFR=estimated glomerular filtration rate. *To convert to mg/dL, divide by 88·4. †Anaemia is defined as haematocrit value <0·36 L/L for women and <0·39 L/L for men.

Table 1: **Baseline characteristics**

Outcomes

The primary endpoint was the incidence of contrast-induced nephropathy defined as the between-group difference in proportion of patients with an increase in serum creatinine by more than 25% or 44 μmol/L[23] within 2–6 days of contrast exposure, and cost-effectiveness of no prophylaxis compared with intravenous prophylactic hydration in the prevention of contrast-induced nephropathy. Secondary endpoints were mean change in serum creatinine from baseline at 2–6 and 26–35 days after contrast administration, as well as major adverse events.

Major adverse events were defined as all-cause mortality, renal replacement therapy, intensive care admission, and sequelae of fluid administration. Major renal adverse events were defined as renal failure (defined as eGFR <15 mL per min/1·73 m²), renal decline with >10 eGFR units, renal decline to eGFR lower than 30 mL per min/1·73 m², or a combination of the latter two, at 26–35 days. Clinical sequelae of fluid administration included symptomatic heart failure, hypernatraemia or hyponatraemia, and supraventricular or ventricular arrhythmias. Events were confirmed by personnel uninvolved with the trial, and monitored by an independent data safety monitoring board.

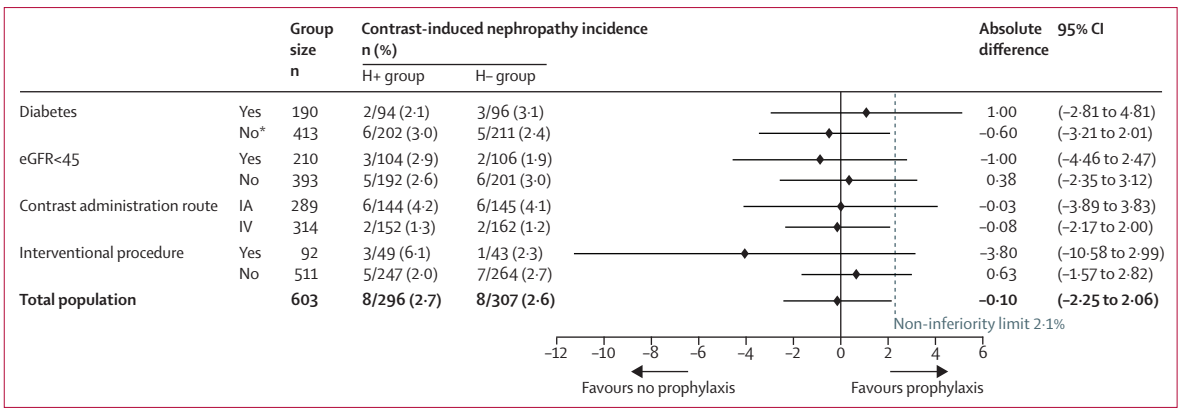

Figure 2: **Incidence of contrast-induced nephropathy in the total study population and by patient subgroup**
The dashed line indicates the non-inferiority margin of 2·1%. Error bars indicate two-sided 90% CIs. Bullets indicate the absolute difference (no hydration minus hydration) in proportion with contrast-induced nephropathy. eGFR=estimated glomerular filtration rate. IA=intra-arterial. IV=intravenous. *The no diabetes subgroup represents the guideline high-risk group with eGFR <60 mL per min/1·73 m² and two risk factors. p values for interaction: diabetics *vs* non-diabetics, p=0·5722; eGFR <45 *vs* eGFR ≥45; p=0·6040; intra-arterial *vs* intravenous contrast administration, p=0·9608; interventional *vs* diagnostic procedure, p=0·3289.

Statistical analysis

We reported continuous data as mean (SD) and presented categorical data as absolute numbers and percentages. For the primary endpoint, the absolute difference in proportions with contrast-induced nephropathy between randomised groups (ie, the percentage of patients with contrast-induced nephropathy in the non-hydrated group minus that in the hydrated group), was calculated with a one-sided 95% confidence interval of the difference.

For the cost analysis, multiple imputation was applied for missing data for items of questionnaires. We used bootstrap simulation (1000 replications) for costs to estimate the uncertainty surrounding mean costs. Similarly, bootstrap simulation was applied to cost-effectiveness data. Cost prices were obtained from the hospital financial department or the Dutch manual for costing research.[24]

We did pre-planned subgroup analyses within pre-specified subgroups: diabetes (yes *vs* no), eGFR (<45 *vs* ≥45 mL per min/1·73 m²), contrast administration route (intra-arterial *vs* intravenous), and procedure type (diagnostic *vs* interventional). To test for differences in treatment effect within the various subgroups, p values for interaction were derived from multivariable logistic regression models including treatment, covariate coding for subgroup level, and an interaction term.

For comparison of secondary endpoints between the hydrated and non-hydrated groups, we used the Chi square test to test for statistical differences in categorical variables. Differences in mean values of continuous variables were assessed using the Student's *t* test for independent samples. Two-sided p values of 0·05 and lower were considered to indicate statistical significance. We did both intention-to-treat and per-protocol analyses.

The sample size was based on a literature-based expected proportion of patients with contrast-induced nephropathy after prophylactic hydration of 2·4%.[21] The aim was to include 1300 patients within a 2-year inclusion period, enabling the detection of an absolute difference in contrast-induced nephropathy between groups of more than 2·1% (non-inferiority margin) with a power of 80% and one-sided alpha of 5%. Feasibility considerations led to a sample size calculation revision in December, 2015, in consultation with the research ethics committee. It was considered feasible to include 600 patients. Assuming that data on serum creatinine change from baseline might not be available for 10% of patients, 660 patients were randomly assigned.

Analyses were done with statistical software package Epi Info 7 (Centers for Disease Control and Prevention, Atlanta, GA, USA), and SPSS (version 23; SPSS Inc, Chicago, IL, USA).

This trial is registered with ClinicalTrials.gov, number NCT02106234.

Role of the funding source

The funder was not involved in trial design, patient recruitment, data collection, analysis, interpretation or presentation, writing or editing of the reports, or the decision to submit for publication. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

During the recruitment period between June 17, 2014, and July 17, 2016, we registered 28 803 referrals for elective procedures with intravascular iodinated contrast material at the Maastricht University Medical Centre (figure 1; details of referrals are provided in appendix p 2). Of these, 1833 (6%) patients had known eGFR lower than 60 mL per min/1·73 m², which is in line with the incidences found in Europe and the Netherlands in particular.[25,26] 1120 (4%) met the inclusion criteria (see details of exclusions in appendix p 3). 660 (59%) patients gave informed consent, and were randomly assigned to

receive either prophylactic intravenous hydration (H+ group; n=328) or no prophylaxis (H– group; n=332). All randomly assigned patients received their allocated treatment (figure 1). Therefore, in this study, the intention-to-treat population is the same as the per-protocol population, and results from per-protocol analyses did not differ from those of intention-to-treat analyses. In the hydrated group, 170 (52%) of 328 patients received a short hydration protocol and 158 (48%) of 328 patients received a long hydration protocol.

Baseline characteristics were well balanced between H+ and H– groups (table 1). Baseline characteristics were also consistent with, and representative of, those of the whole eligible population. The mean age was 72·2 years (SD 9·3), 407 (62%) of 660 participants were men, 57 (9%) were inpatients, and 215 (33%) had diabetes. Mean total intravenous hydration volume given to H+ group patients was 1637 mL (SD 950). Mean volume contrast material administered was 91 mL (SD 41).

Data for serum creatinine level at 2–6 days post-contrast were available for 603 (91%) of 660 patients. The 2–6 day follow-up measurements were similarly distributed over the timeframe for both groups (appendix p 4). 57 patients were excluded from the primary endpoint analysis, which was done on a modified intention-to-treat basis. Reasons for loss to follow-up were mostly logistics, and none were related to the study intervention; baseline characteristics of patients excluded from the analysis were similar to those of patients included in the analysis (appendix p 5).

Mean 2–6 day change in serum creatinine was 0·31 µmol/L in the H+ group (SD 13·79), and 1·30 µmol/L in the H– group (SD 15·09; p=0·4049). An increase of more than 25% or 44 µmol/L increase in serum creatinine from baseline (ie, contrast-induced nephropathy) was recorded for eight (2·7%) of 296 patients in the H+ group and for eight (2·6%) of 307 patients in the H– group. The absolute difference in proportions with contrast-induced nephropathy (no hydration *vs* hydration) was –0·10% (one-sided 95% CI –2·25 to 2·06; one-tailed p=0·4710). The upper limit being lower than 2·1% excludes a difference in favour of the hydration group of more than 2·1% (figure 2).

Figure 2 also shows results for subgroup analyses on contrast-induced nephropathy incidence. The difference in risk of contrast-induced nephropathy between hydrated and non-hydrated groups is small within all subgroups, but because of limited sample size one-sided 95% confidence intervals are wide and exceed the non-inferiority margin of 2·1% in all but two cases. P values for interaction are non-significant: diabetics versus non-diabetics, p=0·5722; eGFR <45 mL per min/1·73 m² versus eGFR ≥45 mL per min/1·73 m², p=0·6040; intra-arterial versus intravenous contrast administration; p=0·9608; interventional versus diagnostic procedure; p=0·3289 (figure 2).

Table 2 provides an overview of mean costs per patient (appendix p 6 shows unit prices used). Missing information about costs concerned productivity loss, general practitioner or specialist visits or telephone consultations, and renal diagnostics. The percentage of missing cases on these items varied between 9% and 15%. For multiple imputation we used the variables age, sex, and allocated treatment as predictor variables. Five datasets with imputed values were generated and pooled results were used for the cost analysis. No hydration was significantly cost-saving compared with hydration. Largest savings were due to reduced hospitalisation costs. Savings due to sequelae of intravenous hydration

	H+ group given standard prophylactic treatment (n=296)		H– group given no prophylactic treatment (n=307)		€ Difference in costs: H- group minus H+ group* (95% CI)
	Resource use	Mean costs (€)	Resource use	Mean costs (€)	
In-hospital costs					
Duration of hospitalisation					
None	..	..	50%	0†	
Day care (0 nights)	45%	162	27%	82	–80 (–105 to –55)
24 h (including 1 night)	27%	174	12%	76	–98 (–137 to –60)
Long stay (including ≥2 nights)‡	18%	257	3%	49	–208 (–275 to –137)
Long stay inpatients (including ≥2 nights)§	9%	765	8%	560	–205 (–833 to 245)
Materials					
1 L 0·9% NaCl intravenous bags	1·60	4·50	0	0	–4·50 (–5 to –4)
Sequelae of intravenous hydration					
Extra hospitalisation days (24 h)	0·06	37	0	0	–37 (–72 to 11)
Extra in-hospital specialist consultations	0·04	2·31	0	0	–2·31 (–4 to –1)
Extra in-hospital diagnostics (ECG, ultrasound, laboratory)	0·02	0·88	0	0	–0·88 (–1 to 0)
Outside hospital costs within 35 days					
Renal diagnostics					
Blood tests	0·14	0·88	0·13	0·78	–0·01 (0 to 0)
Urine tests	0·13	2·26	0·09	1·38	–0·88 (–2 to 0)
Ultrasound exams	0·07	4·30	0·04	1·30	–4 (–5 to –1)
Other					
General practitioner consultation	0·19	3·67	0·25	6·13	2·5 (0 to 6)
Productivity loss (h)¶	1·3	50·50	0·44	16·80	–34 (–77 to 0)

Resource use is given as % of patients using the resource or as mean number of units used per patient. Mean total costs were €1455 for the H+ patient and €792 for the H– patient (mean difference H– minus H+: €–663, 95% CI –1234 to –191). For unit prices see appendix p 6. All cost prices were indexed to the year 2015. Major renal events did not incur extra costs. ECG=electrocardiogram. *Obtained from the bootstrap analysis. †50% of the non-hydrated group was not hospitalised at all surrounding the contrast procedure and therefore incurred no hospitalisation costs. ‡Hospitalisation of patients specifically admitted for the procedure. §Hospitalisation of patients admitted for other reasons, before referral for the contrast procedure. ¶Productivity loss was calculated as the number of hours patients were absent from work multiplied by the gross wage per hour for men and women.

***Table 2*: Cost analysis**

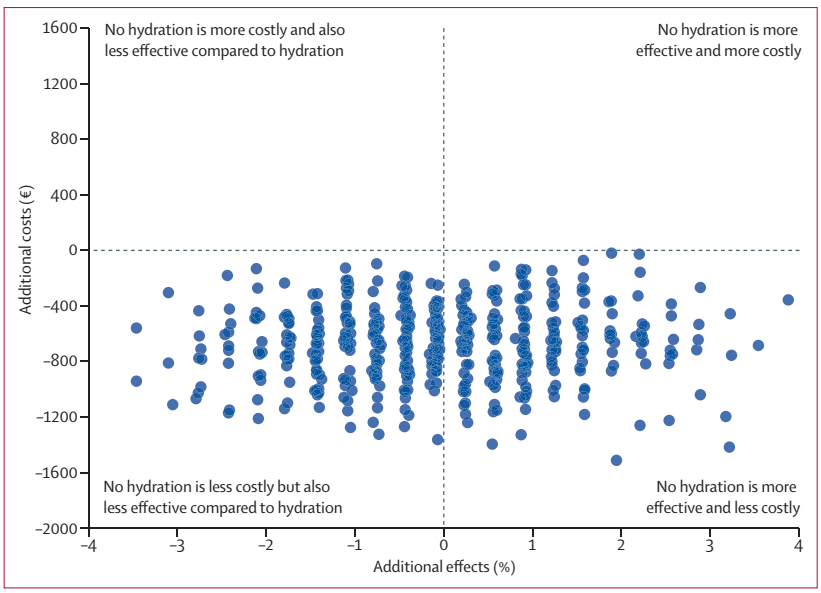

***Figure 3*: Cost-effectiveness plane of no hydration versus intravenous hydration**
Data were generated using bootstrap simulation (1000 replications), based on the data of the trial. The x-axis shows difference in effectiveness (ie, in percentage of contrast-induced nephropathy cases prevented), the y-axis shows difference in costs in €. This figure was generated using Microsoft Excel 2010 (Microsoft, Redmond, WA, USA).

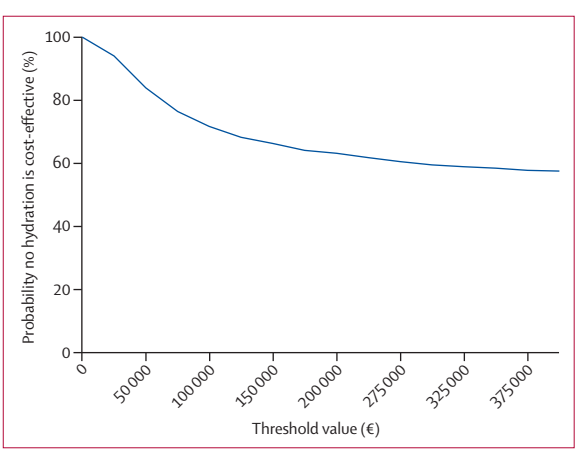

***Figure 4*: Acceptability curve**
Currently no threshold value for a loss in effectiveness in the prevention of contrast-induced nephropathy has been defined. A low monetary threshold value would be sufficient if the effect of contrast-induced nephropathy on quality of life and incurred costs was limited. A higher threshold value would be required if long-term and costly consequences such as dialysis exist.

and productivity loss were minor. Major renal events did not lead to extra costs because no patient required dialysis or was admitted to intensive care, and a decline in renal function as defined in our study was not actively treated and did not lead to extra diagnostics within 35 days. The mean number of diagnostic tests and GP consultations were very low. No extra specialist consultation or hospitalisation due to adverse events following the procedure occurred within 35 days (table 2).

The cost-effectiveness plane in figure 3 shows 55% of simulated cost-effectiveness ratios are situated in the quadrant where no hydration is more effective and less costly. 45% are located in the southwest quadrant where no hydration is cost-saving albeit less effective, but the majority of these fall within the non-inferiority margin. For this southwest quadrant the acceptability curve in figure 4 shows the probability that no hydration will be considered cost-effective for different monetary threshold values. This probability is always greater than 50%, varying from 96% (threshold value €20 000) to 58% (threshold value €375 000).

At 26–35 days post-contrast, serum creatinine values were available for 520 patients, therefore 140 patients were excluded from the 26–35 day serum creatinine analysis. Again, reasons for loss to follow-up were mostly logistics, and none were related to the study intervention. Baseline characteristics were similar between patients included versus those excluded from analysis (appendix p 5). Mean change at 26–35 days was 1·44 µmol/L in the H+ group (SD 17·10), and 1·39 µmol/L in the H– group (16·12; p=0·9705).

Table 3 provides incidences of major adverse events in the standard prophylactic treatment (H+) and no prophylaxis (H–) groups. We recorded no instances of renal failure (eGFR <15 mL per min/1·73 m²). At 26–35 days post-contrast, a renal decline of more than 10 eGFR units occurred in seven (2·7%) of 260 patients in the H+ group, and in 11 (4·2%) patients in the H– group (p=0·3512). Renal function decline to eGFR lower than 30 mL per min/1·73 m² occurred in seven (2·7%) patients in the H+ group, and in six (2·3%) patients in the H– group (p=0·7881). A decline of more than 10 eGFR units bringing renal function eGFR to a level lower than 30 mL per min/1·73 m² occurred in two (0·8%) patients in the H+ group, and in two (0·8%) patients in the H– group (p>0·9999). Three patients died of unrelated causes in the H– group (causes of death: cardiac arrest in a terminal cancer patient, internal haemorrhage in an aneurysm patient, and suspected stroke in a patient admitted for severe infection of extremity). Zero instances of intensive care admission or dialysis were recorded within 35 days. 18 (5·5%) of 328 patients in the standard prophylactic treatment (H+) group experienced sequelae of intravenous hydration. 13 (4·0%) patients experienced complications which led to hydration being stopped prematurely, forced diuresis, or extended hospitalisation. One (0·3%) patient had hyponatraemia and four (1·2%) had arrhythmia during hydration treatment. No similar events were recorded in the H– group (table 3).

Discussion

We found no prophylactic treatment to be non-inferior to prophylactic intravenous hydration in the prevention of contrast-induced nephropathy. No hydration was significantly cost-saving relative to intravenous hydration,

and probability of no hydration being cost-effective is always higher than 50%. Differences in renal function or safety endpoints between high-risk patients receiving prophylaxis and those not receiving prophylaxis were small and non-significant. Intravenous hydration was not without risk as 18 (5·5%) patients experienced complications.

Many clinical trials of how to prevent contrast-induced nephropathy have been done, but most have focused on comparing one form of prophylaxis with another. Furthermore, these studies were done in populations receiving various contrast media types, focused on either intravenous or intra-arterial procedures, and often involve only inpatients or patients with specific and severe disease profiles. We identified only three clinical trials on the prevention of contrast-induced nephropathy including a randomly assigned group not receiving prophylaxis. Two were done in patients with ST-elevation myocardial infarction, most of whom had normal renal function, and both found prophylaxis superior which might be explained by other factors inherent to this population. One included patients suspected of pulmonary embolism, comparing no prophylaxis to intravenous 1·4% sodium bicarbonate pre-hydration, and found no prophylaxis non-inferior.[27–29] Most studies comparing intravenous hydration to oral prophylaxis find oral prophylaxis non-inferior.

To the best of our knowledge, no randomised trial has prospectively compared intravenous hydration as proposed by the guidelines to no prophylaxis in the high-risk population targeted by the guidelines. The AMACING study population represents the high-risk population the guidelines were written for—ie, all patients considered at risk of contrast-induced nephropathy, rather than a specific clinical setting. Only 9% were inpatients, and all procedures included in the AMACING study were done using minimum volume pre-warmed, low-osmolar, monomer, non-ionic, contrast material. The latter might explain why contrast-induced nephropathy incidences found in the AMACING trial were low (2·6–2·7%). However, baseline contrast-induced nephropathy incidence in an untreated high-risk population is unknown, and we did not influence contrast administration parameters but rather recorded clinical practice. Therefore, the results suggest that standardised, safe and effective use of iodinated contrast material is possible across procedure types, even in high-risk patients.

We did pre-planned subgroup analyses to explore whether specific groups of patients are especially vulnerable to withholding prophylaxis. These data suggest that between-group differences in proportions with contrast-induced nephropathy are small. In patients with diabetes, risk of contrast-induced nephropathy was slightly higher in the no hydration group, whereas in the subgroup with eGFR lower than 45 mL per min/1·73 m² the no hydration group had a slightly lower risk of contrast-induced nephropathy. Because of the small subgroup sample sizes confidence intervals are wide, upper levels often exceeding the non-inferiority margin of 2·1%. Nevertheless, interaction p values were not significant, suggesting a consistency of effect across subgroups and a general trend that none of the subgroups are at a clear disadvantage without prophylaxis.

	H+ group	H– group	Absolute difference: H–group minus H+ group (95% CI)	p value
Renal events within 26–35 days post-contrast				
Renal failure (eGFR <15 mL per min/1·73 m²)	0	0	0	1·0000
>10 eGFR unit renal function decline from baseline	7/260 (2·7%)	11/260 (4·2%)	1·5 (–1·60 to 4·68)	0·3512
Renal function decline to eGFR <30 mL per min/1·73 m²	7/260 (2·7%)	6/260 (2·3%)	–0·4 (–3·07 to 2·30)	0·7881
Both >10 eGFR unit decline from baseline and a decline to eGFR <30 mL per min/1·73 m²	2/260 (0·8%)	2/260 (0·8%)	0·0 (–1·50 to 1·50)	>0·9999
Mortality, dialysis, and intensive care admission within 35 days post-contrast				
All-cause mortality	0/328	3/332 (0.9%)	0·9 (–0·11 to 1·92)	0·1267
Dialysis	0/328	0/332	0	1·0000
Intensive care admission	0/328	0/332	0	1·0000
Sequelae of intravenous hydration in the standard prophylactic treatment group				
Symptomatic heart failure	13/328 (4·0%)	0/332	–4·0 (–6·08 to –1·85)	0·0001
Hypernatraemia	0/328	0/332	0	1·0000
Hyponatraemia	1/328 (0·3%)	0/332	–0·3 (–0·90 to 0·29)	0·4970
Arrhythmia	4/328 (1·2%)	0/332	–1·2 (–2·41 to –0·03)	0·0604

eGFR=estimated glomerular filtration rate.

***Table* 3: Incidence of major adverse events in the standard prophylactic treatment (H+) and no prophylactic treatment (H–) groups**

Baseline contrast-induced nephropathy incidence in an untreated population being unknown at the time, we did not include patients with eGFR lower than 30 mL per min/1·73 m² out of safety considerations. We excluded 157 patients for this reason (0·5% of 28 803 referrals), which reflects the prevalence of this degree of chronic kidney disease reported for the general population (0·2–0·5%).[5] Thus, only a small portion of the high-risk population targeted by the guidelines was excluded from the AMACING trial by applying this criterion. However, future research could focus on this subgroup to establish whether intravenous hydration is beneficial. We also excluded emergencies and intensive care patients from our study population. Our results, therefore, cannot be generalised to include such cases, where other factors such as higher contrast volume or haemodynamic instability might play a part and where some benefit of hydration has been found.[27,28]

Our definition of contrast-induced nephropathy differed from the most commonly used definition. We maintained the criterion of an increase in serum creatinine by more than 25% or 44 µmol/L, but allowed a larger timeframe of 2–6 days post-contrast instead of the more widely accepted 48–72 h. Where 48–72 h is feasible in inpatient groups, in clinical practice with outpatients 2–6 days is more realistic.

Although serum creatinine rises within 48 h, it peaks between 4 and 5 days post-contrast on average,[30] and therefore we expect only very transient changes would be missed by early or late measurements.

Cost prices used within the cost analysis are specific for the Dutch situation and might differ depending on specific prices in different countries. However, data on resource use should allow others to determine applicability to their own situation.

A limitation of the AMACING study is that it was a single-centre study. However, Maastricht University Medical Centre is a local and regional hospital, and patients come from all over the Netherlands. Furthermore, Maastricht University Medical Centre uses national protocols implemented in most hospitals. The sample size was smaller than planned, but nevertheless the upper limit of the 95% CI, expressing the uncertainty around the recorded difference in proportions of patients with contrast-induced nephropathy, falls below the pre-defined non-inferiority margin of 2·1%. The data observed in this trial therefore support the hypothesis that not giving prophylaxis is non-inferior to prophylactic hydration. The study had an open-label design because masking was almost impossible. However, the primary endpoint serum creatinine was determined by laboratory personnel masked to allocated treatment. Therefore, we do not think the open nature of the trial affected results. Post-contrast serum creatinine measurements were not available for all patients. However, baseline characteristics of patients included were similar to those not included in the analyses, and absence of serum creatinine values within the pre-specified timeframes was unrelated to the study intervention.

Setting a non-inferiority margin for contrast-induced nephropathy is not straightforward. Because of the paucity of placebo-controlled trials on effectiveness of prophylactic hydration, a formal approach basing the non-inferiority margin on meta-analysis estimates was not an option. Estimates of the difference in proportions of contrast-induced nephropathy with 95% CIs were simply not available. Based on the assumption that contrast-induced nephropathy incidence would be 2·4% in a population that had received prophylaxis,[21] we chose a non-inferiority margin of 2·1%. This margin was considered acceptable, because although contrast-induced nephropathy might be associated with increased morbidity and mortality, contrast-induced nephropathy itself usually resolves leaving no lasting effects, and clinically relevant consequences are reported to occur in fewer than 1% of cases.[6–8] In addition, although an association between increased risk of mortality and dialysis and contrast-induced nephropathy has been reported in some of the relevant literature, there is no evidence of a causal relationship, and contrast-induced nephropathy might be a marker only. Importantly, it has not been shown that standard care prophylactic hydration reduces the risk of long-term effects. The true long-term consequences of contrast-induced nephropathy in terms of renal dysfunction and related morbidity and mortality are unknown, and research into renal damage biomarkers, which might elucidate the underlying mechanisms, is only just emerging. We found no evidence of progression to dialysis or death within 35 days of contrast exposure, and there was no suggestion of differences in persisting renal problems between groups.

The AMACING study found no prophylaxis to be non-inferior to prophylactic intravenous hydration in the prevention of contrast-induced nephropathy, as well as cost-saving. Additionally, we noted that hydration by itself sometimes leads to complications. This is a substantial problem, considering the 6–12 million high-risk patients that undergo procedures with intravascular iodinated contrast administration every year worldwide. Based on these findings and assuming optimal contrast media administration, withholding prophylaxis for high-risk patients with eGFR higher than 29 mL per min/1·73 m² might be considered without compromising patient safety.

Contributors

ECN had full access to the data and takes responsibility for the integrity of the data and accuracy of the analysis. JEW, RJR, VvO, MMJ, and MAV came up with the study concept. ECN, JEW, RJR, VvO, PJN, BAE, MMJ, and MAV developed the study protocol and designed the study. ECN and JEW supervised the study, ECN gathered the data. JEW secured funding. ECN and PJN analysed and interpreted the data. PJN did the statistical analysis. BAE and ECN did the cost analysis. ECN drafted the report. JEW, RJR, VvO, BAE, and PJN critically revised the report. MMJ and MAV provided administrative and material support.

Declaration of interests

We declare no competing interests.

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