Research Paper

Prophylactic Intravenous Hydration to Protect Renal Function From Intravascular Iodinated Contrast Material (AMACING): Long-term Results of a Prospective, Randomised, Controlled Trial

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ABSTRACT

Background: The aim of A MAastricht Contrast-Induced Nephropathy Guideline (AMACING) trial was to evaluate non-inferiority of no prophylaxis compared to guideline-recommended prophylaxis in preventing contrast induced nephropathy (CIN), and to explore the effect on long-term post-contrast adverse outcomes. The current paper presents the long-term results.

Methods: AMACING is a single-centre, randomised, parallel-group, open-label, phase 3, non-inferiority trial in patients with estimated glomerular filtration rate [eGFR] 30–59 mL/min/1.73 m^2 combined with risk factors, undergoing elective procedures requiring intravenous or intra-arterial iodinated contrast material. Exclusion criteria were eGFR <30 mL/min/1.73 m^2, dialysis, no referral for prophylaxis. The outcomes dialysis, mortality, and change in renal function at 1 year post-contrast were secondary outcomes of the trial. Subgroup analyses were performed based on pre-defined stratification risk factors. AMACING is registered with ClinicalTrials.gov: NCT02106234.

Findings: From 28,803 referrals, 1120 at-risk patients were identified. 660 consecutive patients agreed to participate and were randomly assigned (1:1) to no prophylaxis (n = 332) or standard prophylactic intravenous hydration (n = 328). Dialysis and mortality data were available for all patients. At 365 days post-contrast dialysis was recorded in two no prophylaxis (2/332, 0.60%), and two prophylaxis patients (2/328, 0.61%; p = 0.9909); mortality was recorded for 36/332 (10.84%) no prophylaxis, and 32/328 (9.76%) prophylaxis patients (p = 0.6490). The hazard ratio was 1.118 (no prophylaxis vs prophylaxis) for one-year risk of death (95% CI: 0.695 to 1.801, p = 0.6449). The differences in long-term changes in serum creatinine were small between groups, and gave no indication of a disadvantage for the no-prophylaxis group.

Interpretation: Assuming optimal contrast administration, not giving prophylaxis to elective patients with eGFR 30–59 mL/min/1.73 m^2 is safe, even in the long-term.

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1. Introduction

Contrast-induced nephropathy (CIN), also known as contrast-induced acute kidney injury (CI-AKI), is marked by a decline in renal function typically occurring 2 to 5 days after intravenous or intra-arterial iodinated contrast material administration [1–4]. This phenomenon primarily affects patients whose renal function is already compromised. It usually resolves spontaneously, leaving no lasting effects, but is associated with increased morbidity and mortality [1,5–7]. No treatment for CIN/CI-AKI exists, therefore the focus lies on prevention.

Guidelines on the use of intravascular iodinated contrast material administration exist in most countries and are implemented in most hospitals [8–13]. They generally recommend intravascular volume expansion with isotonic saline as standard prophylaxis for those considered at risk of CIN/CI-AKI [8–15]. This recommendation has far-reaching consequences for patient, hospital, and health care budgets, because the peri-procedural prophylactic treatment requires hospitalisation for up to 24 h. Furthermore, the impact is substantial given the estimated >75 million procedures with intravascular iodinated contrast material done worldwide annually [16].

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Research in context

Evidence before this study

The aim of the AMACING trial was to evaluate efficacy of current clinical practice guidelines for the prevention of contrast-induced nephropathy, notably of the proposed prophylactic peri-procedural intravenous hydration with normal saline. Ideally, this is achieved by comparing efficacy of the guideline standard prophylaxis to no prophylaxis in preventing CIN/CI-AKI and other unfavourable outcomes associated with intravascular iodinated contrast administration. Furthermore, the population thus studied must consist of those patients the guidelines prescribe prophylaxis for. Such trials evaluating the guidelines were non-existent before AMACING. Indeed, randomised trials comparing intravenous hydration to no prophylaxis in the context of CIN/CI-AKI are scarce, and literature searches aiming to find trials including a group randomised to receive no prophylaxis yield at most 4 publications. However, even these studies cannot be used when looking for data on guideline efficacy: three have been done in the acute setting, for which the guideline advice deviates, and also include patients not considered at risk of CIN/CI-AKI according to the guideline (with eGFR higher than 60 mL/min/1.73 m^2). A fourth study randomised 71 at-risk patients from one specialty to no prophylaxis, but compared them to 67 at-risk patients who received one-hour pre-contrast intravenous hydration with sodium bicarbonate, which is different from the guideline standard peri-procedural intravenous hydration with normal saline.

Added value of this study

To the best of our knowledge, no randomised trial other than AMACING has prospectively compared intravenous hydration as proposed by the guidelines to no prophylaxis, in the bulk of the at-risk population targeted by the guidelines. Furthermore, the trial population was from all specialties, and 48% received intra-arterial and 52% intravenous iodinated contrast administration. Most studies limit their reporting to a follow-up to the primary outcome, or to short-term in-hospital outcomes. This paper reports clinically relevant, long-term outcomes up to one year post-contrast exposure. This is the first systematic report of such outcomes in this population in the context of CIN/CI-AKI and including outcomes of a large group of patients randomised to receive no prophylactic treatment. The analyses include all patients, including any patients in whom CIN/CI-AKI may have gone undetected, and reflect efficacy of prophylaxis in reducing adverse post-contrast outcomes.

Implications of all the available evidence

Withholding prophylactic intravenous hydration with normal saline can be considered safe for elective patients with eGFR higher than 29 mL/min/1.73 m^2.

Evidence for prevention of CIN/CI-AKI by the recommended prophylactic treatment is scarce, as it had not previously been properly evaluated in the population targeted by the guidelines and against a group not receiving prophylaxis [9,17]. Clinical trials on the prevention of contrast-induced nephropathy are manifold, but most focus on comparing one form of intravenous prophylaxis with another. Only relatively recently were randomised trials published in which a group not receiving any prophylaxis was included. Four such trials, comparing prophylactic intravenous hydration to a group not receiving any prophylaxis, were published in 2014 and 2015 [18–21]. Two of these were done in

the acute setting of primary percutaneous intervention in patients with ST-elevation myocardial infarction [18,19]. Both found significantly lower incidences of CIN/CI-AKI after prophylaxis (22/108 vs 38/108[18] and 22/204 vs 43/204 [19]). One of these trials reported less in-hospital mortality for the prophylaxis group (3/108 vs 10/108) [18], whereas the other found no difference between groups [19]. A third trial was done in the setting of computed tomography for suspected pulmonary embolism, and no prophylaxis was found to be non-inferior to prophylactic intravenous hydration with sodium bicarbonate (CIN/CI-AKI 5/70 vs 6/65) [20]. The fourth trial was done in normal and chronic kidney disease hospitalised patients with computed tomography, and found no difference in efficacy between pre-hydration with sodium bicarbonate and no prophylaxis (CIN/CI-AKI 3/43 vs 4/44) [21]. The reports do not go beyond in-hospital outcomes. In patients at risk, post-contrast increased risk of dialysis and mortality in the long term is consistently reported, and it is unknown whether prophylactic intravenous hydration mitigates these [5–7].

Efficacy of guideline-recommended prophylactic intravenous hydration cannot be determined form the above reports, because the trials were small and/or done in the acute setting, where other factors such as haemodynamic instability play a role. Furthermore, patients with estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2 were included, and these are not considered to be at high risk of post-contrast adverse events [1,8–15].

In 2017 the results on the primary outcome of A MAastricht Contrast-Induced Nephropathy Guideline (AMACING) trial were published. The aim was to evaluate efficacy of prophylaxis according to clinical guidelines in the prevention of post-contrast adverse outcomes in elective patients with estimated glomerular filtration rate [eGFR] 30–59 mL/min/1.73 m^2 combined with risk factors for CIN/CI-AKI [22]. All elective procedures requiring iodinated contrast material administration from all specialties over a two-year period were screened for the trial, and 48% of participants received intra-arterial 52% intravenous iodinated contrast administration. Not giving prophylaxis was found to be non-inferior to standard prophylaxis with normal saline: CIN/CI-AKI 8/296 vs 8/307, no haemodialysis or related deaths occurred within 35 days, and 5.5% of intravenously hydrated patients suffered complications such as heart failure from the prophylactic treatment.

CIN/CI-AKI itself being asymptomatic, the concern is that post-contrast acute renal injury might result in higher rates of mortality and renal function decline in the long term. Prophylaxis is recommended by clinical practice guidelines to prevent such. Furthermore, renal reserve may be affected even in those without defined CIN/CI-AKI, or CIN/CI-AKI may go undetected for other reasons. In evaluating efficacy of guideline-recommended prophylaxis therefore, analysis of long-term mortality and renal function data of all patients with and without prophylaxis and with or without CIN/CI-AKI is imperative. The current paper presents the one-year follow-up results of the AMACING trial: the secondary trial outcomes renal function decline, dialysis, and mortality.

2. Methods

2.1. Study Design and Participants

The AMACING trial is a single-centre, prospective, randomised, phase 3, parallel-group, open-label, controlled trial designed to assess the safety, clinical- and cost-effectiveness of guideline-recommended standard prophylactic intravenous hydration. A non-inferiority design was chosen based on the assumption that although post-contrast adverse events might occur more often in absence of prophylaxis, withholding intravenous hydration might have the advantage of reducing patient burden and health-care costs. Study details and primary results have been published elsewhere [22].

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 were prospectively screened to establish whether they met the study criteria. Patients were eligible for inclusion if they had eGFR between 45 and 59 mL/min/1.73 m^2 combined with diabetes, or at least two guideline-specified 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 (heart failure; arterial disease); non-steroidal anti-inflammatory drug or diuretic nephrotoxic medication); or eGFR between 30 and 44 mL/min/1.73 m^2; or multiple myeloma or lymphoplasmacytic lymphoma with small chain proteinuria. These criteria corresponded to the criteria for identifying patients at-risk according to guidelines current at the time of inclusion [23]. eGFR was calculated with serum creatinine concentrations and the Modification of Diet in Renal Disease (MDRD) study equation as recommended by the same guidelines.

Exclusion criteria were inability to obtain informed consent, eGFR <30 mL/min/1.73 m, 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).

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.

2.2. Randomisation and Masking

Eligible and consenting patients were randomly assigned (1:1) to receive either no prophylaxis (H − group), or prophylactic intravenous hydration (H + group). Randomisation was stratified by diabetes (yes *vs* no), renal function (eGFR 30–44 *vs* 45–59 mL/min/1.73 m^2), contrast administration route (intra-arterial *vs* intravenous), and procedure type (interventional *vs* diagnostic). Randomisation was computer generated using the ALEA screening and enrolment application software (version v3.0.2083.212r; Formsvision BV, Abcoude, the Netherlands).

Laboratory personnel processing samples for serum creatinine values were masked to treatment allocation, with samples being labelled with coded stickers only. Minimisation with stratification factors 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 no prophylaxis and intravenously hydrated patients. Therefore an open label design was chosen.

2.3. Procedures

Procedures for obtaining data on: baseline characteristics, prophylactic hydration, contrast procedure, complications of intravenous hydration, primary endpoint (CIN/CI-AKI), one-month renal function, changes in use of medication, use of resources, and presence or absence of major adverse events up to one month post-contrast exposure are detailed elsewhere [22].

Prophylactic hydration protocols used for patients randomised to the standard prophylaxis group were according to the guidelines and prescribed by the treating physician: [23] standard protocol intravenous 0.9% NaCl 3–4 mL/kg mL/min h, during 4 h before and 4 h after contrast administration; long protocol intravenous 0.9% NaCl 1 mL/kg mL/min 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. Drinking habits of participants were not influenced.

All patients received pre-warmed (37 °C) intravascular contrast material with 300 mg iodine mL/min mL (iopromide, Ultravist, Bayer Healthcare, Berlin, Germany), which is a non-ionic, monomeric, low-osmolar iodinated contrast medium. Contrast administration parameters were not interfered with. Our institution uses personalised parameters (P3T, Certegra, Bayer) for optimal contrast volume and flow rate determination.

One-year follow-up data were obtained by consulting the hospital electronic file, through contact with the participant, their GP, their local hospital, or their local laboratory. The following data were recorded: serum creatinine and eGFR, renal replacement therapy including dates of first and (where applicable) last treatments, and mortality, including date and primary cause.

2.4. Outcomes

Clinical outcomes at one-year post-contrast exposure were pre-defined secondary outcomes of the AMACING trial. The main one-year outcomes were incidences of dialysis and all-cause mortality within 365 days post-contrast administration. Long-term change in renal function was analysed by comparing mean serum creatinine, mean change in serum creatinine from baseline, and incidence of major renal adverse events. Major renal adverse events were defined as 1. renal failure (defined as eGFR <15 mL/min/1.73 m^2); 2. renal decline with more than 10 eGFR units; 3. renal decline to eGFR <30 mL/min/1.73 m^2; 4. a combination of the latter two.

Change in renal function over time was evaluated at 2 to 6 days, 26 to 35 days and one-year post-contrast exposure. Where a value at one year post-contrast exposure was unavailable, the available value closest to 365 days post-contrast was used, with a maximum allowable range of 180 to 450 days. For patients receiving dialysis, last known serum creatinine in absence of dialysis was recorded.

2.5. Statistical Analysis

The sample size was based on detection of non-inferiority of no prophylaxis compared to standard prophylaxis with respect to the primary outcome CIN/CI-AKI. Based on the literature, the expected proportion of patients with CIN/CI-AKI after prophylaxis was 2.4%, and the non-inferiority margin was set at 2.1%, the power at 80% and (one-sided) alpha at 5%. Details are published elsewhere [22]. In absence of available data on incidences, it was not possible to predefine non-inferiority margins for the secondary outcomes as is explained in the discussion. Such margins must be defined in terms of demonstrating that part of the effect of prophylactic intravenous hydration will be retained. However, trials evaluating the effect on 1 year morbidity and mortality after contrast administration are not available in the literature.

Continuous data is reported as mean (standard deviation, SD), or median (interquartile range, IQR), and categorical data is presented as absolute numbers and percentages. The results are given as absolute differences with two-sided 95%/one-sided 97.5% confidence intervals (CI). We can have 97.5% confidence that an increase in unfavourable clinical outcomes (no prophylaxis minus prophylaxis) will not exceed the upper limit of the confidence intervals.

For comparison of categorical variables between the no prophylaxis and intravenously hydrated groups, the Chi square test was used to test for statistical differences. Differences in mean values of continuous variables were assessed using the Student's *t* test for independent samples. Survival analyses were used (Kaplan Meier and Cox regression) to evaluate whether deaths occurred earlier in the no prophylaxis group than in the intravenously hydrated group. A hazard ratio with 95% confidence interval (CI) was calculated. Between-group difference in (change in) serum creatinine over time was evaluated by using a linear mixed model, which accounts for correlation between repeated measurements as well as for missing values.

Pre-planned subgroup analyses were done within pre-specified subgroups: diabetes (yes *vs* no), renal function (eGFR 30–44 *vs* 45–59 mL/min/1.73 m^2), contrast administration route (intra-arterial *vs* intravenous), and procedure type (interventional *vs* diagnostic). To test for

differences in treatment effect between 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.

p values of 0.05 and lower were considered to indicate statistical significance. Both intention-to-treat and per-protocol analyses were done.

Analyses were done with IBM SPSS Statistics for Windows (version 23; IBM Corp., Armonk, N.Y., USA) and STATA (version 13.1).

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

2.6. Role of the Funding Source

The funder, Stichting de Weijerhorst, 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.

3. Results

During the recruitment period between June 17, 2014, and July 17, 2016, 28,803 referrals for elective procedures with intravascular iodinated contrast material were registered at the Maastricht University Medical Centre. 1833 patients with known eGFR <60 mL/min/1.73 m^2 were identified, and 1120 patients met the trial inclusion criteria: 432 patients with eGFR 30–44 mL/min/1.73 m^2 (1.5%), and 688 patients with eGFR 45–59 mL/min/1.73 m^2 (2.4%) combined with risk factors for CIN/CI-AKI. In total 157 patients were excluded because of eGFR <30 mL/min/1.73 m^2 (0.5%) [24].

660/1120 patients gave informed consent and were randomly assigned to receive either no prophylaxis (H− group; n = 332), or standard prophylactic intravenous hydration (H+ group; n = 328). All randomly assigned patients received their allocated treatment (Fig. 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. Baseline characteristics were well balanced between H− and H+ groups (Table 1) [22]. In the hydrated group, 52% received a short hydration protocol and 48% received a long hydration protocol. Intra-arterial contrast procedures were 2/3 coronary catheterisations, 1/3 percutaneous coronary intervention, 1/10 other. Intravenous contrast procedures were computed tomography in 99% of cases.

Data on dialysis and all-cause mortality within 365 days post-contrast administration were available for all 660/660 (100%) patients (Table 2).

Dialysis within 365 days was recorded in two (0.60%) of 332 no prophylaxis, and in two (0.61%) of 328 intravenously hydrated patients, with an absolute difference (H− minus H+) of −0.01% (95% CI −1.19 to 1.18; p = 0.9909).

Death within 365 days was recorded for 36 (10.84%) of 332 no prophylaxis patients, and for 32 (9.76%) of 328 intravenously hydrated patients, with an absolute between-group difference (H− minus H+) of +1.01% (95% CI −3.55 to 5.72; p = 0.6490). Primary causes of deaths in the H− group were: cancer 23/36, cardiovascular 7/36, sepsis 3/36, respiratory 1/36, unknown 2/36. Primary causes of deaths in the H+ group were: cancer 18/32, sepsis 3/32, pneumonia 3/32, cardiovascular 2/32, cerebral oedema 1/32, old age 1/32, heart- and renal- failure 1/32 (renal failure in this case was eGFR 7 mL/min/1.73 m^2), pulmonary embolism 1/32, unknown 2/32.

Table 2 also shows the results for subgroup analyses on comparative incidences of dialysis and mortality within 365 days post-contrast exposure. The difference in risk between no prophylaxis and intravenously hydrated patients is small within all subgroups, and p values for interaction were not significant.

Fig. 2 shows the Kaplan Meier survival plot for the H− and H+ groups. Cox regression analysis comparing no prophylaxis to intravenous hydration resulted in a non-significant hazard ratio of 1.118 (95% CI: 0.695 to 1.801, p = 0.6449) for one-year risk of death.
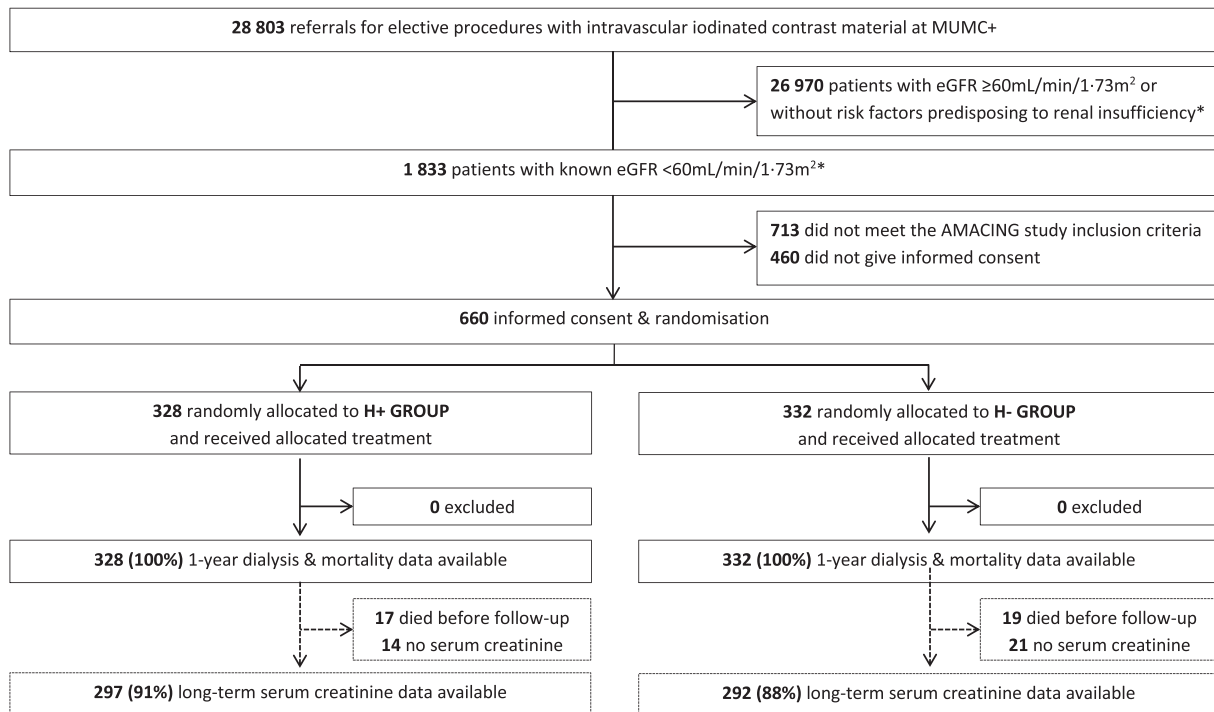

Fig. 1. Trial profile. MUMC+ = Maastricht University Medical Centre; eGFR = estimated glomerular filtration rate. H+ group = received standard 0.9% NaCl prophylactic intravenous hydration. H− group = received no prophylaxis. *Our institution follows the screening guidelines that propose renal function needs only be assessed if one of the following risk factors is present: age >60 years, diabetes mellitus, use of nephrotoxic medication, urologic or nephrologic history, hypertension, peripheral vascular/cardiac disease, multiple myeloma/lymphoplasmacytic lymphoma.

Table 1
Baseline characteristics.

	H+ group standard prophylaxis (n = 328)	H− group no prophylaxis (n = 332)
Men	194 (59%)	213 (64%)
Age at time of contrast administration	71.9 (9.3)	72.6 (9.3)
BMI (kg/m^2)	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/min/1.73 m^2)	47.30 (7.95)	47.59 (8.01)
Serum creatinine (μmol/L[a])	118.78 (27.63)	117.71 (24.62)
Guideline risk groups		
eGFR 45–59 mL/min/1.73 m^2 and two risk factors	138 (42%)	151 (45%)
eGFR 45–59 mL/min/1.73 m^2 and diabetes	74 (23%)	65 (20%)
eGFR 30–44 mL/min/1.73 m^{2b}	114 (35%)	115 (35%)
Multiple myeloma or lymphoplasmacytic lymphoma[c]	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[d]	81 (25%)	103 (31%)
Cardiovascular disease	236 (72%)	257 (77%)
Administered volumes (mL)		
300 mg iodine/mL contrast	92 (41)	89 (41)
Intravenous 0.9% sodium chloride		
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.
  [a] To convert to mg/dL, divide by 88.4.
  [b] 76 of the 231 patients with eGFR < 45 mL/min/1.73 m^2 had diabetes.
  [c] 1 H+ group and 1 H− group multiple myeloma or lymphoplasmacytic lymphoma patient also had an eGFR 30–44 mL/min/1.73 m^2.
  [d] Anaemia is defined as haematocrit value <0.36 L/L for women and <0.39 L/L for men.

Long-term serum creatinine data were available for 589/660 (89%) patients: for 292/332 (88%) of the H− group, and for 297/328 (91%) of the H+ group. Median follow-up time was 339 days post-contrast exposure for the H− group (IQR 285-375), and 339 days post-contrast exposure for the H+ group (IQR 292-376). Reasons for loss to follow-up for serum creatinine were mostly logistic and not related to the study treatment, and included 36 deaths within 180 days post-contrast exposure (19 in the H− group and 17 in the H+ group).

Observed mean serum creatinine values and mean changes in serum creatinine for the H− and H+ groups at baseline, 2 to 6 days, 26 to 35 days, and long-term (range 180 to 450 days) post-contrast exposure are shown in Fig. 3. Observed long-term mean change in serum creatinine from baseline was +6.66 μmol/L (SD 42.17) in the H− group, and +7.30 μmol/L (SD 29.31) in the H+ group (p = 0.8317). Short-term changes in serum creatinine were published elsewhere: [22] mean changes in serum creatinine at 2 to 6 and 26 to 35 days were +1.30 μmol/L (SD 15.09) in the H− group, and +0.31 μmol/L (SD 13.79) in the H+ group (p = 0.4049), and +1.39 μmol/L (SD 16.12) in the H− group, and +1.44 mol/L (SD 17.10) in the H+ group (p = 0.9705) respectively.

The estimated results of the linear mixed model with random intercept indicated that creatinine levels significantly increased over time in both groups, but the model estimates a non-significant long-term between-group difference in serum creatinine change of −0.682 μmol/L (H− minus H+; 95% CI −4.95 to +3.59; p = 0.754).

Table 3 provides incidences of major adverse events in the no prophylaxis (H−) and standard prophylactic treatment (H+) groups. One instance of renal failure (eGFR <15 mL/min/1.73 m^2) was recorded in the H− group (1/292, 0.34%), and zero in the H+ group, with an absolute between-group difference (H− minus H+) of +0.34% (95% CI −0.97 to 1.91; p = 0.3150). A renal decline of more than 10 eGFR units occurred in 56 patients: in 28 of 292 (9.59%) patients in the H− group, and in 28 (9.43%) of 297 patients in the H+ group, with an absolute between-group difference (H− minus H+) of +0.16% (95% CI −4.65 to 4.99; p = 0.9473). Renal function decline to eGFR 15 to 29 mL/min/1.173 m^2 occurred in 17 patients: in eight of 292 (2.74%) patients in the H− group, and in nine of 297 (3.03%) patients in the H+ group, with an absolute between-group difference (H− minus H+) of −0.29% (95% CI −2.65 to 3.24; p = 0.8337). A decline of more than 10 eGFR units bringing renal function to eGFR <30 mL/min/1.73 m^2 occurred in 21 patients: in ten of 292 (3.42%) patients in the H− group, and in 11 of 297 (3.70%) patients in the H+ group, with an absolute between-group difference (H− minus H+) of 0.28% (95% CI −2.92 to 3.49; p = 0.8547).

Of the patients of the AMACING trial diagnosed with CIN/CI-AKI none had dialysis, one patient died within 365 days post-contrast (H− group; primary cause: cancer), and one patient had an eGFR below 30 mL/min/1.73 m^2 at one year post-contrast (H+ group).

4. Discussion

The differences in the secondary outcomes one-year dialysis, one-year mortality, long-term change in serum creatinine from baseline, or renal events between no prophylaxis and intravenously hydrated groups were small and not significant, and did not show a consistent disadvantage for the no prophylaxis group. Subgroup analyses yielded consistently small differences in one-year dialysis and mortality between the intravenously hydrated and no prophylaxis patients (with vs without diabetes; eGFR 30–44 vs 45–59 mL/min/1.73 m^2; intra-arterial vs intravenous contrast administration; interventional vs diagnostic procedures).

In non-inferiority trials, 95% confidence intervals around the absolute differences between randomised groups are used to decide whether unacceptable loss of effectiveness can be excluded. This unacceptable loss has to be pre-defined by the non-inferiority margin. However, it was not possible to set such margins for the secondary outcomes. What is an acceptable or unacceptable loss in effectiveness can only be judged when the degree of prevention of prophylactic intravenous hydration is known. A prerequisite is therefore the availability of good historical data from previous trials comparing standard care with placebo (or no prophylaxis). Such trials evaluating long-term effects are not available in literature. Without non-inferiority margins definite conclusions on non-inferiority with respect to long-term outcomes cannot be made. However, the extremely small absolute differences observed suggest that there are no substantial negative consequences of withholding prophylaxis, especially considering the observed 5.5% complications incurred by the prophylactic treatment. Similar trials with much larger sample sizes would give more certainty, but it is unlikely that these will be carried out, especially considering the logistic and financial requirements of such trials.

A limitation of the AMACING trial is that post-contrast serum creatinine measurements were not available for all patients, but absence of serum creatinine values was unrelated to the study intervention. Another limitation is that not all long-term serum creatinine values were determined at the same laboratory. Fortunately the laboratories concerned all use the same standardised assay, and Dutch laboratories do comparatively well in accuracy and precision (ca. 4.5%; source: Stichting Kwaliteitsbewaking Ziekenhuis Laboratoria).

Only 9% of the included population were inpatients, and patients with eGFR <30 mL/min/1.73 m^2 were excluded for safety reasons. Emergency and intensive care patients were also excluded from our study population. Our results cannot be generalised to these settings, where other factors such as higher contrast volume or haemodynamic

Table 2
One-year dialysis and mortality in the standard prophylactic treatment (H+) and no prophylactic treatment (H−) groups and pre-defined subgroups.

		H+ group n (%)	H− group n (%)	Absolute difference in proportions (H− minus H+)	95% confidence interval	p value	p value for inter-action
A. Dialysis within 365 days							
Total group		2/328 (0.61%)	2/332 (0.60%)	−0.01	−1.19 to 1.18	0.9909	–
Diabetes	Yes	1/106 (0.94%)	1/109 (0.92%)	−0.03	−2.54 to 2.59	0.9860	0.9906
	No	1/222 (0.45%)	1/223 (0.45%)	−0.00	−1.25 to 1.24	0.9978	
eGFR < 45 mL per min/1.73 m^2	Yes	1/116$^\$$ (0.86%)	1/115 (0.87%)	+0.01	−2.38 to 2.40	0.9957	0.9872
	No	1/212 (0.47%)	1/217 (0.46%)	−0.01	−1.30 to 1.28	0.9883	
Contrast administration route	IA	2/159 (1.26%)	0/160 (0.0%)	−1.26	−2.99 to 0.47	0.2476	[a]
	IV	0/169 (0.0%)	2/172 (1.16%)	+1.16	−0.44 to 2.77	0.2537	
Interventional procedure	Yes	0/53 (0.0%)	0/50 (0.0%)	0.00	–	1.0000	[a]
	No	2/275 (0.73%)	2/282 (0.71%)	−0.02	−1.42 to 1.39	0.9811	
B. Mortality within 365 days							
Total group		32/328 (9.8%)	36/332 (10.8%)	+1.01	-3.55 to 5.72	0.6490	–
Diabetes	Yes	16/106 (15.09%)	15/109 (13.76%)	−1.33	−10.73 to 8.06	0.7848	0.4426
	No	16/222 (7.21%)	22/223 (9.87%)	+2.66	−2.53 to 7.84	0.3227	
eGFR < 45 mL per min/1.73 m^2	Yes	17/116$^\$$ (14.66%)	19/115 (16.52%)	+1.87	−7.49 to 11.22	0.7007	0.9507
	No	15/212 (7.08%)	17/217 (7.83%)	+0.76	−4.21 to 5.73	0.7696	
Contrast administration route	IA	8/159 (5.03%)	4/160 (2.50%)	−2.53	−6.70 to 1.64	0.2539	0.1282
	IV	24/169 (14.20)	32/172 (18.60%)	+4.40	−3.44 to 12.25	0.2775	
Interventional procedure	Yes	3/53 (5.66%)	3/50 (6.00%)	+0.34	−8.72 to 9.40	0.9443	0.9502
	No	29/275 (10.55%)	33/282 (11.70%)	+1.16	−4.06 to 6.38	0.6677	

eGFR = estimated glomerular filtration rate.
[a] No value for interaction could be calculated due to zero events.

instability might play a part, and where some benefit of hydration has been found [25,26].

We did not influence contrast administration parameters and the contrast volumes reflect our clinical practice. At our institution we use personalised protocols to determine optimal contrast volume, but not all centres will similarly minimise contrast volumes or use the same contrast material.

Although the terms CIN/CI-AKI imply a causal relationship, in practice it is not often possible to distinguish between an increase in serum creatinine that is contrast-induced, and one that is caused by another aetiology. CIN/CI-AKI is a correlative diagnosis, and therefore the term post-contrast acute kidney injury (PC-AKI), would perhaps be more accurate [1,10,14]. However, we chose to use the terms CIN/CI-AKI because these are the terms most widely known and used in literature.

The aim of the current trial was to evaluate efficacy of intravenous hydration. We chose to limit ourselves to that aim and have therefore not compared outcomes of patients with and without CIN/CI-AKI, because it would detract from the main research question. Furthermore, comparing patients with and without CIN/CI-AKI would mean carrying out an observational study within the RCT. This would make the paper more complicated and bias results; due to confounding by differences in baseline characteristics between patients with and without CIN/CI-AKI biased results cannot be excluded.

The AMACING trial was about guideline efficacy, not about the (risk of) CIN/CI-AKI. Whether CIN/CI-AKI is synonymous to renal damage and

whether all renal damage is reflected in CIN/CI-AKI incidence cannot be answered from our data. However, the analyses were done amongst all patients, including any patients in whom CIN/CI-AKI may have gone undetected, and reflect efficacy of prophylaxis in reducing adverse post-contrast outcomes.

Earlier randomised controlled trials with a group randomised to receive no prophylaxis included patients with normal renal function, were done in the acute setting in specific specialties and specific procedures, and long-term outcomes were not reported [18–20]. This, to the best of our knowledge, is the first systematic report of long-term post contrast adverse outcomes in this elective population with chronic kidney disease, especially with a large group of patients randomised to receive no prophylaxis. The AMACING trial participants all have eGFR 30–59 mL/min/1.73 m^2 combined with risk factors (diabetes, cardiovascular disease, old age, anaemia, nephrotoxic medication), are from miscellaneous specialties in the elective setting, and received either intravenous (52%) or intra-arterial (48%) iodinated contrast material. Furthermore, all elective procedures with either intravenous or intra-arterial iodinated contrast material administration were screened for inclusion in this trial, and the results therefore reflect daily clinical practice in the elective setting.

After the publication of the AMACING primary results the discussion arose as to whether the included population could be considered to be at (high) risk of CIN/CI-AKI [27–29]. The trial being about guideline efficacy, the population included in the AMACING trial was selected strictly according to the then current guideline-criteria. The results show no
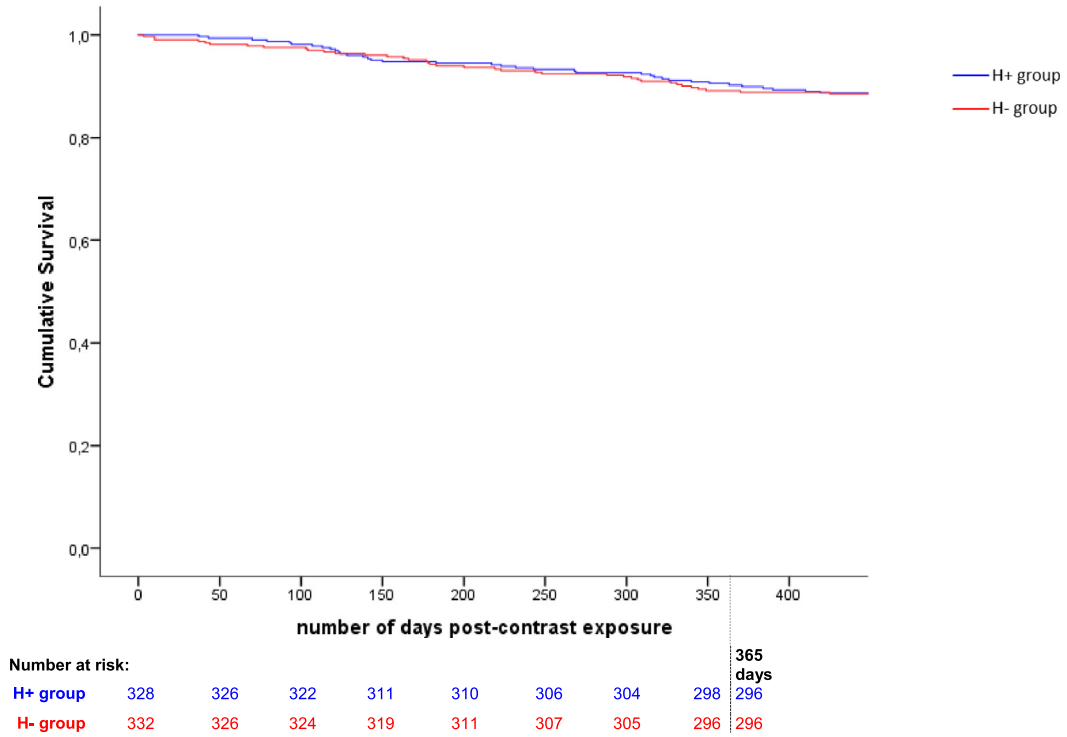
Fig. 2. Kaplan–Meier Survival Plot for the standard prophylactic treatment (H+) and no prophylactic treatment (H−) groups. Hazard ratio for 1-year risk of death 1.118 (95% CI 0.695 to 1.801, n = 660, p = 0.6449).

substantial difference in patient safety over the short- or long-term between the no prophylaxis and standard prophylaxis groups, even when not taking into account the 5.5% complications of intravenous hydration recorded in the prophylaxis group. Exploration of differences within the subgroups with eGFR 30–44 vs 45–59 mL/min/1.73 m^2, and intra-arterial or intravenous contrast administration yielded a similar picture.

It is mostly agreed that the risk of CIN/CI-AKI becomes clinically important from eGFR <60 mL/min/1.73 m^2, but after recent updates a

lower prophylaxis threshold is recommended by most guidelines [1, 8–15]. The KDIGO-, Canadian-, and British- guidelines recommend a threshold of eGFR <45 mL/min/1.73 m^2; others, such as the European guidelines, now recommend a prophylaxis threshold of eGFR <30 mL/min/1.73 m^2 [1,8–15]. These updates were done in absence of data on long-term consequences. Our trial results suggest that for the current population, in the elective setting, and assuming optimal contrast administration, not giving prophylaxis is safe, even in the long-term.
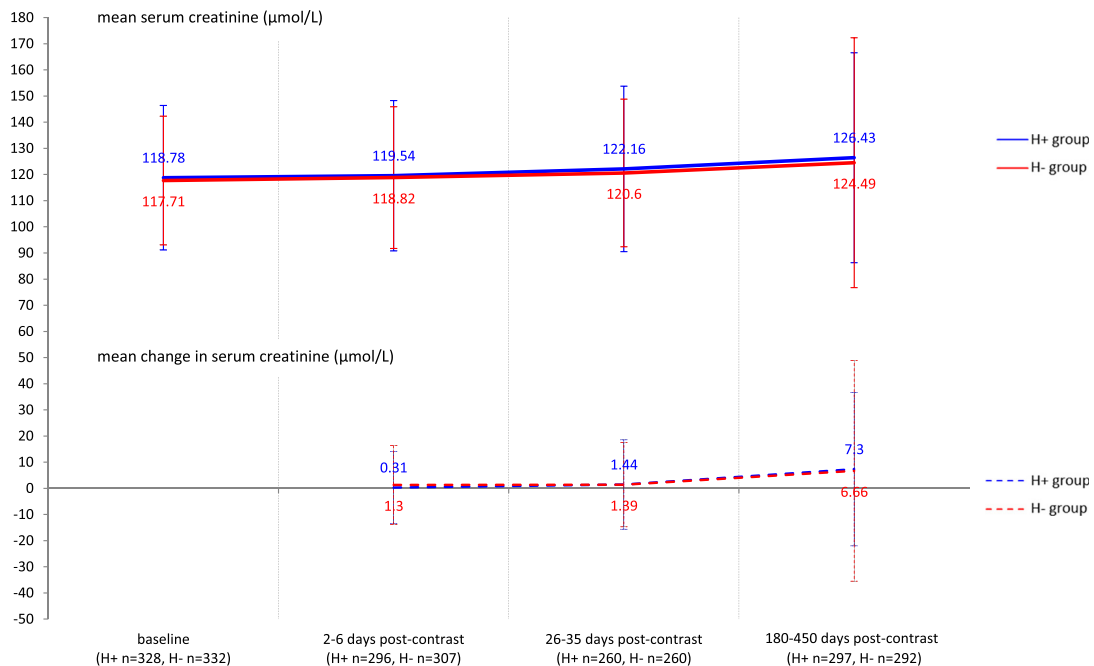

Fig. 3. Observed mean serum creatinine and changes in serum creatinine in the standard prophylactic treatment (H+) and no prophylactic treatment (H−) groups. Error bars show standard deviations.

Table 3
Incidence of long-term renal events in the standard prophylactic treatment (H+) and no prophylactic treatment (H−) groups.

	H+ group[a] n (%)	H− group[a] n (%)	Absolute difference H− in H+	95% confidence interval	p value
Renal failure (eGFR <15 mL/min/1.73 m²)	0/297 (0.00)	1/292 (0.34)	+ 0.34	− 0.97 to 1.91	0.3150
>10 eGFR unit renal function decline with from baseline	28/297 (9.43)	28/292 (9.59)	+ 0.16	− 4.65 to 4.99	0.9473
Renal function decline to eGFR <30 mL/min/1.73 m²	9/297 (3.03)	8/292 (2.74)	− 0.29	− 2.65 to 3.24	0.8337
Both >10 eGFR unit decline from baseline and a decline to eGFR <30 mL/min/1.73 m²	11/297 (3.70)	10/292 (3.42)	+ 0.28	− 2.92 to 3.49	0.8547

eGFR = estimated glomerular filtration rate.

[a] Long-term serum creatinine data were available for 589/660 (89%) patients: for 297/328 (91%) of the H+ group and for 292/332 (88%) of the H− group.

Contributors

ECN had full access to the data and takes responsibility for the integrity of the data and accuracy of the analysis. JEW, RJR, GVO ECN, and PJN 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 and ECN did the statistical analysis. ECN and JEW drafted the report. RJR, GVO, and PJN critically revised the report.

Declaration of Interests

We declare no competing interests.

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