AMACING

AMA**CIN**G

COLOPHON

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AMA**CIN**G

A MAastricht Contrast-Induced Nephropathy Guideline project

EVALUATION OF GUIDELINE-RECOMMENDED PROPHYLAXIS TO PREVENT CONTRAST-INDUCED NEPHROPATHY

DISSERTATION

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Summary

Summary

This dissertation describes studies evaluating clinical practice guidelines on the use of intravascular iodinated contrast material, specifically the effectiveness of guideline-recommended prophylactic intravenous hydration.

Chapter 1 contains the introduction, which explains why guidelines for the use of intravascular iodinated contrast material have been issued worldwide, and describes the events that led to the design of A MAastricht Contrast-Induced Nephropathy Guideline (AMACING) trial. This includes two earlier publications by the Contrast-Induced Nephropathy (CIN) group of Maastricht University Medical Centre (Maastricht UMC+): a pilot study published in Medisch Contact in 2010, and a letter to the editor in reaction to a Dutch publication on CIN and prophylaxis published in Radiology in 2012. The chapter concludes with a description of the AMACING trial study design.

Even though modern contrast materials are relatively inert, injection still may have haemodynamic consequences. Because the kidneys are charged with elimination of contrast from our bodies, they are likely to be the organs most at risk of injury. This risk of contrast-induced nephropathy (CIN) exists mainly for patients with pre-existing renal insufficiency. Although CIN usually resolves without clinically relevant consequences, it is sometimes associated with increased risk of dialysis and mortality.

Guidelines on safe use of iodinated contrast materials have been issued and implemented worldwide to prevent such potential adverse events. The main recommendation is intravenous prophylactic hydration in high-risk patients in order to prevent CIN and long-term post-contrast adverse outcomes. The prophylaxis requires 8-24 hour hospitalisation. The impact of this recommendation on patient burden, hospital burden, and health care budgets is considerable. However, prior to worldwide introduction of the recommendation for prophylaxis neither positive nor negative effects had been properly investigated.

In the Netherlands the impact was especially large, because the government incorporated the guideline recommendations into a nationwide programme for

improving hospital safety. The guidelines were imposed quite strictly, and adherence levels were used in audits as one of the indicators of hospital quality and safety.

The CIN group Maastricht UMC+ decided to carry out a retrospective exploratory study in the specialty setting of elective coronary angiography or percutaneous coronary intervention. The aim was to investigate the impact of the government-issued guidelines on clinical practice. It became clear from the data that hospitalisation for prophylactic treatment would increase five-fold. On the other hand, contrary to what was expected from literature incidences of CIN were low (2.1%), even amongst patients high-risk according to the guidelines who had not received prophylaxis.

In the meantime, a Dutch study on CIN was published, and the authors' conclusion was that the low CIN incidence found in their study (2.4%) reflected efficacy of prophylaxis. All patients in the study received prophylaxis, however; a control group not receiving prophylaxis was lacking. In a letter to the editor the CIN group pointed out that neither positive nor negative effects of prophylaxis had been properly investigated, and that conclusions with regards to its efficacy could not be drawn without a control group not receiving any prophylaxis. Furthermore, the group expressed its concern about the complications of prophylaxis encountered during the study, which necessitated transfer of some patients to intensive care and to which little attention was given.

The government-imposed guidelines, the pilot study, and the letter set the stage for the AMACING trial. The aim of the trial was to evaluate the clinical and cost-effectiveness of prophylactic hydration according to the guidelines, by comparing patients at risk of CIN who received prophylaxis to those who did not. A non-inferiority randomised controlled trial design was chosen because, even though not giving prophylaxis might be expected to increase CIN incidence, it would also reduce patient burden, hospital burden, and health care costs. Furthermore, not giving prophylaxis would mean avoiding complications of intravenous hydration. Lastly, although associated with an increased risk of long-term morbidity and mortality, CIN usually resolves without clinically relevant consequences.

Chapters 2 and 3 contain the publications of the primary and long-term results of the AMACING trial.

All 28 803 referrals for elective procedures with intravascular iodinated contrast material at Maastricht UMC+ over the course of a two-year period were prospectively screened for inclusion. 1 120 patients met the inclusion criteria (i.e. high-risk patients according to the guidelines with estimated glomerular filtration rate (eGFR) 30-59 ml/min/1.73m² combined with risk factors for CIN). 660 patients agreed to participate in the trial, and were randomised 1:1 to standard prophylactic hydration according to the guidelines, or to no prophylaxis. Based on an expected incidence of CIN of 2.4% after prophylaxis, a maximum increase in CIN of 2.1% in absence of prophylaxis was deemed acceptable (non-inferiroity margin).

The primary results were published in 2017 in the Lancet. Not giving prophylaxis was found non-inferior to standard guideline-recommended prophylaxis in the prevention of CIN; no dialysis or related deaths occurred within 1 month; 5.5% of intravenously hydrated patients suffered complications from the prophylactic treatment (symptomatic heart failure, arrhythmia, and hyponatremia); and medical costs up to one month post-contrast were almost twice as high for prophylaxis patients than for no prophylaxis patients.

The 1-year follow-up results were published in EClinicalMedicine, the online journal by the Lancet, in 2018. No significant differences in risks of dialysis, mortality, change in serum creatinine from baseline, or renal events were found between the no prophylaxis and intravenously hydrated groups. Long-term observed differences between no prophylaxis and prophylaxis groups were consistently small and not significant.

The AMACING data led to the conclusion that, assuming optimal contrast media administration, withholding prophylaxis for elective patients with eGFR 30-59 ml/min/1.73m^2 can be considered without compromising patient safety. Withholding

prophylaxis avoids complications, lightens hospital and patient burdens, and reduces health care costs an estimated 50 to 100 million euro a year in the Netherlands alone.

Chapter 2 also includes the authors' reply to four letters written to editor of the Lancet. The following points were emphasized: emergency, intensive care, and eGFR <30 ml/min/1.73m^2 patients were excluded and therefore beyond the scope of the trial; the aim of the AMACING trial was to evaluate efficacy of guideline recommendations, not the risk of CIN; the trial reflects clinical practice and the included population represents 90% of all patients to whom the recommendation for standard prophylaxis applies. Finally, in response to the suggestion that it was premature to withhold prophylaxis for patients with eGFR >29 ml/min/1.73m^2: would it be ethical to continue giving a treatment that is unproven, carries proven risks, confers substantial burden in the patient and hospital, and is so costly?

Chapter 4 describes the reception of the study results, the profound and swift consequences for clinical practice, and the impact upon the focus of the AMACING project research.

Soon after the publication of the AMACING trial results, clinical practice guidelines were updated. Thus, prophylaxis was no longer recommended for the population represented by the participants in the AMACING trial: the threshold was reduced to include patients with eGFR <30 ml/min/1.73m^2, only.

The updated recommendation of the guidelines was not introduced because of evidence of efficacy of prophylaxis in patients with eGFR <30 ml/min/1.73m^2, however. These patients are relatively scarce, and data in the context of CIN was absent in literature. The aim of the AMACING project being the evaluation of prophylaxis according to current guidelines, research-focus shifted to accommodate the updated recommendations. The focus thus became patients with eGFR <30 ml/min/1.73m^2.

Chapter 5 contains the 2018 publication in Investigative Radiology of a retrospective comparison between the 157 eGFR <30 ml/min/1.73m^2 patients primarily excluded

from the AMACING trial (the population currently eligible for prophylaxis), and AMACING trial participants (the population formerly eligible for prophylaxis). The aim was to evaluate whether eGFR <30 ml/min/1.73m^2 patients had higher-risk of post-contrast renal adverse events, whether this risk was mitigated by prophylaxis, and whether this mitigation outweighed the risk of complications.

Post-contrast outcomes were compared between the eGFR 30-59 ml/min/1.73m^2 and eGFR <30 ml/min/1.73m^2 patient groups who received standard prophylactic hydration. Incidences of post-contrast adverse events were substantially higher in patients with eGFR <30 ml/min/1.73m^2 who also presented more outliers with extreme post-contrast increase in serum creatinine, suggesting this population truly is at higher-risk. Whether prophylaxis mitigates this risk could not be deduced from this dataset, because the eGFR <30 ml/min/1.73m^2 subgroup without prophylaxis was too small. In the subgroup with prophylaxis complications of prophylaxis were present and substantial. The higher risk of post-contrast adverse events combined with the risk of complications underscore the importance of a proper evaluation of net efficacy of prophylaxis.

The results obtained for the eGFR <30 ml/min/1.73m^2 population were used as basis for a power calculation. This led to the conclusion that feasibility of a randomised trial comparable to AMACING to evaluate efficacy of prophylaxis according to the updated guidelines is poor: it was estimated that all Dutch hospitals would need to participate during 2-5 years to achieve sufficient sample size.

Chapter 6 details a retrospective study of 4-years' data – from between May 17th 2014 to May 17th 2018 – on elective procedures with intravascular iodinated contrast material at Maastricht UMC+ (Investigative Radiology, 2019). The aim was to gain insight into the positive and negative effects of prophylactic hydration in eGFR <30 ml/min/1.73m^2 patients, by comparing patients having received prophylaxis to those who did not.

All 55 474 elective procedures carried out over 4 years at Maastricht UMC+ were retrospectively screened for inclusion, yielding 362 eligible patients with eGFR <30 ml/min/1.73m^2: 281 with and 81 without prophylaxis. Relative risk of CIN and other adverse outcomes was estimated using multivariable logistic regression adjusting for potential confounders.

Adjusted odds ratios were not significant, but point estimates indicated that there may be a protective effect of prophylaxis versus no prophylaxis against post-contrast adverse renal outcomes (CIN, 1-month dialysis and renal function decline). On the other hand, prophylaxis may increase the risk of short-term mortality. Complications of the prophylaxis occurred in 6.4% of patients and were sometimes fatal. This may have contributed to the increased mortality risk seen.

Comparing patients with and without complications indicated that perhaps complications could be avoided if cardiac parameters were carefully evaluated before deciding to administer prophylaxis. This led to the conclusion that benefits and risks of prophylaxis must be carefully weighed, and we recommend assessing cardiac parameters for each high-risk patient and each procedure.

Chapter 7 contains a concise overview of the lessons learned from the trajectory and results of the abovementioned studies, as well as key findings, strengths, limitations, conclusions, pertinence, and future directions of research.

In **chapter 8** the societal and scientific impact of the studies is described. The local effect was evaluated in the observational Contrast-Induced Nephropathy After Reduction of the prophylaxis Threshold (CINART) project. The resuts showed that abolishing prophylaxis for patients with eGFR 30-59 ml/min/1.73m^2 and administering it only to patients with eGFR <30 ml/min/1.73m^2 led to an estimated 89% reduction in the number of patients suffering complications of prophylaxis such as symptomatic heart failure (99 cases a year); 93% reduction in the number of hospitalisations for prophylaxis (1 544 a year); and 91% reduction in medical costs (€ 1.2 million a year) at Maastricht UMC+.

When extrapolating the results to the estimated 75 million iodinated contrast injections a year carried out worldwide, and assuming a worldwide average adherence to guideline recommendations of 40%, the results estimates would be that >225 000 patients a year no longer suffer complications such as symptomatic heart failure associated with the prophylactic treatment, that >3.5 million patients need no longer be hospitalized for prophylaxis, and that savings for health care budgets are over €2.7 billion, each year.

Besides these individual and societal effects, AMACING has rekindled and changed the international scientific discussion around CIN, prophylaxis and clinical practice guidelines. This is illustrated by the long list of editorials, blogs, news items, double publications in other languages, and Twitter followers from the medical community - currently over 1 million - in the context of the AMACING publication in the Lancet.

Finally, the more recent studies in patients with eGFR <30 ml/min/1.73m^2 have already changed clinical practice at Maastricht UMC+. A dedicated unit has been opened for this high-risk population, with the aims of reducing prophylaxis complications and associated deaths to zero, and increasing post-contrast renal follow-up to 100%.

CHAPTER 1

1. Introduction

The use of contrast agents for medical purposes has a long history. Iodine was first accidentally discovered as a contrast agent almost a century ago, in the early 1920s. At that time iodine-salts were still used to treat syphilis, and Osborne et al. noticed that the urine of their patients was radio-opaque after treatment.[1] The medical community soon saw the usefulness of this effect of iodine, and its use as contrast agent quickly became widespread. In 2005 it was estimated that 75 million injections with iodinated contrast material were carried out each year worldwide in diagnostic and interventional procedures (CT scans, coronary angiographies and interventions, peripheral angioplasties and stenting, etc.).[2] Assuming a yearly increase of 9%, this number will be closer to 250 million in the year 2019. Fortunately contrast media are no longer the extremely toxic cell invading salts used by Osborne et al., but have since undergone a rapid evolution to become relatively inert complex benzene molecules.[3,4]

Despite the tremendous improvement in molecular properties, intravascular injection of iodinated contrast material may still have systemic and haemodynamic consequences. Because >99% of contrast material is eliminated from the body by the kidneys (possibly <1% via liver, gallbladder, intestines, transpiration, tears, saliva),[5] it is the kidneys that are most exposed to contrast-induced injury.

The first report of acute renal failure following contrast media injection dates from 1954.[6] After a period of controversy, groups at high-risk of post-contrast renal failure were recognised.[7,8] Post-contrast renal injury rarely occurs in patients with normal kidney function, but rather develops in the presence of other renal insults, particularly those that lead to reduced renal perfusion.[9,10] Diabetes mellitus, advanced age, cardiovascular disease, reduction in effective intravascular volume (dehydration, congestive heart failure, hypotension, liver cirrhosis, …), and concurrent use of nephrotoxic medication are all compounding risk factors.[11-14] However, the main characteristic of high-risk patients is pre-existing renal insufficiency.

The reason for this is twofold. First, diseased kidneys do not excrete as efficiently as normal kidneys do. Consequently, the duration of exposure to contrast after a given

dose is prolonged compared to normal kidneys, exacerbating any toxic effects. Although the actual transit times will vary per individual, dosage and specific contrast used, in general contrast will be excreted with a half-life of about two and a half hours with relatively normal kidney function; in the setting of advanced kidney insufficiency, the excretion half-life may be more than 10 hours.[15,16] Second, diseased kidneys by definition already have reduced numbers of functional nephron units, potentially chronically ischemic areas, and reduced renal adaptation mechanisms. Chronically injured kidneys do not therefore have the renal reserve to compensate and preserve glomerular filtration rate (GFR) in the case of contrast-induced injury, and if sufficient nephrons are irreversibly damaged, reduced filtration rate will persist.

1.1 Contrast-Induced Nephropathy (CIN) and Iodinated Contrast Material

The first use of the term Contrast-Induced Nephropathy (CIN) in literature to indicate post-contrast renal injury dates from 1984.[8] CIN and associated increased risk of dialysis and mortality have been consistently reported since.[13, 14, 16-21]

There are no clear symptoms accompanying CIN itself, it is primarily a biochemical diagnosis determined by measuring post-contrast change in the surrogate marker for renal function, serum creatinine.[22] Creatinine is a by-product of muscle metabolism in which muscle creatine is converted to creatinine. Because the total body content of muscle creatine is fairly constant, there is a continual production of creatinine and a continual excretion of it in urine. The serum creatinine level therefore largely depends on the rate of clearance through the kidneys, and serum creatinine values are used to give an indication of GFR. In this dissertation the estimated GFR (eGFR) is calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) equation:[22]

$$eGFR\ (ml/min/1.73m^2) = 175 \times serum\ creatinine\ (mg/dL)^{-1.154} \times age\ (years)^{-0.203}$$
$$\times 0.742\ (if\ female) \times 1.212\ (if\ patient\ is\ black)$$

Because serum creatinine levels more or less reflect kidney function, an acute increase in serum creatinine is taken as an indication of acute renal injury. Although there is some debate as to the optimal definition of CIN, an increase from baseline greater than

25% or 44µmol/l in serum creatinine within a few days post-contrast administration is most widely used.[23-28] This is also the definition used throughout this dissertation.

The physiological pathway through which contrast materials may cause CIN or kidney injury is unclear. Most information comes from in vitro and animal studies. In vitro experiments shed light on direct interaction with cells, but cannot reflect the complex physiological interactions typical of biological systems. Animal models may better achieve the latter, but post-contrast renal injury is difficult to induce in animal models. Normal and healthy animals seem to tolerate even extremely high doses of iodinated contrast material without any effect on renal function,[29] and therefore animal models are prepared in various ways with renal insult. Subsequent experiments may not accurately reflect the (human) situation.[30]

However, two main likely effects through which contrast may cause renal injury have been proposed.[31-38] The first centres on haemodynamic effects of iodinated contrast materials, alterations in blood flow and/or viscosity which may cause reduced blood flow through the kidneys and renal ischemia. Plausible mechanisms are: direct and/or indirect induction of vasoconstriction of blood vessels; increased intra-renal pressure due to hyper osmolality; increase in blood viscosity; red blood cell aggregation and stiffness with ensuing reduced oxygen release; and stimulation of the tubuloglomerular feedback system, causing afferent vasoconstriction.

The second proposed effect is contrast toxicity to cells. Direct contrast cytotoxicity has been demonstrated in glomerular mesangial, renal epithelial, and renal tubular cells.[39-46] Especially in renal tubular cells, contrast agents may directly and indirectly increase cell apoptosis (programmed cell death) and /or vacuolisation; increased processing in the tubules may induce increased secretion of the vasoconstrictor adenosine, and increase oxygen use leading to ischemia; contrast molecules may cause obstruction, stacking, and/or shearing; and contrast may induce increased free radical generation.[31-37; 41, 42, 45,46]

In vivo, haemodynamic effects and direct toxicity of contrast probably work in tandem:[35-38] iodinated contrast material initially causes transient vasodilation (minutes), followed by sustained vasoconstriction (hours or even days) and ischemic damage in the kidneys. The ischemic damage leads to a cascade of processes, mainly driven by reactive oxygen species, leading to cell apoptosis, inflammation and other organ damage processes. The sustained vasoconstriction directly influences glomerular filtration rate; serum creatinine will not be filtered out of the blood at the normal rate and will rise. Furthermore, the vasoconstriction and the natural renal concentration processes will exacerbate any direct toxic effects of contrast, due to contrast stagnation in the tubuli. In a human nephron, osmolalities range from 300 mOsm/kg H_2O in the proximal and distal tubulus (approximate to osmolality of blood), to up to 1200 mOsm/kg H_2O in the loop of Henle. This process greatly increases contrast viscosity and concentration in the tubules, and likely causes delayed elimination and temporal renal contrast accumulation.

The main toxic properties of contrast molecules that generate the abovementioned effects are ionicity (positive or negative charge of the molecule), osmolality (the number of molecules per volume), and viscosity (fluidity, mixability).[3,4,47,48] Hydrophilicity (solubility), and the type of molecule (monomeric or dimeric structure), influence osmolality, viscosity, obstruction, stacking, and shearing.

A contrast agent is least toxic when it resembles blood in osmolality and viscosity, has no ionic charge, is readily soluble and mixable, and has a simpler, smaller molecular structure. In other words, it is least toxic when it interacts as little as possible with blood (haemodynamics) and tubular cells, and is least affected by the renal concentration process.

Since the initial iodine salts, the largest step in reducing contrast toxicity was the discovery of the triiodinated benzene ring.[3,4] Used as the basis for contrast molecules, the benzene ring enables optimisation of contrast quality through the fixation of multiple iodine atoms to the ring, as well as a reduction of osmolality. The first such contrast agents were ionic monomers, but these were soon replaced by non-ionic

compounds. This eliminated the electric charge and reduced reactivity of contrast molecules, which was considered to be responsible for most of the immediate adverse reactions such as nausea and vomiting. Today ionic contrast is seldom used.[49]

The introduction of non-ionic contrast agents left osmolality and viscosity as the two main remaining toxic properties. Earlier contrast agents had osmolalities up to about 6 times that of blood, and viscosity up to about 4 times that of blood (figure 1.1); later contrast agents achieved better and better reductions in both.

The most recent development in the world of iodinated contrast was the introduction of non-ionic dimers, incorporating two benzene rings per molecule.[4] This achieved iso-osmolality relative to blood, but at the cost of increased viscosity due to dimeric structure of the molecule. Larger molecules containing more atoms tend to be more viscous: for the same number of carbon atoms, viscosity increases sharply with the number of rings. The negative influence of the number of benzene rings on viscosity is compounded by the fact that the concentration processes in the kidney tubules differentially affect monomeric and dimeric contrast material. Dimers are concentrated to a greater extent, which results in greater exposure of the kidneys after administration of dimeric relative to monomeric contrast.[50,51]

Over the years, adaptations to the benzene-based molecular structure have led to contrast agents with viscosity and osmolality values approximating those found for blood (figure 1.1). These two properties have not yet been combined in one and the same molecule however.

At Maastricht University Medical Centre (Maastricht UMC+) the contrast agent iopromide at 300 mg iodine per ml is uniformly used. This agent has neither the lowest viscosity nor the lowest osmolality, but contains one of the better approximations to osmolality and viscosity of blood currently to be found in one molecule (figure 1.1).

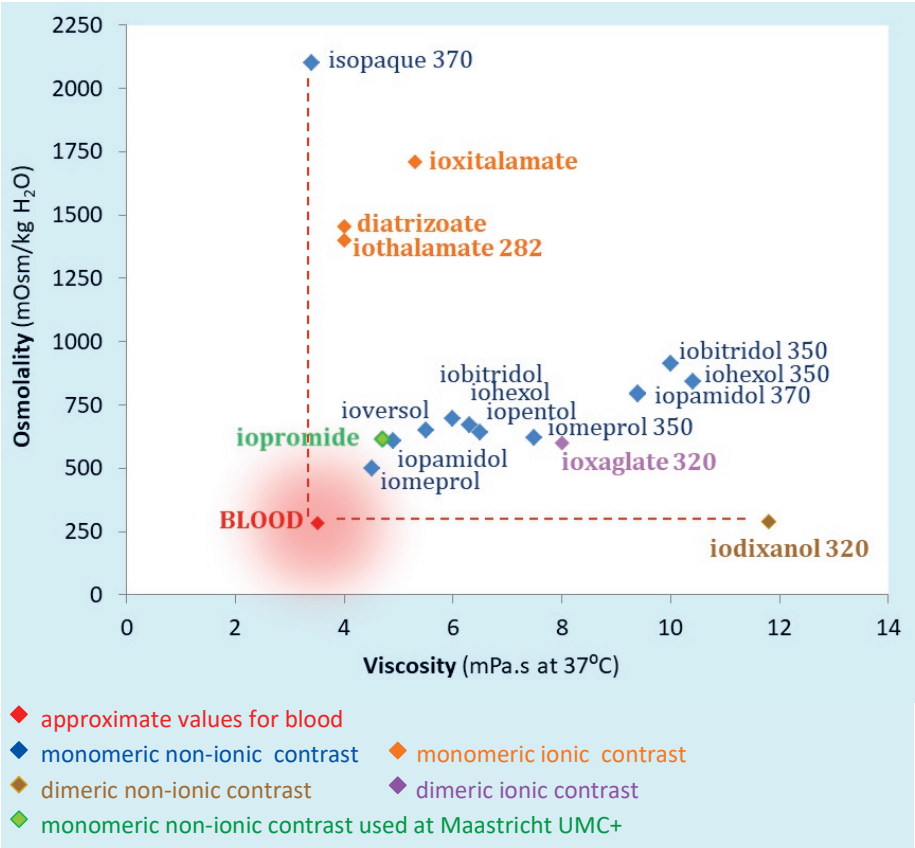


Figure 1.1. Viscosity and osmolality of blood and various iodinated contrast materials (iodine concentration is 300 mg iodine per ml unless otherwise stated).

Aside from molecular properties, various other factors affect the effects of contrast media. These include factors related to each patient's unique characteristics such as age, sex, height, weight, and renal/cardiovascular status. Of equal importance are factors related to the contrast material injection. Factors such as temperature, iodine concentration, overall volume, total iodine load, and iodine delivery rate all affect the degree of enhancement that is achieved with an injection of contrast material, as well as contrast toxicity. Warming iodinated contrast to body temperature (37°C) greatly reduces its viscosity, smaller volumes are favourable for obvious reasons, and whilst a sufficient radiopaque iodine load is crucial to obtain images of diagnostic quality,

viscosity increases exponentially as a function of iodine concentration. The latter must therefore be optimised, since even a small increase in concentration will lead to a large increase in viscosity (figure 1.1).[52]

Injection protocol parameters have been the subject of many optimisation studies, and many advances have been made.[52-64] Reductions in contrast volumes of up to 75% have been achieved using relatively low-iodine concentration contrast agents whilst maintaining sufficient diagnostic image quality.

At Maastricht UMC+ contrast injection protocols are optimized per individual and procedure.

1.2 Prophylactic Intravenous Hydration for the Prevention of CIN

The first paper on the use of intravenous hydration to prevent CIN was published in 1981.[65] Since the 1980s peri-procedural intravenous hydration has been strongly recommended.

The mechanism by which intravenous hydration should protect renal function is unclear, mainly because the physiological pathway of CIN is unclear. However, it is consensus amongst experts that administering intravenous fluids before and after contrast exposure may mitigate some of the haemodynamic effects of contrast material by reducing blood osmolality and viscosity.[23,28] The main mechanism by which intravenous hydration is thought to work, however, is by producing an infusion rate-dependent increase in tubular fluid volume.[66]

Water infusion alone could reduce intra-tubular contrast concentration. In standard prophylaxis sodium chloride is added to induce a tubular reaction to increase salt and water excretion, which may theoretically promote contrast excretion. Furthermore, increased salt excretion may cause a slight reduction in tubular acidity. Because the acid load that a kidney handles remains relatively constant over short periods of time, increasing tubular volume will dilute acid concentration and will lead to a slight rise in tubular pH. In vitro cell culture studies using human and animal cell lines show that

apoptosis (programmed cell death) occurring after free radical generation is markedly accelerated in an acid environment.[67,68] Thus, saline may attenuate free radical induced damage within the kidney.

The effect of saline infusion in the prevention of renal injury is likely to be rate-dependent, and requires that the infusion be maintained throughout the period of contrast excretion by the kidney.

1.3 Clinical Practice Guidelines & a History of AMACING

Since the second half of the last century, iodinated contrast injections have consistently been associated with acute kidney injury, defined as the acute rise in serum creatinine that is CIN.[13-21,23,26] Although CIN usually resolves within one to two weeks, in some cases the acute injury progresses to further renal function decline, dialysis, and mortality.[18,20,21] Because there is no treatment to mitigate possible effects of CIN once it has occurred, the focus lies on prevention.

The identification of high-risk patients around the 1980s enabled a more structured approach and standardisation of preventive measures.[6,7] In the 1990s several radiological committees were formed to that end. Around the year 2000 national and umbrella radiologic societies began issuing guidelines on the safe use of intravascular iodinated contrast material. The Institute of Medicine defines clinical practice guidelines as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances."[69] As such they include concise instructions on patient selection, diagnostic/screening tests, medical/surgical procedures, and other clinical practice details. They are regularly updated, based on systematic reviews of available literature, and thus reflect current evidence-based knowledge in the field. Within a few years, such guidelines for iodinated contrast administration were issued the world over. Examples of umbrella organisations are ESUR for Europe, ACR for America, CAR for Canada, RANZCR for New Zealand and Australia, and ASCI for Asia.[70-74]

The guidelines for the prevention of CIN specify how to identify patients at risk and how best to prevent CIN in these patients.[70-79] Patients at risk of CIN are those with pre-existing renal insufficiency in combination with risk factors. The prophylaxis used for the prevention of CIN is intravenous hydration.

In the Netherlands, the guideline on the prevention of CIN was incorporated into a nationwide programme to improve hospital safety: the VMS programme issued by the government in 2008-2012.[75] The guideline was imposed quite strictly, and accreditation programmes used the level of adherence to the recommendations to reflect hospital quality and safety.

In the VMS guideline, high-risk patients were defined as having estimated GFR (eGFR) <60 ml/min/1.73m^2 combined with risk factors such as diabetes, age, cardiovascular disease, anaemia, and nephrotoxic medication, or <45 ml/min/1.73m^2 in absence of risk factors. The recommended standard prophylaxis was intravenous normal saline (0.9% NaCl) during 4-12 hours before and 4-12 hours after contrast administration.

These recommendations had far-reaching effects on patient, hospital, and health care budgets. First of all, all patients referred for a procedure with iodinated contrast administration must be screened in order to identify the 5-10% high-risk patients eligible for prophylaxis. However, the increased burden on hospital and patient is mainly due to the required hospitalisation to enable prophylactic intravenous hydration. For example, instead of an outpatient coming in for a CT scan and leaving the hospital within the hour, patients considered high-risk now had to be hospitalised for one to two days.

In response to the introduction of the VMS guideline the CIN group Maastricht UMC+ was formed. In this group experts from the departments of radiology, cardiology, and internal medicine came together, including two quality and safety staff members. The group wondered how often CIN occurs in practice, what impact the recommendations would have on clinical practice, and what evidence existed to support the effectiveness of the recommendations.

In order to answer some of these questions, the CIN group carried out a retrospective exploratory analysis of data on elective patients who underwent a coronary angiography or intervention.[80] They evaluated the number of high-risk patients eligible for prophylaxis according to protocols before and after implementation of the new guidelines, the number of required hospitalisations before and after implementation of the new guidelines, and incidences of CIN, dialysis and mortality.

1.4 Exploratory Study

Vermeeren MA, on behalf of the CIN group Maastricht UMC+. Veiligheidsregels jagen kosten op [Safety guidelines raise costs]. *Medisch Contact* 2010; 45: 2378-80. Dutch.

https://www.medischcontact.nl/nieuws/laatste-nieuws/artikel/veiligheidsregels-jagen-kosten-op-1.htm

Key points

- The CIN group carried out an exploratory study, retrospectively screening 419 patients who underwent an elective coronary angiography or intervention (CAG or PCI) at Maastricht UMC+. The aim was to evaluate the impact of new clinical practice guidelines on the use of intravascular iodinated contrast material issued by the Dutch government (VMS).
- Implementation of the VMS guidelines has large consequences, and would result in a 5-fold increase in patients to receive intravenous prophylactic hydration.
- The increase in prophylaxis treatments would lead to approximately 200 extra hospitalisation days a year at Maastricht UMC+ for this population (elective CAG/PCI) alone.
- CIN incidence was low amongst high-risk patients of this population (2.1%).
- Clinically relevant long-term effects (dialysis, mortality) were absent.
- **Conclusion**: Although the study is small and retrospective, benefits of prophylactic intravenous hydration are unclear, whereas increases in hospital and patient burden are certain.

Meer ligdagen door strengere preventie contrastnefropathie:
Veiligheidsregels jagen kosten op

Marja A Vermeeren, namens de CIN-groep Maastricht UMC

Introductie

Een van de thema's van het VMS Veiligheidsprogramma is het voorkomen van nierinsufficiëntie bij intravasculair gebruik van jodiumhoudende contrastmiddelen.[75] Patiënten met een verminderde nierfunctie hebben een sterk verhoogde morbiditeit en mortaliteit.[81] Medisch onderzoek en behandelingen waarbij intravasculair contrast wordt gebruikt kunnen een (vaak tijdelijke) serumcreatininestijging induceren.[82,83] Een stijging kan ernstige consequenties hebben bij patiënten met pre-existerend ernstig gestoorde nierfunctie of een minder gestoorde nierfunctie met comorbiditeit en/of medicatiegebruik.[81-84] Er zijn verder aanwijzingen dat het contrastmiddel directe tubulaire cel schade kan veroorzaken.[41]

De creatininestijging kan in de meeste gevallen worden voorkomen door hydratie voor- en achteraf.[85-87] Binnen het MUMC+ gebruikt men een protocol dat voorschrijft dat een patiënt wordt opgenomen voor pre- en posthydratie als zijn creatininewaarde circa 2 weken voor de ingreep hoger is dan 150µmol/l.[88] VMS adviseert echter om alle hoog risico patiënten op te nemen voor pre- en posthydratie.

Volgens de VMS Praktijkgids Nierinsufficiëntie is er sprake van een hoog risico bij een geschatte klaring (estimated glomurelar filtration rate, eGFR) <45ml/min/1.73m^2, eGFR <60 ml/min/1.73m^2 in combinatie met diabetes mellitus of een eGFR <60 ml/min/1.73m^2 in combinatie met twee of meer andere risicofactoren. De belangrijkste risicofactoren zijn leeftijd >75 jaar, perifeer vaatlijden, hartfalen, >150 ml contrastvolume en gebruik van diuretica of nefrotoxische geneesmiddelen (zoals NSAID's).

Extra ligdagen

Strikte invoering van dit VMS-protocol heeft consequenties voor de klinische praktijk met betrekking tot screening, opname en behandeling van patiënten. Om die reden heeft MUMC+ in het voorjaar van 2010 een onderzoek uitgevoerd onder patiënten die electief coronaire angiografie moesten ondergaan. Doel was om een onderbouwde inschatting te maken van de extra kosten als gevolg van invoering van het VMS-protocol. Die kosten zijn uitgedrukt in extra verwachte ligdagen bij het hanteren van het VMS-protocol in vergelijking met het MUMC+-protocol.

Patiënten die een electief coronair angiogram met of zonder interventie ondergingen, werden geïncludeerd, tenzij het een spoedinterventie betrof of de patiënt elders was opgenomen en alleen voor de interventie naar MUMC+ kwam.

De creatininewaarden van circa 2 weken voor en 2 tot 3 dagen na het angiogram werden verzameld en de eGFR werd voor elke patiënt berekend.[i;89] De gehanteerde definitie van contrastnefropathie was: een toename van de concentratie serumcreatinine van >44 µmol/l of >25 procent van de uitgangswaarde binnen 48 tot 72 uur na intravasculaire toediening van een jodiumhoudend contrastmiddel. Dit is in overeenstemming met de VMS-Praktijkgids.[75] Als contrastmiddel is iopromide (Ultravist) gebruikt, met 300 mg jodium/ml.

Lage prevalentie

In de periode van 15 maart tot en met 2 juli 2010 voldeden 419 patiënten aan de criteria. Van 358 van hen is tussen 48 en 72 uur na interventie een creatininewaarde ontvangen (85%). In tabel 1 staan de gegevens van de 358 geïncludeerde patiënten. Van hen hadden er 5 (1.4%) een stijging van het serumcreatinine van >25 procent ten opzichte van de uitgangswaarde (zie tabel 2). Van hen was alleen patiënt 5 bekend met comorbiditeit (diabetes mellitus). Dit was tevens de enige patiënt die voldeed aan de VMS-definitie van hoog risico.

[i] http://www.kidney.org/professionals/KDOQI/gfr_calculator.cfm, (geraadpleegd op 11 jan 2011)

De patiënten met creatinine >150 µmol/l (MUMC+ beleid, n=9) hebben pre- en posthydratie gekregen tijdens een klinische opname. Conform de gehanteerde definitie was er geen sprake van contrastnefropathie bij deze 9 patiënten. Volgens de VMS-criteria hadden 47 patiënten opgenomen moeten worden in plaats van 9 patiënten. Dat is 5 maal zoveel. Ervan uitgaande dat een klinische opname twee nachten kost, betekent dit dat er in het MUMC+ voor deze patiëntenpopulatie op jaarbasis 200 ligdagen extra nodig zijn. Uit de resultaten blijkt dat de prevalentie van contrastnefropathie laag was bij de patiënten die een electief coronair angiogram hebben ondergaan in het MUMC+.

Bij de 5 patiënten met contrastnefropathie was de creatinine stijging verder van korte duur en er waren geen aanwijzingen voor persisterende nierschade op langere termijn. Contrastnefropathie was dus niet klinisch aantoonbaar.

Opvallend is verder dat de patiënten met contrastnefropathie (volgens de gehanteerde definitie) niet altijd geïdentificeerd werden als hoogrisico patiënten: van de 5 patiënten met contrastnefropathie vielen er 4 niet binnen de VMS-definitie van een hoogrisico patiënt.

Weinig bewijs

Het VMS-thema is opgezet om patiënten te identificeren met een verhoogd risico op contrastnefropathie en om bij deze patiënten preventieve maatregelen in te zetten bij toediening van een jodiumhoudend contrastmiddel. Bewijzen ten aanzien van de effectiviteit op morbiditeit en mortaliteit van de preventieve maatregelen zijn echter schaars door het ontbreken van gerandomiseerde studies. Dat terwijl de implementatie van een dergelijk omvangrijk veiligheidsprogramma blijkens dit onderzoek wel aanzienlijke kosten met zich meebrengt. Daarnaast is er, voor zover bekend, geen informatie over de veiligheid van de pre- en posthydratieschema's in de verschillende patiënten categorieën.

Tabel 1. Karakteristieken van de patiëntenpopulatie

Kenmerken	N=358
Mannen *%*	72
Gemiddelde leeftijd *jaar (±standaardvariatie)*	65 (±10)
Leeftijd mannen *jaar (±standaardvariatie)*	64 (±9)
Leeftijd vrouwen *jaar (±standaardvariatie)*	67 (±10)
eGFR	
eGFR pre *ml/min/1.73m^2 (±standaardvariatie)*	76 (±20)
eGFR <45 *%*	6
eGFR 45-59 + DM *%*	5
eGFR 45-59 en ≥2 risicofactoren *%*	2
eGFR 45-59 zonder DM of risicofactoren *%*	8
eGFR ≥60 *%*	79
Comorbiditeit en medicatie	
Diabetes mellitus *%*	21
Hartfalen *%*	3
Perifeer vaatlijden *%*	6
Diuretica *%*	18
NSAID's *%*	2

Tabel 2. Patiënten met Contrastnefropathie.

Patiënt	**Leeftijd** (jaar)	**Creatine pre-contrast** (µmol/l)	**Creatinine post-contrast** (µmol/l)	**Creatinine stijging** (µmol/l)	**Creatinine stijging** (%)	**Contrast-middel** (ml / gram jodium)
1. man	67	69	88	19	57	10 / 30.6
2. man	57	70	90	20	28	82 / 24.6
3. vrouw	73	72	96	24	33	104 / 31.2
4. vrouw	53	42	58	16	38	55 / 16.5
5. vrouw	71	106	148	42	39	124 / 37.2

Van de 358 geïncludeerde patiënten voldeden er 5 (1.4%) aan de definitie van contrastnefropathie: een toename van de concentratie van serum creatinine van meer dan 44 µmol/l of meer dan 25 procent.

Als externe procesindicator van het VMS thema wordt het bepalen van de eGFR vóór de contrasttoediening gevraagd. Echter, als echte uitkomstparameter van het meten van patiëntveiligheid is de creatininewaarde vóór interventie minder geschikt dan de incidentie cijfers van contrastnefropathie. Om de incidentie van contrastnefropathie te kunnen meten is de waarde van 48-72 uur ná de procedure onontbeerlijk. Verder is het de vraag of de algemeen gehanteerde definitie van contrastnefropathie een goede weergave is van de schade veroorzaakt door contrastvloeistof.

Consequenties

Dit onderzoek kent enkele beperkingen. De onderzochte groep is relatief klein en betreft alleen cardiologische patiënten met intra-arteriële contrasttoediening, zodat deze uitkomsten niet zomaar generaliseerbaar zijn. Desondanks dragen deze gegevens bij aan de discussie over het VMS-programma die sinds enige tijd wordt gevoerd.[90,91]

Het onderzoek laat immers zien dat contrastnefropathie zeldzaam is bij electieve cardiologische interventies. In onze populatie had het optreden van contrastnefropathie bovendien geen aantoonbare blijvende schade tot gevolg. Het implementeren van het huidige VMS protocol heeft verregaande organisatorische en financiële consequenties. Daarom is er behoefte aan een goede registratie van het optreden van contrastnefropathie, onder andere door systematische meting van het creatinine 2 tot 3 dagen na de interventie. Ook zou er een gerandomiseerd onderzoek moeten worden gedaan naar de korte- en lange termijn effecten van de voorgestelde strategie met pre- en posthydratie.

Geen belangenconflicten gemeld.

The preliminary results of the exploratory study done by the CIN group were telling:[80] it was estimated that for elective coronary angiographies or interventions the number of patients to receive prophylaxis would increase 5-fold when implementing the VMS guidelines. On the other hand, in the population studied CIN incidence was low (2.1%), and clinically relevant consequences were absent.

It soon became apparent that neither positive nor negative effects of prophylactic intravenous hydration had ever been investigated against a control group not receiving any prophylaxis.[28] Furthermore, intravenous hydration with normal saline can lead to complications such as symptomatic heart failure, arrhythmias, hypo- or hypernatremia. At Maastricht UMC+ such negative effects of intravenous hydration had been encountered in patients with poor cardiac function who could not handle the extra intravenous fluid. Although a single cause of death is rarely obvious, it is probable that a few patients were lost to complications of intravenous hydration. Based on these and other deaths deemed avoidable in retrospect, the Commissie Onderzoek Overleden Patiënten of Maastricht UMC+ (COOP: a committee which investigates all in-hospital deaths) opened the discussion on burdens of interventions that exceed the coping ability of fragile patients and lead to serious complications and death.[92] In literature serious complications occurring due to the administration of intravenous prophylactic hydration were only seldom mentioned, and not given importance in discussions.

Not many health professionals were ready to accept the implications of the CIN group findings. Intravenous hydration with normal saline had been advocated as cornerstone for the prevention of CIN since the 1980s, and it came to be considered the absolute gold standard for the prevention of CIN. Questioning this gold standard was not done in scientific literature at the time, and there appeared to be a predominant atmosphere discouraging such an approach. For example, the 2011 publication of a European guideline update states:[28] “Randomised double-blinded trials comparing hydration with a proper control group of no hydration are not available. However, conducting such randomised trials would be ethically unacceptable given the current understanding of CIN.” In other words, despite lack of evidence efficacy of prophylaxis was simply assumed to exist.

This attitude is also revealed in scientific literature on CIN since the widespread introduction of clinical practice guidelines. An exponential increase in publications on CIN was seen from the year 2000 onwards (figure 1.2), but even though these publications included a very large number of randomised trials on the prevention of CIN, most of these compared standard intravenous hydration with normal saline to another form of prophylaxis.

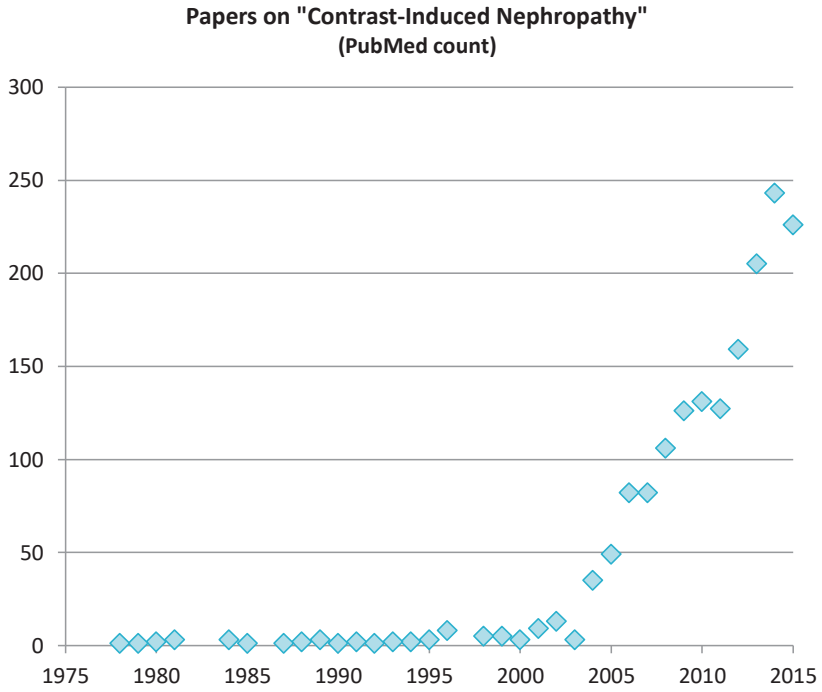


Figure 1.2. Count of papers on contrast-induced nephropathy per year (source: PubMed)

In 2012 a Dutch study was published on the prevention of CIN which illustrates the trends in such publications of the time.[93] The CIN group wrote a letter to the editor to address conclusions made by the authors, which in their view were not justified by the data, to draw attention to the complications of prophylaxis encountered in the study, and to conclude that randomised trials of sufficient power including a control group not receiving intravenous prophylactic hydration were needed.[94]

1.5 Letter to the Editor

In response to: *Balemans CE, Reichert LJ, van Schelven BI, van den Brand JA, Wetzels JF.* Epidemiology of contrast material–induced nephropathy in the era of hydration. *Radiology* 2012;263:706–13.

Letter: *Nijssen EC, Vermeeren MA, Janssen MM, Kessels FA, van Ommen GV, Rennenberg RJ, Wildberger JE.* Contrast material–induced nephropathy in the era of hydration*. Radiology* 2012;265:978.

doi: https://doi.org/10.1148/radiol.12121162

Key points

- The letter concerns a Dutch study by Balemans et al published in Radiology in 2012. The aim of that study was to evaluate the incidence of CIN in patients who received intravenous contrast media and underwent treatment in accordance with current guidelines.

- The authors concluded that their findings support efficacy of hydration regimens. In our opinion, this conclusion was not justified by the results:

- In the high-risk population, 10/419 hydrated patients developed CIN (2.4%), compared with 1/35 patient who did not receive hydration for unspecified reasons (2.9%; OR 0.83; p=0.9).
- The incidence of CIN did not greatly differ in the total hydrated and non-hydrated populations (2.7% and 2.1%, respectively; OR 1.33; p=0.5).
- Data on incidences of CIN without prophylaxis are not available; therefore, the results cannot indicate that CIN incidence was altered after hydration.

- The mention of adverse effects of hydration regimens in the results is of some concern: 6 patients had severe kidney failure, cardiac disease, or pleural effusion, two of whom were admitted to intensive care.

- **Conclusion**: Randomised trials of sufficient power including a control group not receiving intravenous prophylactic hydration are a prerequisite to forming conclusions about CIN and the effects of hydration regimens.

Contrast material–induced nephropathy in the era of hydration

Estelle C Nijssen, Marja A Vermeeren, Marga M Janssen, Fons A Kessels, Vincent van Ommen, Roger J Rennenberg, Joachim E Wildberger

Editor:

The article about contrast material-induced nephropathy (CIN) by Balemans and colleagues in the June 2012 issue of Radiology piqued our interest.[93] The purpose of the study was to evaluate the incidence of CIN in patients who received treatment in accordance with current guidelines.[75] The incidence of CIN found in that study was subsequently used as evidence of the efficacy of the prophylactic hydration treatment given, and current guidelines were not strictly followed: 92 low-risk patients were given hydration and 35 high-risk patients were not, for which no further explanation was given.

Seen from our perspective, the results presented by Balemans and colleagues do not justify the conclusion that their findings support the efficacy of hydration regimens. First, in the low-risk population, the non-hydrated group showed the expected low incidence of CIN (2.0%), but the hydrated group had a higher incidence of CIN than any other group (4.3%; odds ratio 0.45; p=0.2). Second, in the high-risk population, 10 of 419 hydrated patients developed CIN (2.4%), compared with one of 35 patients who did not receive hydration (2.9%; odds ratio 0.83; p=0.9). Third, the incidence of CIN did not greatly differ in the total hydrated and non-hydrated populations (2.7% and 2.1%, respectively; odds ratio 1.33; p=0.5) and was equivalent in high- and low-risk populations (both 2.4%; odds ratio 0.99; p=0.99). Fourth, the incidences of CIN at baseline in this study population are not available; therefore, the results cannot indicate that CIN incidence was altered in the high-risk population after hydration. Last, but not least, we are concerned by the results presented on possible adverse effects of hydration regimens during the study: six patients had severe kidney failure, cardiac disease, or pleural effusion—two of whom were admitted to intensive care.

In addition, the clinical relevance of CIN and the efficacy of prophylactic measures are complex: the incidence of CIN, measured according to current definitions, may often reflect a temporary and reversible increase in the serum creatinine level;[95] concrete evidence for hydration as an effective and appropriate prophylactic is still lacking;[96,97] and adverse effects of hydration should probably be taken into account for specific patient subgroups.[98] Therefore, randomized trials of sufficient power are a prerequisite to forming conclusions about CIN and the effects of hydration regimens with potentially enormous impact on health care systems.

Disclosures of Conflicts of Interest

ECN No relevant conflicts of interest to disclose. MAV No relevant conflicts of interest to disclose. MMJ No relevant conflicts of interest to disclose. FAK No relevant conflicts of interest to disclose. VvO No relevant conflicts of interest to disclose. RJR No relevant conflicts of interest to disclose. JEW Financial activities related to the present article: none to disclose. Financial activities not related to the present article: institution has a grant or grant pending with Siemens Healthcare, Philips Healthcare, GE Healthcare, Bracco, and Bayer; receives payment for lectures including service on speakers bureaus from Siemens Healthcare, GE Healthcare, Bayer, and Boston Scientific; institution receives payment for lectures including service on speakers bureaus from Siemens Healthcare, GE Healthcare, Bayer, and Boston Scientific. Other relationships: none to disclose.

After years of assuming that prophylactic intravenous hydration with normal saline protected renal function from iodinated contrast materials and ignoring the potentially serious complications, it was high time for a randomised trial including a control group not receiving prophylaxis.

Before AMACING no such trial existed. A PubMed search on 10 may 2017 using the MeSH term "contrast media" and the keyword "hydration" yielded a total of 557 papers, 159 of which were clinical trials. Four small trials done in 2014 and 2015 even included a randomised group not receiving prophylaxis, but none compared not giving prophylaxis to intravenous prophylactic hydration according to the guidelines in high-risk patients targeted by the guidelines.[99-102] The bulk of patients targeted for prophylaxis by the guidelines are elective outpatients; guideline recommendations deviate for emergency situations and in acute settings other factors such as haemodynamic instability play a role. Three of the four aforementioned trials were done in emergency/acute settings[99,101,102] and the fourth included inpatients only.[100] Also, three of the four trials included low-risk patients with eGFR higher than 60 ml/min/1.73m^2 not considered at risk of CIN and not eligible for prophylaxis according to the guidelines;[99-101] the one trial including high-risk patients only (N=130) evaluated 1-hour pre-hydration with sodium bicarbonate instead of the peri-procedural intravenous hydration with normal saline recommended by the guidelines.[102] In short, there was no trial to shed light on efficacy of guideline-recommended prophylactic intravenous hydration.

The strict imposition of the guidelines in the Netherlands, together with the results of the exploratory study done by the CIN group, the paucity of available data, and the undeniable existence of complications of intravenous hydration, made it imperative to our minds to evaluate standard prophylactic intravenous hydration: in a randomised controlled trial of prophylaxis versus no prophylaxis, and taking into account complications of the prophylaxis.

This led to the AMACING trial, a randomised controlled trial (RCT) registered at ClinicalTrials.gov under registration number NCT02106234 (April 8th 2014).[103]

1.6 AMACING Trial Design: A MAastricht Contrast-Induced Nephropathy Guideline Evaluation

AMACING was designed to evaluate (cost-) effectiveness of standard prophylactic intravenous hydration according to current guidelines compared to giving no prophylaxis (figure 1.3).

Like most of the medical community, our group assumed the standard prophylactic intravenous hydration would protect renal function to some extent, lowering incidence of CIN and long-term increased risk of dialysis and mortality. However, the question was whether this preventive effect weighed against the risk of complications and increased patient- and hospital burden. The more so because most cases of CIN resolve spontaneously, and clinically relevant consequences are reported in less than 1% of cases.[18,21] These are the reasons why a non-inferiority design was chosen.

A non-inferiority trial necessitates setting a non-inferiority margin, i.e. the maximum difference in CIN incidence between prophylaxis and no prophylaxis, which would be deemed acceptable given the advantages no prophylaxis might bring in the form of avoidance of complications, relief of hospital and patient burden, and reduction in costs. The trial design was based on an expected 2.4% CIN incidence after prophylaxis, as had been reported in a recent Dutch trial.[93] The non-inferiority margin was set at 2.1%.

The basic design of the trial was straightforward (figure 1.3): the guidelines were followed in screening for elective patients eligible for standard prophylaxis, which corresponded to the inclusion criteria for the trial. Eligible and consenting patients were subsequently randomised 1:1 to either standard prophylaxis or no prophylaxis. The only patients high-risk according to the guidelines and eligible for elective standard prophylaxis that were excluded were patients with poor renal function (eGFR <30 ml/min/1.73m^2), and high-risk patients who could not receive prophylaxis on medical grounds.

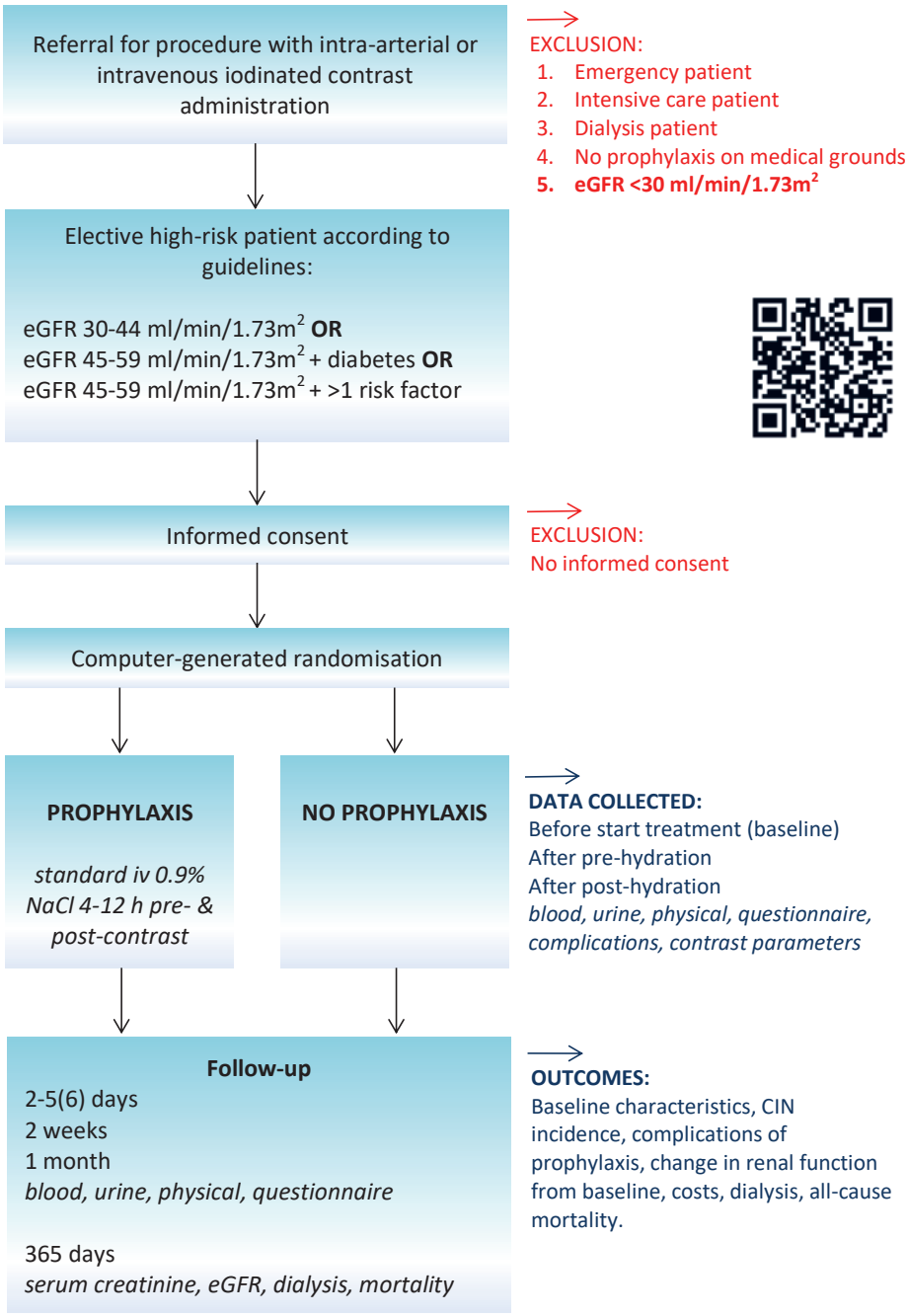


Figure 1.3. AMACING randomised controlled trial design, data collection & outcomes (ClinicalTrials.gov Identifier: NCT02106234 – see QR).

The latter were excluded because they could not be randomised to prophylaxis. The former were excluded for safety reasons, because in absence of data in literature it was not known what would happen with CIN and other adverse outcome incidences without prophylaxis; eGFR <30 ml/min/1.73m^2 patients were considered too vulnerable to further renal function decline and dialysis to be included in the trial.

Participating patients were intensely followed on the day of the prophylaxis and/or contrast procedure, up to one month post-contrast, and again at one year post-contrast (figure 1.3). Clinical practice was followed in all but the randomisation for prophylaxis or no prophylaxis. The study was professionally monitored and had a dedicated data safety monitoring board (a panel of independent experts charged with supervising patient safety). The primary outcome was CIN, defined as a >25% or >44µmol/l increase in serum creatinine from baseline. Secondary outcomes were complications of the prophylaxis, medical costs up to one month post-contrast, and change in renal function, dialysis and mortality up to one month and one year post-contrast.

The first patient was included on June 17th 2014, the last on July 15th 2016. The last 1-month follow-up data was collected on August 15th 2016. The primary to 1-month follow-up results were accepted for publication by the Lancet on October 4th 2016, and published online on February 20th 2017.[104]

The final 1-year data on dialysis and mortality was collected on July 15th 2017; the final long-term renal function follow-up data was collected within 3 months after that. EClinicalMedicine, the online journal by the Lancet, accepted the 1-year follow-up results for publication on October 25th 2018.[105]

CHAPTER 2

Verschlimmbesserung?

‘Good samaritan attempts DIY restoration of 19th century fresco’- Borja, Spain, 2012.
Source: NOS.nl

2. AMACING Primary Results: Non-Inferiority of No Prophylaxis

2.1 *Nijssen EC, Rennenberg RJ, Nelemans PJ, Essers BA, Janssen MM, Vermeeren MA, van Ommen GV, Wildberger JE.* 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. *Lancet* 2017;389(10076):1312-1322.

doi: https://doi.org/10.1016/S0140-6736(17)30057-0

Key Points

- All 28 803 referrals for an elective procedure with intravascular iodinated contrast over a period of 2 years at Maastricht UMC+ were prospectively screened.
- Inclusion criteria correspond to the criteria for high-risk patients eligible for standard prophylaxis according to current clinical practice guidelines.
- Patients with eGFR <30 ml/min/1.73m^2 were excluded for safety reasons.
- 660 high-risk patients consented to participate and were randomised 1:1 to prophylaxis (iv 0.9% NaCl 4-12 hours before and after contrast administration) or no prophylaxis.
- Primary outcome CIN occurred in 2.7% prophylaxis and 2.6% no prophylaxis patients (absolute difference -0.10%; one-sided 95% CI -2.25 to 2.06; one tailed p=0.47). The upper limit of the 95% CI was lower than the pre-defined non-inferiority margin: no prophylaxis is non-inferior in the prevention of CIN.
- No prophylaxis was cost saving relative to prophylaxis (mean savings 663 € per patient).
- No haemodialysis or related deaths occurred within 1 month.
- 5.5% prophylaxis patients suffered complications of prophylaxis such as heart failure and arrhythmia.
- **Conclusion:** Assuming optimal contrast administration, withholding prophylaxis for patients with GFR >29 ml/min/1.73m^2 might be considered without compromising patient safety.

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

Estelle C Nijssen, Roger J Rennenberg, Patty J Nelemans, Brigitte A Essers, Marga M Janssen, Marja A Vermeeren, Vincent van Ommen, Joachim E Wildberger

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/min/1.73m^2) 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/min/1.73m^2, 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.

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 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) 30-59 ml/min/1.73m^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 Iopromide (300 mg iodine/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/min/1.73m^2 versus those with eGFR above 45 ml/min/1.73m^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 ≥30 ml/min/1.73m^2, and the substantial health-care costs, patient burden, and logistical complications of this prophylaxis might henceforth be avoided while maintaining patient safety.

Introduction

Procedures with intravascular iodinated contrast material pose a risk for renal function, especially in patients whose renal function is already compromised.[106] Contrast-induced nephropathy or contrast-induced acute kidney injury was recognised more than 60 years ago,[6] and is the third most common cause of acute kidney injury in patients admitted to hospital.[6,19,107,108] 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.[18,20,21]

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.[70,71,75,109] This recommendation has far-reaching 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.[2] Taking into account chronic kidney disease prevalence of 8–16%,[110] 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.[28,70,75] 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.[28]

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.[111-113] Prophylactic intravenous hydration is not without risk, and patients can have mild to serious complications ranging from phlebitis to pulmonary oedema.[93, 113-115] 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/min/1.73m^2, 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/min/1.73m^2 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/min/1.73m^2; 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.[28,70,75] 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/min/1.73m^2, 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.[18,20,21]

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/min/1.73m^2), 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.[116]

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 Supplementary Appendix 1.

Prophylactic hydration protocols used were according to current guidelines:[75] 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.

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 the one 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 time points (Supplementary Appendix 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.

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 (eGFR <15 ml/min/1.73m^2), renal decline with >10 eGFR units, renal decline to eGFR lower than 30 ml/min/1.73m^2, 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.

Statistical analysis

We reported continuous data as mean (SD) and presented categorical data as absolute numbers and percentages. For the primary endpoint, contrast-induced nephropathy (CIN), the absolute difference in proportions with CIN between randomised groups (i.e., 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 (1 000 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.[117]

We did pre-planned analyses within pre-specified subgroups: diabetes (yes *vs* no), eGFR (<45 *vs* ≥45 ml/min/1.73m^2), 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 for differences in categorical variables. Differences in mean values of continuous variables were assessed using the Student's *t* test for independent samples. P values of <0.05 were considered to indicate statistical significance. We did both intention-to-treat and per-protocol analyses.

The sample size was calculated using a literature-based expected proportion of patients with CIN after prophylactic hydration of 2.4%.[93] The aim was to include 1 300 patients within a 2-year inclusion period, enabling the detection of an absolute difference in contrast-induced nephropathy between groups of >2.1% (non-inferiority margin; power 80%, one-sided alpha 5%). Feasibility considerations led to a revision in December, 2015, in consultation with the research ethics committee. It was considered feasible to include some 600 patients. Assuming data on serum creatinine might not be available for 10% of patients, 660 patients were randomly assigned.

Analyses were done using 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.

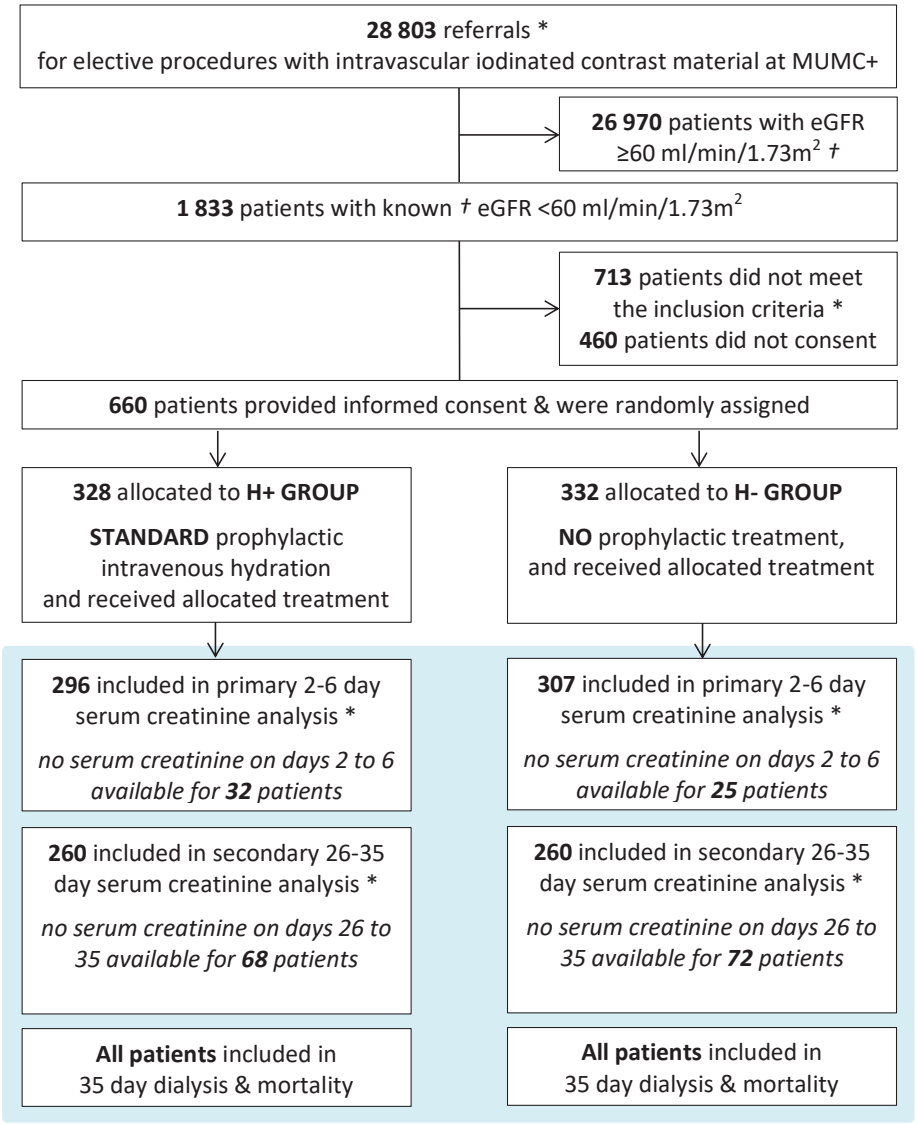


Figure 2.1. Trial profile

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. *see supplementary appendices for details. †Or without risk factors predisposing to renal insufficiency: 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.

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 2.1; details of referrals are provided in Supplementary Appendix 2). Of these, 1 833 (6%) patients had known eGFR lower than 60 ml/min/1.73m^2, which is in line with the incidences found in Europe and the Netherlands in particular.[118,119] 1 120 (4%) patients met the inclusion criteria (see details of exclusions in Supplementary Appendix 3), and 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 2.1). 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 2.1). 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 (Supplementary Appendix 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 (Supplementary Appendix 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 (i.e., 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 2.2).

Figure 2.2 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/min/1.73m^2 versus eGFR ≥45 ml/min/1.73m^2, p=0.6040; intra- arterial versus intravenous contrast administration; p=0.9608; interventional versus diagnostic procedure; p=0.3289 (figure 2.2).

Table 2.1. Baseline characteristics.

	H+ group (N=328)	H- group (N=332)
Men	194 (59%)	213 (64%)
Age	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 (49%)	160 (48%)
Interventional procedure	53 (16%)	50 (15%)
Baseline renal function		
eGFR (ml/min/1.73m^2)	47.30 (7.95)	47.59 (8.01)
Serum creatinine (µmol/l*)	118.78 (27.63)	117.71 (24.62)
Guideline risk groups		
eGFR <60 ml/min/1.73m^2 & >1 risk factors	138 (42%)	151 (45%)
eGFR <60 ml/min/1.73m^2 and diabetes	74 (23%)	65 (20%)
eGFR <45 ml/min/1.73m^2	114 (35%)	115 (35%)
Multiple myeloma /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 NSAID	157 (48%)	162 (49%)
Anaemia†	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% NaCl		
Pre-hydration	822 (486)	0
Post-hydration	809 (539)	0
Total	1637 (950)	0

Data are n (%) or mean (SD). eGFR=estimated glomerular fi ltration rate. *To convert to mg/dl, divide by 88.4. †Anaemia is defined as haematocrit <0.36 l/l for women and <0.39 l/l for men.

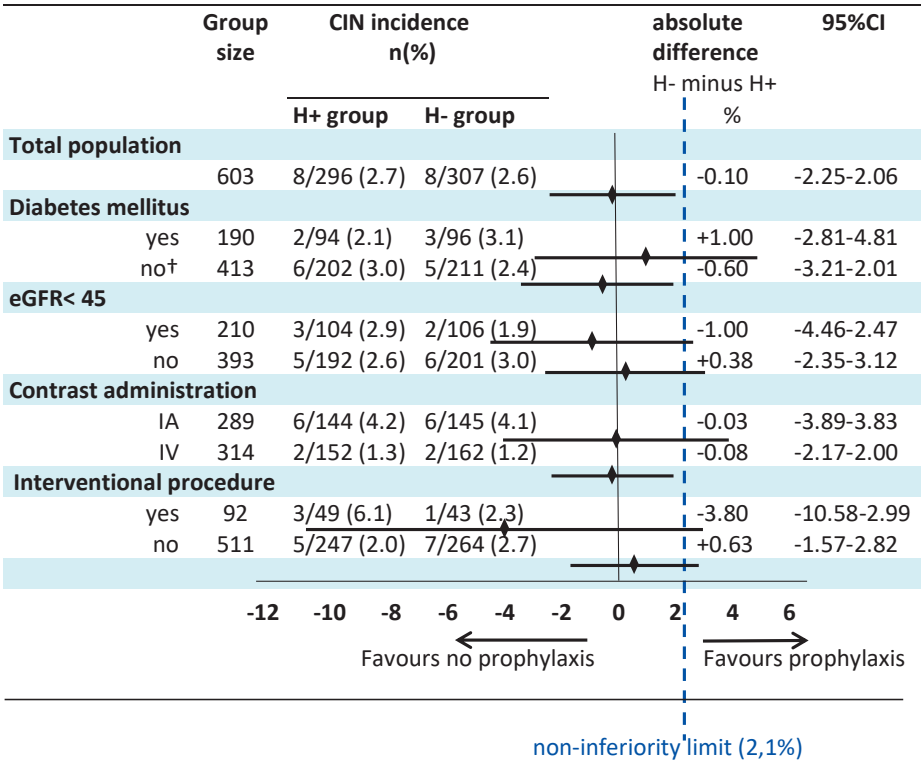


Figure 2.2. Incidence of contrast-induced nephropathy in the total study population and by patient subgroup. P values for interaction are: diabetics vs non-diabetics, p=0.5722; eGFR <45 vs eGFR ≥45; p=0.6040; intra-arterial vs intravenous contrast administration, p=0.9608; interventional vs diagnostic procedure, p=0.3289.

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 includes the guideline high-risk group with eGFR <60 ml/min/1.73m² and two or more risk factors.

Table 2.2 provides an overview of mean costs per patient (Supplementary Appendix 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 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 2.2).

The cost-effectiveness plane in figure 2.3 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 2.4 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).

Table 2.2. Cost analysis

	H+ group (N=296)		H- group (N=307)		Difference (H- minus H+)* € (95% CI)
	use	mean costs (€)	use	mean costs (€)	
IN-HOSPITAL COSTS					
Hospitalisation					
none	..	..	50%	0†	
day care (0 nights) ‡	45%	162	27%	82	-80 (-105 to -55)
24 h (1 night) ‡	27%	174	12%	76	-98 (-137 to -60)
long stay (≥2 nights) ‡	18%	257	3%	49	-208 (-275 to -137)
long stay inpatients §	9%	765	8%	560	-205 (-833 to 245)
Materials					
1L 0.9% NaCl iv bags	1.60	4.50	0	0	-4.50 (-5 to-4)
Sequelae of prophylaxis					
hospitalisation (24 h)	0.06	37	0	0	-37 (-72 to 11)
hospital consultations	0.04	2.31	0	0	-2.31 (-4 to -1)
in-hospital diagnostics (ECG, ultrasound, lab)	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 Supplementary Appendix 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 hours patients were absent from work multiplied by the gross wage per hour for men and women.

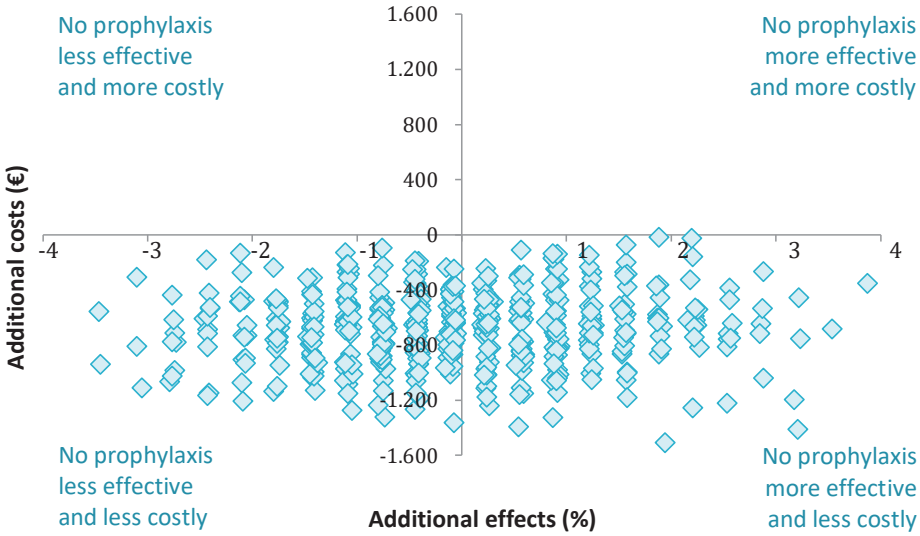


Figure 2.3. Cost-effectiveness plane of no hydration versus intravenous hydration

The x-axis shows difference in effectiveness (i.e., in percentage of contrast-induced nephropathy cases prevented), the y-axis shows difference in costs in €. Data were generated using bootstrap simulation (1 000 replications), based on the data of the trial; the figure was generated using Microsoft Excel 2010 (Microsoft, Redmond, WA, USA).

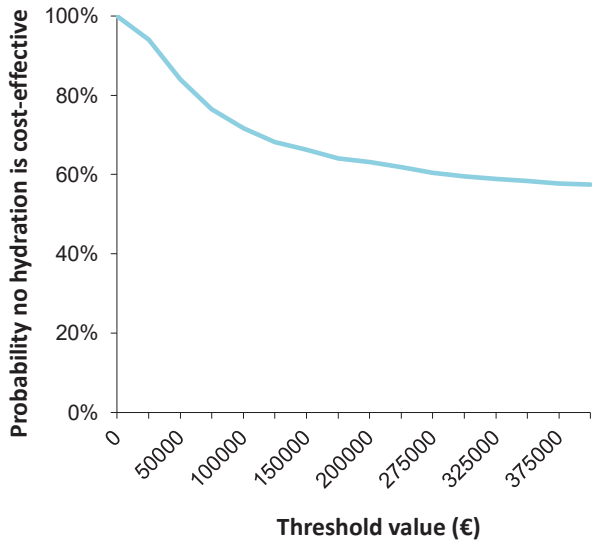


Figure 2.4. Acceptability curve

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 CIN on quality of life and incurred costs is limited. A higher threshold value would be required if long-term costly consequences (e.g. dialysis) exist.

At 26–35 days post-contrast, serum creatinine values were available for 520 patients; 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 (Supplementary Appendix 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 2.3 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/min/1.73m^2).
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/min/1.73m^2 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/min/1.73m^2 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 2.3).

Table 2.3. Incidence of major adverse events in the standard prophylactic treatment (H+) and no prophylactic treatment (H–) groups

	H+ group	H– group	Absolute difference between H+ group and H– group (95% CI)	p value
Renal events within 26–35 days post-contrast				
Renal failure (eGFR <15 ml/min/1.73m^2)	0	0	0	1.0000
>10 eGFR unit renal function decline with from baseline	7/260 (2.7%)	11/260 (4.2%)	1.5 (–1.10 to 4.17)	0.3512
Renal function decline to eGFR <30 ml/min/1.73m^2	7/260 (2.7%)	6/260 (2.3%)	–0.4 (–2.64 to 1.87)	0.7881
Both >10 eGFR unit decline from baseline and a decline to eGFR <30 ml/min/1.73m^2	2/260 (0.8%)	2/260 (0.8%)	0.0 (–1.26 to 1.26)	>0.999 9
Mortality, dialysis, and intensive care admission within 35 days post-contrast				
All-cause mortality	0/328 (0.0%)	3/332 (1.0%)	1.0 (+0.05 to 1.76)	0.1267
Dialysis	0/328 (0.0%)	0/332 (0.0%)	0	1.0000
Intensive care admission	0/328 (0.0%)	0/332 (0.0%)	0	1.0000
Sequelae of intravenous hydration in the standard prophylactic treatment group				
Symptomatic heart failure	13/328 (4.0%)	0/332 (0.0%)	–4.0 (–5.74 to –2.19)	0.0001
Hypernatremia	0/328 (0.0%)	0/332 (0.0%)	0	1.0000
Hyponatremia	1/328 (0.3%)	0/332 (0.0%)	–0.3 (–0.81 to 0.20)	0.4970
Arrhythmia	4/328 (1.2%)	0/332 (0.0%)	–1.2 (–2.22 to –0.22)	0.0604

eGFR=estimated glomerular filtration rate.

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.[57,99,101] 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—i.e., 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/min/1.73m^2 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.

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/min/1.73m^2 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%).[19] 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.[99,101]

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 48–72h. 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,[120] 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,[93] 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.[18,20,21] 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 ≥30 ml/min/1.73m^2 might be considered without com- promising 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.

Acknowledgments

The AMACING study was funded by Stichting de Weijerhorst, Limburg, the Netherlands. We thank Guy Peeters and Hans Fiolet for their support of this study; and Maureen Wollaert and Joelle Sondeijker for their valuable work in data collection.

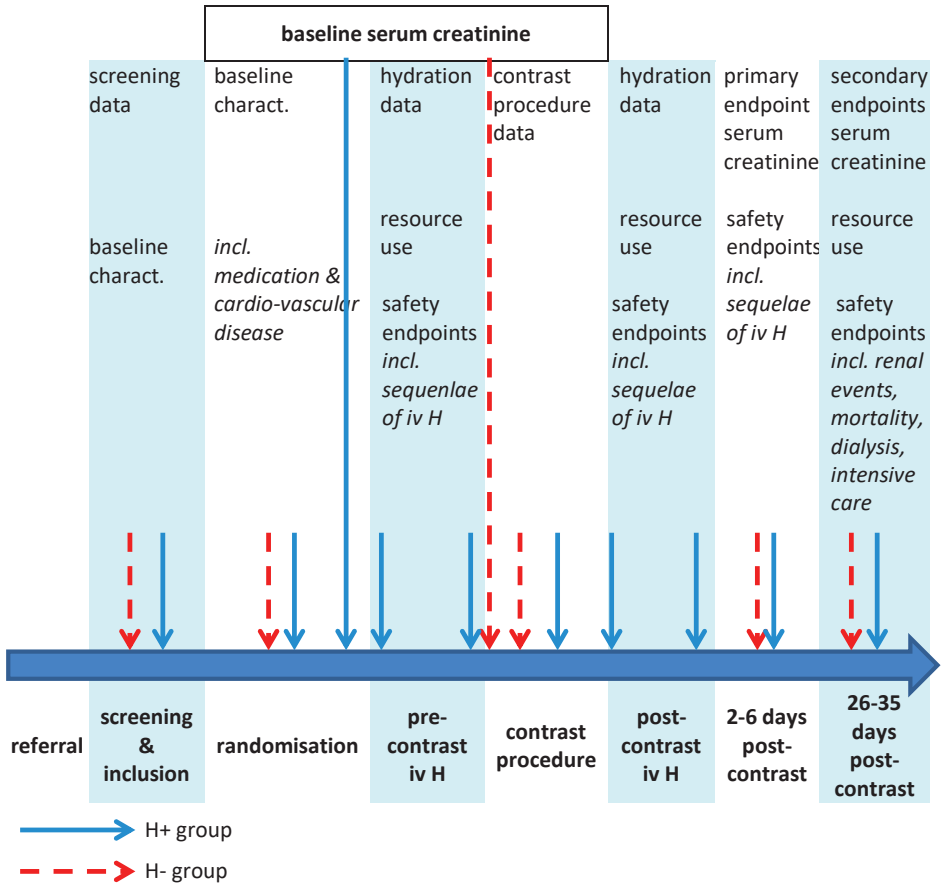
2.2 The Lancet Supplementary Appendices

This supplementary material formed part of the original submission and has been peer reviewed.

Supplement to: Nijssen EC, Rennenberg RJ, Nelemans PJ, et al. 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, non-inferiority trial. Lancet 2017; published online Feb 20. http://dx.doi.org/10.1016/S0140-6736(17)30057-0.

https://www.thelancet.com/cms/10.1016/S0140-6736(17)30057-0/attachment/a2e708be-99ce-4f83-9c1c-095495c98421/mmc1.pdf

Supplementary Appendix 1. Timeline AMACING data collection.



iv H indicates 4-12 h 0.9% NaCl intravenous hydration

Supplementary Appendix 2. Referrals for elective procedure with iodinated contrast material at MUMC+ between 17th June, 2014, and 17th July, 2016.

Contrast enhanced computed tomography (CECT)	21 136
Peripheral angiography	706
Peripheral intervention	1 773
Coronary angiography or Percutaneous Coronary intervention	5 188

Supplementary Appendix 3. Detail of patients who did not meet the AMACING inclusion criteria.

eGFR <60 ml/min/1.73m^2 without risk factors	169
eGFR <30 ml/min/1.73m^2	157
renal replacement therapy	29
emergency /intensive care before procedure	15
deceased before procedure	6
inability to allow measurement at 2-6 days	50
inability to give informed consent	63
No referral for intravenous hydration (due to contra-indications such as severe aortic valve stenosis, heart failure, or low ejection fraction)	74
participation in other RCT	55
no participation on doctor's advice	25
procedure cancelled/rescheduled	66
patient isolation (infection control)	4

Supplementary Appendix 4. Time of primary and secondary endpoint serum creatinine measurements.

Days post contrast	H+ group n(%)	H- group n(%)
2-4	191/296 (64.5)	194/307 (63.1)
5-6*	105/296 (35.5)	113/307 (36.8)
26-30	162/260 (62.3)	153/260 (58.8)
31-35	98/260 (37.7)	107/260 (41.1)

*number of measurements on day six were 39/296 (13.2%) in the hydrated group, and 39/307 (12.7%) in the non-hydrated group.

Supplementary Appendix 5. Baseline Characteristics of patients included vs NOT included in analyses.

	2-6 days post-contrast serum creatinine analysis		26-35 days post-contrast serum creatinine analysis	
	Population included in analysis	Population NOT included in analysis	Population included in analysis	Population NOT included in analysis
	n=603	n=57	n=520	n=140
Male	370 (61)	42 (64)	330 (63)	77 (55)
Age	72.2 ±9.3	72.5 ±9.2	72.07±9.3	72.77 ±9.2
Inpatient	51 (9)	6 (9)	40 (8)	17 (12)
Intra-arterial contrast	289 (48)	35 (53)	238 (46)	81 (58)
Interventional procedure	92 (15)	11 (19)	75 (14)	28 (20)
Renal function				
Baseline serum creatinine *(µmol/l*)*	118.36 ± 26.13	117.00 ±25.90	119.96 ±26.14	111.86 ±26.19
eGFR*(ml/min/1.73m^2)*	47.39 ±7.95	47.68 ±8.22	47.02 ±7.96	49.03 ±7.98
Guideline risk groups				
eGFR<60 + >1 risk factor	269 (45)	25 (38)	221 (43)	68 (49)
eGFR <60 + DM	123 (20)	18 (27)	109 (21)	30 (21)
eGFR<45	208 (35)	23 (35)	188 (36)	41 (29)
multiple myeloma†	3 (0.5)	0	2 (0.4)	1 (1)
Guideline risk factors				
Diabetes mellitus	*190 (32)*	*28 (42)*	173 (33)	42 (30)
Age >75 years	262 (43)	28 (42)	215 (41)	71 (51)
Prescribed diuretic medication	*279 (46)*	*30 (46)*	240 (46)	67 (48)
Prescribed NSAID medication	*287 (48)*	*37 (56)*	252 (48)	67 (48)
Anaemia‡	*170 (28)*	*17 (26)*	141 (27)	43 (31)
Cardiovascular disease	452 (75)	49 (74)	396 (76)	97 (69)

Data are given as number (%) or mean (± SD). DM=Diabetes mellitus; eGFR=estimated glomerular filtration rate. *to convert to mg/dl, divide by 88.4. †or lymphoplasmacytic lymphoma ‡Anaemia is defined as haematocrit <0.36 l/l for women; <0.39 l/l for men.

Supplementary Appendix 6. Unit prices

	Price per unit (€)	Source*
In-hospital costs, University Hospital		
Day care without prophylactic hydration	305	Manual for cost research
Day care with prophylactic hydration, *including 2 hours nursing care (excl. Premium Pay*)	360.48	Manual for cost research
University Hospital day *(24-hours, including 1 night)*	650	Manual for cost research
1L 0.9% NaCl iv bag	2.80	Maastricht UMC+
30-minute specialist consultation	57	Manual for cost research
Diagnostics costs		
Echo lower extremities	80	Manual for cost research
ECG	24	Maastricht UMC+
blood test	7.30	Maastricht UMC+
urine test	20.30	Maastricht UMC+
Outside hospital costs		
Consultation general practitioner	33	Manual for cost research
Visit general practitioner at home	50	Manual for cost research
Telephone consultation general practitioner	17	Manual for cost research

*Manual for cost research: see reference number 24 / Maastricht UMC+ = Maastricht University Medical Centre. All cost prices were indexed to the year 2015.

2.3 Letters to Editor of the Lancet

Four letters written to the Lancet in response to the AMACING article were published, to which we were invited to write a reply:[121-125]

Nijssen EC, Nelemans PJ, Rennenberg RJ, van Ommen GV, Wildberger JE, for the CIN group Maastricht UMC+. Hydration and contrast-induced nephropathy - authors' reply. *Lancet 2017;390:454-455.*

doi: https://doi.org/10.1016/S0140-6736(17)31809-3

Key points

- **Comment:** The population included in the AMACING trial may not truly be at high-risk of CIN.

Reply: The aim of the trial was evaluating efficacy of guideline-recommended standard prophylaxis, not the risk of CIN. The included population represents 90% of the patient population for which the guidelines recommend standard prophylaxis.

- **Comment**: Results may not be generalizable to emergency settings; patients with lower eGFR; or inpatients with poor health.

Reply: Emergency, intensive care, and eGFR <30 ml/min/1.73m^2 were exclusion criteria of the AMACING trial, and such patients were beyond the scope of the trial.

- **Comment:** Results may not be generalizable to procedures with higher contrast volume or other contrast materials. Contrast administration route (intravenous vs. intra-arterial) and NSAIDs are factors that influence CIN incidences.

Reply: Contrast volumes were not influenced – clinical practice was followed.

Risk factors mentioned were amply present in participants of the AMACING trial, and reflect prevalence in the population concerned: contrast volumes >2x eGFR in 42% patients; >3x eGFR in 15% patients; >140 ml in 10%; contrast administration route

intra-arterial in 48% of patients; 48% of patients used prescribed NSAIDs; 9% were inpatients referred for elective procedures.
In no instance is there an indication that standard prophylaxis confers a benefit to subgroups.

- **Comment**: CIN incidence found is (too) low.
Reply: CIN incidence is similar to those found in elective settings in other studies. It is in acute settings that higher incidences are found.

- **Comment**: It may be premature to advocate withholding prophylaxis in patients with eGFR >29 ml/min/1.73m^2.
Reply: Would it be ethical to continue giving a treatment that is unproven, carries proven risks, confers substantial burden to patient and hospital, and is so costly? We should not forget that the implementation of standard prophylaxis according to the guidelines incurs risk of clinical complications: in the AMACING trial this concerned 18 (5.5%) of 328 intravenously hydrated patients.

Hydration and contrast-induced nephropathy - authors' reply

Estelle C Nijssen, Patty J Nelemans, Roger J Rennenberg, Vincent van Ommen, Joachim E Wildberger, for the CIN group MUMC+

We thank Hitinder Gurm and Simon Dixon, Ivan Pavlov, Brian Weiner, and Viktoria Schwarz and colleagues for opening up the discussion and allowing us to clarify a few key points.

Our aim in the AMACING trial[104] was to evaluate current international and national guidelines for the use of intravascular iodinated contrast material, and the study was designed to that end.

To put the study in perspective, our local guideline was introduced in 2008–12 as one of ten measures to increase patient safety in the Netherlands.[75] Since this introduction and to date, these measures have been imposed on hospitals quite strictly, and compliance is part of the annual hospital quality assessment done by the government.

The standard prophylactic treatment recommended by the guideline has enormous impact in its implementation. Despite the recommendations, there is no proven reference standard for the prevention of contrast-induced nephropathy or contrast-induced acute kidney injury. Most trials on the subject have compared one form of intravenous hydration against another in specific clinical settings. Trials that have found some benefit of intravenous hydration in the prevention of contrast-induced nephropathy or contrast-induced acute kidney injury, such as those referred to by Pavlov and Schwarz and colleagues, have been done in emergency settings where factors such as haemodynamic instability might play a role. However, emergency and intensive care status were among our exclusion criteria, and such patients are therefore beyond the scope of our trial.

The fundamental question was not about the risk of contrast-induced nephropathy or contrast-induced acute kidney injury, or about the benefits of intravenous hydration in other settings. The knowledge gap the AMACING trial aimed to fill was the efficacy of guideline-recommended prophylaxis in the prevention of contrast-induced nephropathy or contrast-induced acute kidney injury compared with not giving prophylaxis, and we did this analysis in the population targeted by the guidelines.

The best way to assure external validity is to do the study in a setting that closely resembles the one that the programme would operate in in clinical routine, and to include patients that would typically use that setting. We did not interfere with patients' drinking or aspects of daily clinical practice, other than withholding intravenous hydration in the no prophylaxis group. Furthermore, we included exactly the patient population for which the guidelines recommend prophylactic intravenous hydration with normal saline.[75]

For safety reasons, we excluded all patients (n=157) with estimated glomerular filtration rates (eGFR) <30 ml/min/1.73m². Therefore, the population included in the AMACING trial represented 90% of the patients that received intravenous prophylactic hydration recommended by the guideline. Not clinically high risk perhaps, but at high risk for the development of contrast-induced nephropathy or contrast-induced acute kidney injury as the guidelines suggest.

Risk factors mentioned by Gurm and Dixon, Weiner, and Schwarz and colleagues were amply present in participants of the AMACING trial, and reflect prevalence in the total population concerned: the total population concerned: contrast volumes two-times or more the eGFR were administered to 42%, three times or more the eGFR to 15%, and 140 ml or more to 10%; the contrast administration route was intra-arterial for 48% of the population; 48% used prescribed non-steroidal anti-inflammatory drugs, 47% used prescribed diuretics, and 20% used a combination of both; inpatients referred for elective procedures comprised 9% of the included population. In no instance is there an indication that standard intravenous hydration confers a benefit as prophylaxis.

We agree with Gurm and Dixon and Schwarz and colleagues that low to moderate contrast volume is key for patient safety. Long before this trial, we introduced individualised patient protocols that took into account route of contrast administration, indication, and patient characteristics, resulting in as low as reasonable and achievable contrast volume. The results of the AMACING trial certainly have to be put into this perspective. To quote our conclusion, "…assuming optimal contrast media administration, withholding prophylaxis for high risk patients with eGFR ≥30 ml/min/1.73m² might be considered without compromising patient safety."[104]

The correspondents all express concerns that, for various reasons, the population of the AMACING trial might not benefit from intravenous hydration. Our results concur: we found no prophylaxis to be non-inferior to intravenous hydration in the prevention of contrast-induced nephropathy or contrast-induced acute kidney injury in the population studied, which represents the majority of the population that qualifies for this prophylaxis.[75]

Would it be premature to advocate withholding prophylaxis for elective high-risk patients with eGFR ≥30 ml/min/1.73m², as Gurm and Dixon suggest? We would counter with the following question: would it be ethical to continue giving a treatment that is unproven, carries proven risks, confers substantial burden in the patient and hospital, and is so costly? We should not forget that the implementation of standard prophylaxis according to the guidelines incurs risk of clinical complications: in the AMACING trial this concerned 18 (5.5%) of 328 patients hydrated intravenously.

As James Ellis (University of Michigan, personal communication) so eloquently put it: "What matters is that expensive (and with some risk) hydration is not succeeding in a group of patients where it is commonly used, suggesting that hydration has become a bad habit that needs to stop. The question of why hydration doesn't do anything in this group of patients is not the point of the paper (although that remains an interesting topic)."

John Mandrola summarises on Medscape "…the most provocative aspect of [the] AMACING [trial] is how it prompts us to reexamine the very existence of CIN [contrast-induced nephropathy]. Perhaps hydration does not prevent CIN because our way of thinking about CIN is flawed. […] Results of the AMACING study force us to 1) be suspicious of expert opinion, 2) object to quality measures not backed by randomized trial data, and 3) reconsider the existence of an entire disease entity (CIN), and in doing so, think about how our brains can trick us into seeing signal when there is mostly noise.[134]

We declare no competing interests

CHAPTER 3

3. AMACING Long-Term Results

Nijssen EC, Nelemans PJ, Rennenberg RJ, van Ommen GV, Wildberger JE. Prophylactic intravenous hydration to protect renal function from intravascular iodinated contrast material (AMACING): long-term results of a prospective, randomised, controlled, trial. *EClinicalMedicine by the Lancet* 2018;4-5:109-116.

doi: https://doi.org/10.1016/j.eclinm.2018.10.007

Key Points

- The aim of 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.
- The outcomes dialysis, mortality, and change in renal function at 1 year post-contrast were secondary outcomes of the trial.
- Data on 1-year dialysis and mortality were available for all patients. Dialysis was recorded in 2/332 (0.6%) no prophylaxis and 2/328 (0.6%) prophylaxis patients (p=0.99); mortality for 36/332 (10.8%) no prophylaxis and 32/328 (9.8%) prophylaxis patients (p=0.65).
- The hazard ratio for one-year risk of death was 1.118 (no prophylaxis vs. prophylaxis; 95% CI: 0.70 to 1.80, p=0.65).
- 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.
- **Conclusion:** Assuming optimal contrast administration, not giving prophylaxis to elective patients with eGFR 30–59 ml/min/1.73m^2 is safe, even in the long-term.

Prophylactic intravenous hydration to protect renal function from intravascular iodinated contrast material (AMACING): long-term results of a prospective, randomised, controlled trial

Estelle C Nijssen, Patty J Nelemans, Roger J Rennenberg, Vincent van Ommen, Joachim E Wildberger

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/1.73m^2 combined with risk factors, undergoing elective procedures requiring intravenous or intra-arterial iodinated contrast material. Exclusion criteria were eGFR <30 ml/min/1.73m^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, 1 120 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).

EClinicalMedicine by The Lancet

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/1.73m^2 is safe, even in the long-term.

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 aim 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/1.73m^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 ≥30 ml/min/1.73m^2.

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.[19,25,126,127] 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.[18-21] 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.[70-74,109] They generally recommend intravascular volume expansion with isotonic saline as standard prophylaxis for those considered at risk of CIN/CI-AKI.[70-74,79,109] 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.[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.[28,70] 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.[99-102] Two of these were done in the acute setting of primary percutaneous intervention in patients with ST-elevation myocardial infarction.[99,101] Both found significantly lower incidences of CIN/CI-AKI after prophylaxis (22/108 vs 38/108[99] and 22/204 vs 43/204[101]). One of these trials reported less in-hospital mortality for the prophylaxis group (3/108 vs 10/108),[99] whereas the other found no difference between groups.[101] 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).[102] 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).[100] 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.[18,20,21]

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/1.73m^2 were included, and these are not considered to be at high risk of post-contrast adverse events.[19,70-74,76,79,109]

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/1.73m^2 combined with risk factors for CIN/CI-AKI.[104] 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/CIAKI, 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.

Methods

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.[104] 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/1.73m^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/1.73m^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.[75]

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/1.73m^2, 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.

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/1.73m^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 (versionv3.0.2083.212r; Formsvision BV, Abcoude, the Netherlands).

Laboratory personnel processing samples for serum creatinine values were masked to treatment allocation, and samples were labelled with coded stickers. 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.

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.[104]

Prophylactic hydration protocols used for patients randomised to the standard prophylaxis group were according to the guidelines and prescribed by the treating physician:[75] standard protocol intravenous 0.9% NaCl 3–4 ml/kg/h, during 4 h before and 4 h after contrast administration; long protocol intravenous 0.9% NaCl 1 m/kg/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 per 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.

Outcomes

Clinical outcomes at one-year post-contrast exposure were predefined 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/1.73m^2); 2. renal decline with more than 10 eGFR units; 3. renal decline to eGFR <30 ml/min/1.73m^2; 4. a combination of the latter two.

Change in renal function over time was evaluated at 2 to 6 days, 26to 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.

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.[104] 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/1.73m^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.

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.

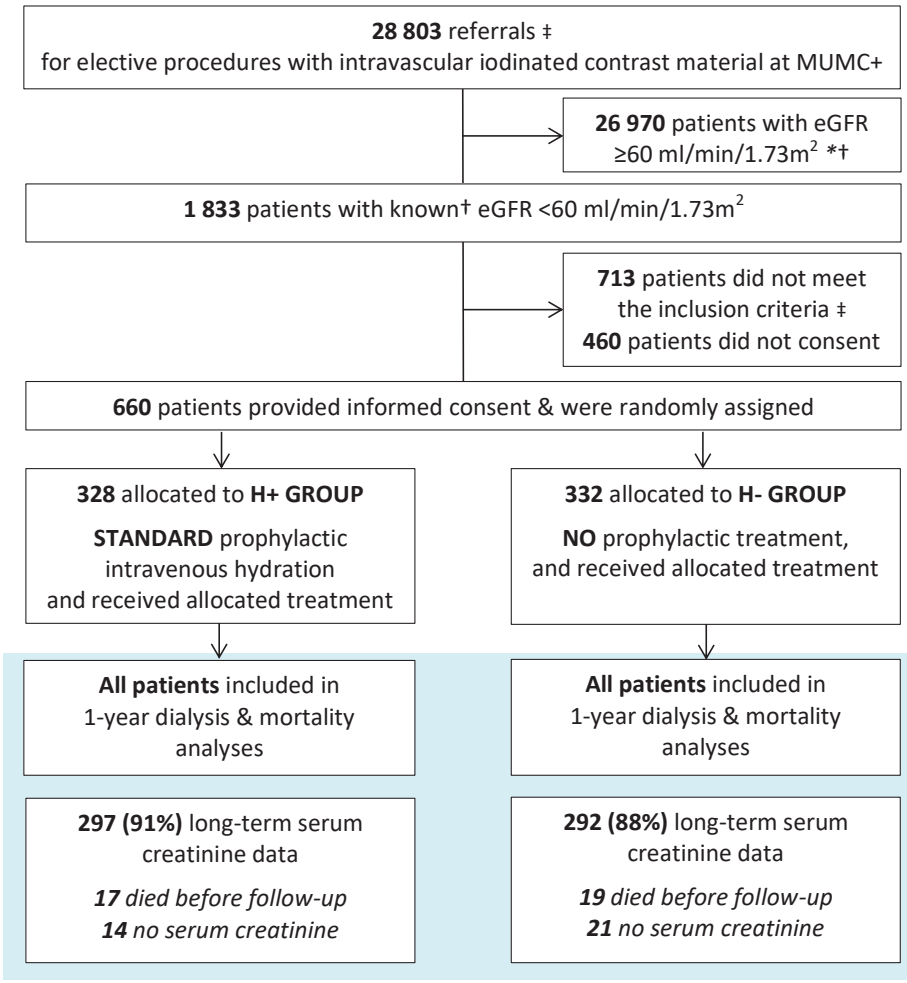


Figure 3.1. Trial profile.

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. *Or without risk factors predisposing to renal insufficiency. †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. ‡Details have been published elsewhere.[104]

Table 3.1: 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/1.73m^2)	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/min/1.73m^2 and two risk factors	138 (42%)	151 (45%)
eGFR 45-59 ml/min/1.73m^2 and diabetes	74 (23%)	65 (20%)
eGFR 30-44 ml/min/1.73m^2 †	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)		
300mg iodine/ml contrast	92 (41)	89 (41)
Intravenous 0.9% NaCl		
Pre-hydration	822 (486)	0
Post-hydration	809 (539)	0
Total iv hydration	1637 (950)	0

Data are n (%) or mean (SD). eGFR=estimated glomerular filtration rate. * To convert to mg/dl, divide by 88.4. † 76/231 patients with eGFR <45 ml/min/1.73m^2 had diabetes. ‡ 1 H+ group and 1 H− group multiple myeloma/lymphoplasmacytic lymphoma patient also had eGFR 30–44 ml/min/1.73m^2. § Anaemia defined as haematocrit <0.36 l/l for women and <0.39 l/l for men.

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 (figure 3.1). 1 833 patients with known eGFR <60 ml/min/1.73m^2 were identified, and 1 120 patients met the trial inclusion criteria: 432 patients with eGFR 30–44 ml/min/1.73m^2 (1.5%), and 688 patients with eGFR 45–59 ml/min/1.73m^2 (2.4%) combined with risk factors for CIN/CI-AKI. In total 157 patients were excluded because of eGFR <30 ml/min/1.73m^2 (0.5%).[128]

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 (figure 3.1). 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 3.1).[104]

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 3.2). 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; table 3.2). 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; table 3.2).

Table 3.2. 1-year dialysis and mortality

A. Dialysis within 365 days		**H+ group** n (%)	**H- group** n (%)	**Absolute difference** H- minus H+	**95% confidence interval**	**p value**	**p for inter-action**
Total group		2/328 (0.61%)	2/332 (0.60%)	-0.01	-1.19 to 1.18	0.99	-
Diabetes	yes	1/106 (0.94%)	1/109 (0.92%)	-0.03	-2.54 to 2.59	0.99	0.99
	no	1/222 (0.45%)	1/223 (0.45%)	-0.00	-1.25 to 1.24	0.10	
eGFR <45 ml/min/1.73m^2	yes	1/116 (0.86%)	1/115 (0.87%)	+0.01	-2.38 to 2.40	0.10	0.99
	no	1/212 (0.47%)	1/217 (0.46%)	-0.01	-1.30 to 1.28	0.10	
Contrast administration route	IA	2/159 (1.26%)	0/160 (0.0%)	-1.26	-2.99 to 0.47	0.25	*
	IV	0/169 (0.0%)	2/172 (1.16%)	+1.16	-0.44 to 2.77	0.25	
Interventional procedure	yes	0/53 (0.0%)	0/50 (0.0%)	0.00	-	1.00	*
	no	2/275 (0.73%)	2/282 (0.71%)	-0.02	-1.42 to 1.39	0.98	

B. Mortality within 365 days		**H+ group** n (%)	**H– group** n (%)	**Absolute difference** H- minus H+	**95% confidence interval**	**p value**	**p for inter-action**
Total group		32/328 (9.8%)	36/332 (10.8%)	+1.01	-3.55 to 5.72	0.65	-
Diabetes	yes	16/106 (15.09%)	15/109 (13.76%)	-1.33	-10.73 to 8.06	0.78	0.44
	no	16/222 (7.21%)	22/223 (9.87%)	+2.66	-2.53 to 7.84	0.32	
eGFR <45 ml/min/1.73m^2	yes	17/116 (14.66%)	19/115 (16.52%)	+1.87	-7.49 to 11.22	0.70	0.95
	no	15/212 (7.08%)	17/217 (7.83%)	+0.76	-4.21 to 5.73	0.77	
Contrast administration route	IA	8/159 (5.03%)	4/160 (2.50%)	-2.53	-6.70 to 1.64	0.25	0.13
	IV	24/169 (14.20)	32/172 (18.60%)	+4.40	-3.44 to 12.25	0.28	
Interventional procedure	yes	3/53 (5.66%)	3/50 (6.00%)	+0.34	-8.72 to 9.40	0.94	0.95
	no	29/275 (10.55%)	33/282 (11.70%)	+1.16	-4.06 to 6.38	0.67	

eGFR=estimated glomerular filtration rate. *no value for interaction could be calculated due to zero events.

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, cardiovascular2/32, cerebral oedema 1/32, old age 1/32, heart- and renal- failure 1/32 (renal failure in this case was eGFR 7 ml/min/1.73m^2), pulmonary embolism 1/32, unknown 2/32.

Table 3.2 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.

Figure 3.2 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. 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 figure 3.3. 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:[104] 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 (SD13.79) in the H+ group (p=0.4049), and +1.39 µmol/l (SD 16.12) in the H− group, and +1.44 µmol/l (SD 17.10) in the H+ group (p=0.9705) respectively.

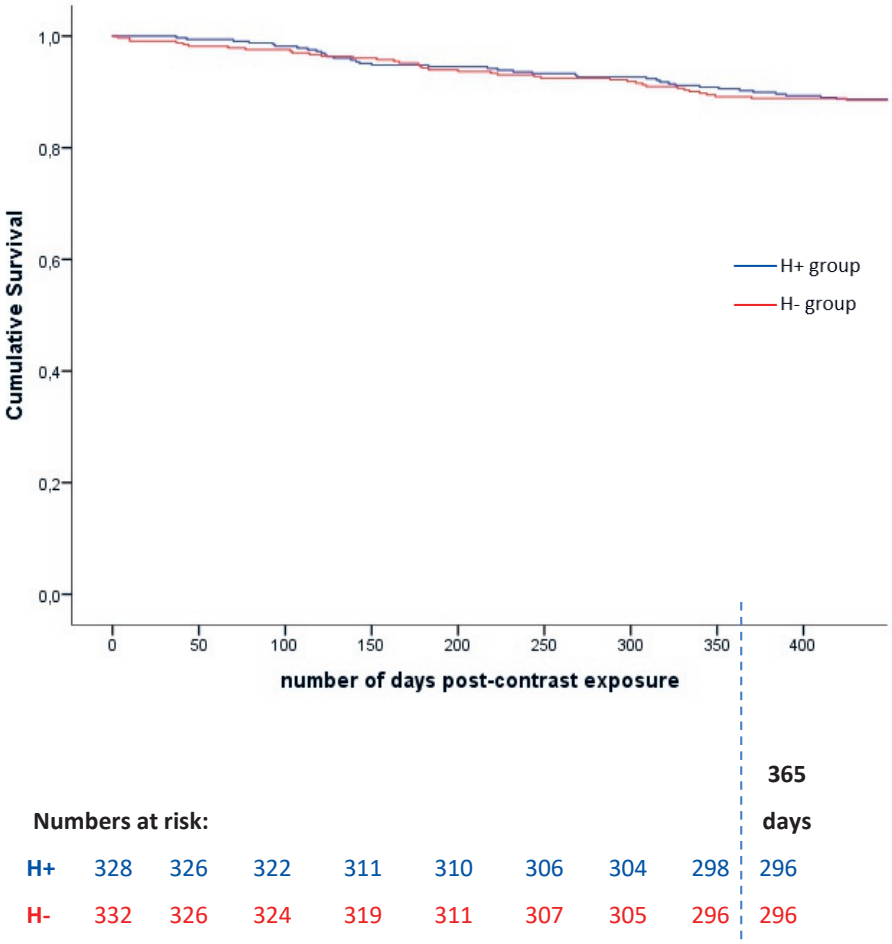


Figure 3.2. Kaplan–Meier Survival Plot for the standard prophylactic treatment (H+) and no prophylactic treatment (H−) groups. Hazard ratio for 1-year risk of death 1.118 (95% CI 0.695 to 1.801, n=660, p=0.6449).

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).

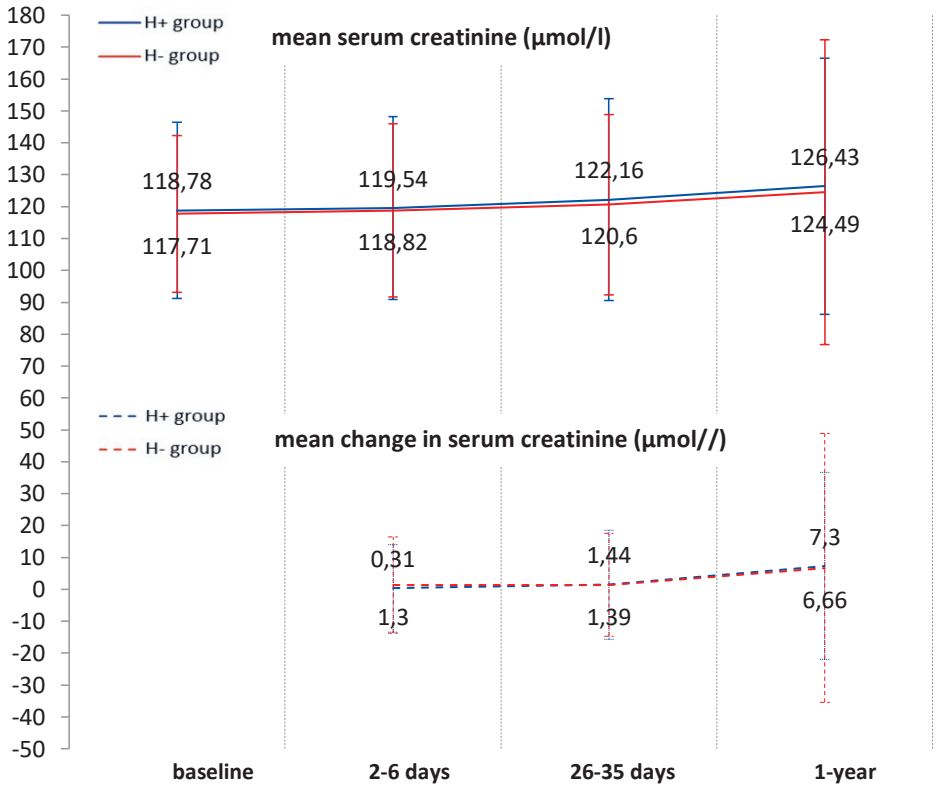


Figure 3.3. Observed mean post-contrast serum creatinine and changes in serum creatinine in the standard prophylactic treatment (H+) and no prophylactic treatment (H−) groups. Error bars show standard deviations.

Table 3.3 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/1.73m^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/1.73m^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/1.73m^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/1.73m^2 at one year post-contrast (H+ group).

Table 3.3. Long-term renal events in prophylaxis (H+) and no prophylaxis (H−) groups.

	H+ group* n(%)	**H- group*** n(%)	**Absolute difference** (H- minus H+)	**95% confidence interval**	**p value**
Renal failure (eGFR <15 ml/min/1.73m^2)	0/297 (0.00)	1/292 (0.34)	+0.34	-0.97 to 1.91	0.32
>10 eGFR unit renal function decline with from baseline	28/297 (9.43)	28/292 (9.59)	+0.16	-4.65 to 4.99	0.95
Renal function decline to eGFR <30 ml/min/1.73m^2	9/297 (3.03)	8/292 (2.74)	-0.29	-2.65 to 3.24	0.83
>10 eGFR unit decline from baseline AND a decline to eGFR <30 ml/min/1.73m^2	11/297 (3.70)	10/292 (3.42)	+0.28	-2.92 to 3.49	0.85

eGFR=estimated glomerular filtration rate. *Long-term serum creatinine data were available for 589/660 (89%) patients: 297/328 (91%) of the H+ group and 292/332 (88%) of the H- group.

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 versus without diabetes; eGFR 30–44 vs 45–59 ml/min/1.73m^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/1.73m^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 instability might play a part, and where some benefit of hydration has been found.[129,130]

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.[19,71,76] However, we chose to use the terms CIN/CIAKI 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/CIAKI 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.[99,101,102] 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/1.73m^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 beat (high) risk of CIN/CI-AKI.[121,122,131] 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 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/1.73m^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/1.73m^2, but after recent updates a lower prophylaxis threshold is recommended by most guidelines.[19,70-74, 76,79,109] The KDIGO-, Canadian-, and British-guidelines recommend a threshold of eGFR <45 ml/min/1.73m^2; others, such as the European guidelines, now recommend a prophylaxis threshold of eGFR <30 ml/min/1.73m^2.[19, 70-74, 76,79,109] 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.

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.

CHAPTER 4

4. Reception of the AMACING Trial Results, Guideline-Updates, and Ensuing Shift in Research-Focus

The AMACING results caused quite a stir in the medical community. Within 3 months of the Lancet publication, the article had over 850 000 followers on Twitter; after publication of the 1-year results this number increased to over a million (QR:https://www.altmetric.com/details/16569356/twitter).

The Lancet article attention score is in the top 5% of all research outputs scored by Altmetric (QR:https://www.altmetric.com/details/16569356#score),

and it has 111 registered citations so far (QR: https://plu.mx/plum/a/?doi=10.1016%2FS0140-6736%2817%2930057-0&theme=plum-jbs-theme&hideUsage=true&display-tab=summary-content).

Several editorials, news items, letters, and blogs were written on AMACING (see list in Appendix I); a double publication in Dutch (for full article see Appendix II),[132] and a reprint in Chinese were published.

Most authors were positive about the AMACING trial and quick to realise the implications. To cite a few examples: in an editorial in Kidney International Dr. Wyatt stated that prophylactic hydration in the population studied in the trial was probably "much ado about nothing";[131] in an editorial in the Nederlands Tijdschrift voor Geneeskunde Prof. Dr. van der Graaf stated that we should stop such unproven interventions and lay the burden of proof at the feet of prophylaxis;[133] in an online article on Medscape Dr. Mandrola stated that " IV hydration may have been uselful in another era".[134]

By the end of 2017/beginning of 2018, several guidelines on the use of iodinated contrast administration were updated to reflect the AMACING results.[70, 76-79] Amongst these were the Dutch (NVvR) and European (ESUR) guidelines.[76,79] From then on, prophylactic intravenous hydration was no longer recommended for the population included in the AMACING trial.[76] Now prophylaxis was only recommended for patients excluded from the AMACING trial, i.e. those with eGFR <30 ml/min/1.73m^2.

There are various reasons why those patients were excluded from the AMACING trial. At the time there were many uncertainties with regard to incidences of adverse outcomes in absence of prophylaxis, because no data in absence of prophylaxis existed in literature. Also, patients with eGFR 30-59 ml/min/1.73m^2 were still considered high-risk, and not giving prophylaxis even to those patients was deemed unethical by some (see for example the section "Hydration (volume expansion)" in the 2011 European Guideline update article by Stacul et al).[28] Furthermore, in absence of relevant data without prophylaxis, eGFR <30 ml/min/1.73m^2 patients were thought too vulnerable to further renal function decline and dialysis. Permission was granted by the Medical Research Ethics Committee to include high-risk patients with eGFR 30-59 ml/min/1.73m^2 in the AMACING trial, but it was agreed that eGFR <30 ml/min/1.73m^2 patients would be excluded for safety reasons.

The result is that the updated recommendation of the guidelines was not introduced because of (new) evidence of efficacy of prophylaxis in patients with eGFR <30 ml/min/1.73m^2. These patients are relatively scarce,[19] and data on this population in the context of CIN was lacking in literature. The aim of the AMACING project being the evaluation of prophylaxis according to current guidelines, our research-focus shifted to accommodate the updated recommendations. The focus thus became patients with eGFR <30 ml/min/1.73m^2.

The following two chapters contain two observational studies on elective procedures with intravascular iodinated contrast administration and prophylaxis for the prevention of CIN in patients with eGFR <30 ml/min/1.73m^2.

The first study, detailed in chapter 5, was carried out on the prospectively screened patients with eGFR <30 ml/min/1.73m^2 excluded from the AMACING trial.[128] The aim was to look at the implicit assumptions underlying the guideline update in the recommendation for prophylactic intravenous hydration: 1) patients with eGFR <30 ml/min/ 1.73m^2 are at higher risk of CIN and other unfavourable outcomes after intravascular iodinated contrast material administration than patients formerly eligible for prophylaxis with eGFR 30-59 ml/min/1.73m^2; 2) prophylactic intravenous hydration

mitigates this risk; 3) the risk of complications due to administering prophylactic intravenous hydration does not outweigh the positive preventive effect.

In the discussion of the article, feasibility of carrying out a randomised controlled trial similar to AMACING in this population was assessed. Investigative Radiology accepted the paper for publication on March 21st 2018.

It was clear from results of this first study that a larger dataset, preferably a randomised controlled trial, was required to be able to draw definite conclusions about efficacy of prophylaxis in this population. However, the feasibility calculation led to the conclusion that a randomised controlled trial of sufficient power similar to the AMACING trial would not be feasible. In view of these findings, the decision was made to expand the dataset of patients with eGFR <30 ml/min/1.73m^2.

This resulted in the second study, detailed in chapter 6.[135] It includes data of all elective procedures with intravascular iodinated contrast carried out at Maastricht UMC+ over the course of 4 years. The inclusion period reflects the maximum available complete years during which the in-house protocol for the prevention of CIN was fully implemented and remained the same for the included population. The aim of the study was to gain insight into positive and negative effects of prophylactic intravenous hydration. This was done comparing post-contrast outcomes in patients with eGFR <30 ml/min/1.73m^2 who did and did not receive prophylaxis.

All 55 474 procedures from the period May 17th 2014 until May 17th 2018 were retrospectively screened; the results were accepted for publication by Investigative Radiology on March 14th 2019.

CHAPTER 5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DOUBLE LETTER SCORE
TRIPLE LETTER SCORE
TRIPLE WORD SCORE

5. Evaluation of Safety Guidelines: Conundrum Continued

Nijssen EC, Nelemans PJ, Rennenberg RJ, van Ommen V, Wildberger JE. Evaluation of safety guidelines on the use of iodinated contrast material: conundrum continued. *Invest Radiol* 2018;53:616-622.

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Key Points

- Data were collected from all patients with eGFR <30 ml/min/1.73m^2 referred for an elective procedure with intravascular iodinated contrast material administration and excluded from the AMACING trial. These patients were then compared with those prospectively included in the AMACING trial (with eGFR 30–59 ml/min/1.73m^2 and risk factors).
- 157 (0.5%) of all elective patients referred for a contrast procedure had eGFR <30 ml/min/1.73m^2 in absence of dialysis, and 155 of these actually received intravascular iodinated contrast material. Standard prophylaxis was given to 119/155 (77%) of these patients.
- Incidences in eGFR <30 ml/min/1.73m^2 versus AMACING trial participants are as follows: CIN 13.6% versus 2.7% (p=0.0019); 35-day dialysis 0.9% versus 0.0% (p=0.2646); 35-day mortality 9.2% versus 0.0% (p<0.0001); complications of prophylactic intravenous hydration 5.9% versus 5.5% (p=0.8529).
- **Conclusions**: Incidences of CIN and mortality at 35 days are significantly higher in the population with eGFR <30 ml/min/1.73m^2 than in the population formerly eligible for prophylaxis with eGFR 30-59 ml/min/1.73m^2, even after prophylactic intravenous hydration. The risk of complications of prophylactic intravenous hydration is similar and substantial in both populations. Obtaining evidence from a randomised trial that efficacy of prophylactic intravenous hydration outweighs the risk of complications is important but may not be feasible.

Evaluation of safety guidelines on the use of iodinated contrast material: conundrum continued

Estelle C Nijssen, Patty J Nelemans, Roger J Rennenberg, Vincent van Ommen, Joachim E Wildberger

Abstract

Objectives Recently, safety guidelines for the use of intravascular iodinated contrast material have been updated, and the recommended threshold for giving prophylaxis to prevent contrast-induced nephropathy (CIN) has been reduced to estimated glomerular filtration rate (eGFR) less than 30 ml/min/1.73m^2. Data on this population in the context of CIN, especially evidence for efficacy of the recommendation of prophylactic intravenous hydration, are lacking. The aim of the current study was to test implicit assumptions underlying the guideline update: (1) patients with eGFR <30 ml/min/1.73m^2, as opposed to former high risk patients with eGFR ≥30 ml/min/1.73m^2, are at high risk of CIN and other unfavourable outcomes after intravascular iodinated contrast material administration; (2) prophylactic intravenous hydration mitigates this risk; and (3) the risk of administering prophylactic intravenous hydration does not outweigh the positive preventive effect.

Materials and Methods Retrospectively, data were collected from all patients with eGFR <30 ml/min/1.73m^2 referred for an elective procedure with intravascular iodinated contrast material administration and excluded from the AMACING trial (A MAastricht Contrast-Induced Nephropathy Guideline trial). We compared these patients with those prospectively included in the AMACING trial (with eGFR 30–59 ml/min/1.73m^2 and risk factors). Main outcomes were CIN (defined as an increase in serum creatinine by more than 25% or 44 µmol/l within 2–6 days post contrast exposure), dialysis and mortality within 35 days post contrast exposure, and complications of prophylactic intravenous hydration.

Results A total of 28 803 patients referred for an elective procedure with intravascular iodinated contrast administration were prospectively screened for inclusion in the AMACING trial. One hundred fifty-seven (0.5%) patients had eGFR <30 ml/min/1.73m^2, and 155 received intravascular iodinated contrast material. Standard prophylaxis was given to 119/155 of these patients. Data on 2-to6-day serum creatinine, 35-day dialysis, 35-day mortality, and complications of prophylactic intravenous hydration were available for 59/119 (50%), 118/119 (99%), 119/119 (100%), and 119/119 (100%) standard prophylaxis patients, respectively. Incidences in eGFR <30 ml/min/1.73m^2 versus AMACING patients are as follows: CIN 13.6% versus 2.7% (p=0.0019); 35-day dialysis 0.9% versus 0.0% (p=0.2646); 35-day mortality 9.2% versus 0.0% (p<0.0001); complications of prophylactic intravenous hydration 5.9% versus 5.5% (p=0.8529).

Conclusions Post contrast incidences of CIN and mortality at 35days are significantly higher in the population with eGFR <30 ml/min/1.73m^2 than in the former high-risk population with eGFR 30 to 59 ml/min/1.73m^2, even after prophylactic intravenous hydration. The risk of complications of prophylactic intravenous hydration is similar and substantial in both populations. Obtaining evidence from a randomised trial that efficacy of prophylactic intravenous hydration outweighs the risk of complications is important but may not be feasible.

Key Words safety guidelines, intravascular iodinated contrast material administration, prophylactic intravenous hydration, contrast-induced nephropathy, contrast-induced acute kidney injury

Introduction

Guidelines on the safe use of intravascular iodinated contrast material exist in most countries.[70-74,136] One of the aims of these guidelines is the prevention of contrast-induced nephropathy (CIN), also known as CI-AKI (contrast-induced acute kidney injury).[106,137-143] Although CIN usually resolves spontaneously leaving no lasting effect, an association with increased risk of dialysis and mortality is consistently reported.[144-147] The main recommendation for prevention is prophylactic intravenous hydration. Three earlier trials comparing prophylactic intravenous hydration to a group not receiving intravenous hydration or other prophylaxis found some benefit, but these were all done in the acute setting where factors such as hemodynamic instability play a role.[99,101,102] Furthermore, in 2 of the 3 cohorts, the mean estimated glomerular filtration rate (eGFR) was >70 ml/min/1.73m^2; patients with eGFR >60 ml/min/1.73m^2 would not have received prophylaxis according to the guidelines.[99,101]

The AMACING trial (A Maastricht Contrast-Induced Nephropathy Guideline trial) evaluated the clinical- and cost-effectiveness of prophylactic intravenous hydration according to clinical practice guidelines on the use of intravascular iodinated contrast material in all high-risk patients referred for elective procedures with intravascular iodinated contrast material administration.[104] The results showed no prophylaxis to be non-inferior to standard prophylactic intravenous hydration in the prevention of CIN. No haemodialysis or related deaths occurred within 35 days. A total of 5.5% intravenously hydrated patients had complications associated with the prophylactic treatment (13/328 symptomatic heart failure, 4/328 arrhythmia, 1/328 hyponatremia).

The AMACING study population included approximately 90% of patients marked as high risk by the then current guidelines in the elective setting (with eGFR 30–59 ml/min/1.73m^2 and risk factors).[75] Patients with eGFR <30 ml/min/1.73m^2 were excluded for safety reasons; also excluded were emergency and intensive care patients. The results led to the conclusion that, assuming optimal contrast media administration, withholding prophylaxis for patients with eGFR ≥30 ml/min/1.73m^2 might be considered without compromising patient safety.

Safety guidelines for the use of intravascular iodinated contrast material have recently been updated. One of the main changes is the threshold beneath which prophylactic intravenous hydration is recommended, which has been reduced to include only patients with eGFR <30 ml/min/1.73m^2 (the European guidelines include a second threshold of eGFR <45 ml/min/1.73m^2 for procedures with intra-arterial contrast administration with first pass renal exposure).[76,79] The change will mean avoiding unnecessary complications of prophylactic treatment, a considerable reduction in hospital and patient burden, and health care budget savings of €50 to €100 million a year in the Netherlands alone.[104]

There is evidence for the risk of CIN after iodinated contrast administration in patients with eGFR <30 ml/min/1.73m^2 after intravenous iodinated contrast.[129,148-152] Retrospective reports suggest that the true risk threshold after intra-arterial administration, at least with second-pass renal exposure, is also eGFR <30 ml/min/1.73m^2.[153-157] Data on post contrast adverse outcomes in the eGFR <30 ml/min/1.73m^2 population, however, especially in the context of efficacy of prophylactic intravenous hydration, are lacking. The number of patients with eGFR <30 ml/min/1.73m^2 included in all studies is low, and where larger numbers of such patients have been included, no subgroup analyses that would enable the extraction of post contrast outcome data are reported.[145-147,158]

The current study focuses on the updated guideline recommendation for prophylactic intravenous hydration. Specifically, on incidences of post contrast adverse outcomes and complications of prophylactic intravenous hydration in patients with eGFR <30 ml/min/1.73m^2 in the elective setting.

The aim of the study was to test implicit assumptions underlying the guideline update in the recommendation for prophylactic intravenous hydration. These are threefold: (1) patients with eGFR <30 ml/min/1.73m^2, as opposed to former high-risk patients with eGFR ≥ 30 ml/min/1.73m^2, are at high risk of CIN and other unfavourable outcomes after intravascular iodinated contrast material administration; (2) prophylactic intravenous hydration mitigates this risk; and (3) the risk of complications due to

administering prophylactic intravenous hydration does not outweigh the positive preventive effect. Any therapy or medicine represents a balancing act between positive and negative effects. Therefore, both the positive effect (i.e., incidence of post contrast adverse outcomes, and the difference in incidences with and without treatment), and the negative effect (i.e., complications due to the treatment), must be known.

Methods

Participants

We used data from 2 populations referred for elective procedures with intravascular iodinated contrast administration: prospective data from the AMACING trial of patients with eGFR 30 to 59 ml/min/1.73m^2 combined with risk factors (former high-risk patients),[104] and retrospective data from patients with eGFR <30 ml/min/1.73m^2 excluded from the AMACING trial. Together, these represent all patients targeted by the guidelines for standard prophylaxis over the course of 2 years at our centre. The eGFR was calculated using the MDRD (Modification of Diet in Renal Disease) study equation.

During recruitment for the AMACING trial between June 17, 2014, and July 17, 2016, all consecutive patients aged 18 years and older, referred for an elective procedure requiring intravascular iodinated contrast material at Maastricht University Medical Centre (MUMC+), and with known eGFR <60 ml/min/1.73m^2, were prospectively screened to establish whether they met the AMACING trial criteria (figure 5.1). Patients with eGFR <30 ml/min/1.73m^2 were excluded from randomisation for safety reasons, but did receive follow-up on clinical indication. For the current study, all patients prospectively screened for the AMACING trial and with eGFR <30 ml/min/1.73m^2 were screened again. Patients with renal replacement therapy, emergency procedures, intensive care status, or no intravascular administration of iodinated contrast material were excluded.

Procedures

Prophylactic hydration protocols used were according to the then current guidelines.[75] Standard protocols were as follows: intravenous 0.9% NaCl 3–4 ml/kg per hour during 4

hours before and 4 hours after contrast administration; intravenous 1.4% $NaHCO_3$ 3 ml/kg in 60 minutes before and 1 ml/kg per hour during 6 hours after contrast administration.

Oral fluid consumption and contrast parameters were not influenced. The MUMC+ uses personalised parameters for optimal contrast volume determination. For the AMACING trial population, we recorded clinical practice in all but the prophylactic hydration given, for which patients were randomised 1:1 to receive either no prophylaxis or standard prophylactic intravenous hydration with normal saline.[104] For the eGFR <30 ml/min/1.73m^2 population, we recorded clinical practice only.

Data Collection

For the eGFR <30 ml/min/1.73m^2 population, the following data were obtained retrospectively from patient electronic files: sex, age, inpatient versus outpatient status, contrast-administration route, serum creatinine and eGFR values before and 2 to 6 days after contrast exposure, details of the prophylactic treatment given, details of the contrast procedure, and dialysis and mortality within 35 days post contrast exposure.

In addition, we searched the nursing records for any mention of complications of prophylactic intravenous hydration occurring around the time of the contrast procedure (symptomatic heart failure, hypernatremia, hyponatremia, and supraventricular or ventricular arrhythmias). In all cases, patient history and patient electronic files were screened for confirmation. An event was registered as complication only if a physician specifically linked the event to the prophylactic treatment.

Data collection for the AMACING trial population was prospective and is detailed elsewhere.[104] All patients participating in the AMACING trial signed informed consent. The Medical Ethical Board MUMC+ waived the requirement to obtain informed consent for use of the recorded data of patients with eGFR <30 ml/min/1.73m^2 excluded from the AMACING trial.

Outcomes

To gain an indication of whether patients with eGFR <30 ml/min/1.73m^2, as opposed to former high-risk patients with eGFR ≥30 ml/min/1.73m^2, are at high risk of CIN and other unfavourable outcomes after intravascular iodinated contrast material administration, the comparative risk between the 2 populations was assessed by comparing incidences of the following: CIN (defined as an increase in serum creatinine by more than 25% or 44 µmol/l within 2–6 days post contrast exposure), dialysis within 35 days post contrast exposure, mortality within 35 days post contrast exposure, and the distribution of percentage change in serum creatinine from baseline within 2 to 6 days post contrast exposure.

To gain an indication of whether prophylactic intravenous hydration mitigates the risk of CIN, dialysis, and mortality, we aimed to compare post contrast adverse outcomes between subgroups of the eGFR <30 ml/min/1.73m^2 population having received standard prophylactic intravenous hydration with normal saline, and the subgroup having received no prophylaxis.

To evaluate whether the risk of administering prophylactic intravenous hydration does not outweigh the positive preventive effect, incidence of complications of prophylactic intravenous hydration in the eGFR <30 ml/min/1.73m^2 population were calculated. To gain an indication of the comparative risk between the 2 populations, we compared incidences of complications due to prophylactic intravenous hydration (symptomatic heart failure, arrhythmias, hyponatremia, and hypernatremia).

Statistics

Continuous data are reported as mean (SD). Categorical data are presented as absolute numbers and percentages. The differences between the 2 populations in proportions with CIN, complications of prophylactic intravenous hydration, dialysis, and mortality were compared using the χ^2 test. Differences in mean values were assessed using Student t test for independent samples. Populations were compared for percentage change in serum creatinine using the Mann-Whitney U test. Levene test was used to assess the equality of variances. P values of 0.05 and lower were considered to indicate

statistical significance. Analyses were done with statistical software package Epi Info 7 (Centers for Disease Control and Prevention, Atlanta, GA), and IBM SPSS Statistics for Windows (version 23; IBM Corp, Armonk, NY).

Results

Of the 28 803 patents referred for an elective procedure with intravascular iodinated contrast administration, 157 were excluded from the AMACING trial because their eGFR was <30 ml/min/1.73m^2 (0.5%). One hundred fifty-five of these ultimately received iodinated contrast material and could be included in the current study (see figure 5.1).

Baseline characteristics for patients included in the AMACING trial and patients with eGFR <30 ml/min/1.73m^2 excluded from the AMACING trial are given in table 5.1. On average, the eGFR <30 ml/min/1.73m^2 patients are significantly older, more often hospitalised, more often given intra-arterial iodinated contrast material, and more often referred for an interventional procedure; they more frequently have diabetes, anaemia, and diuretic medication; they have cardiovascular disease less often and receive smaller volumes of iodinated contrast material. The populations were similar in the number of men, incidence of multiple myeloma/lymphoplasmacytic lymphoma, the use of prescribed nonsteroidal anti-inflammatory drugs, and total volume prophylactic intravenous hydration received.

One hundred nineteen (76.8%) of 155 eGFR <30 ml/min/1.73m^2 patients received standard prophylaxis with 0.9% intravenous sodium chloride (the NaCl-hydrated subgroup), 12/155 (7.7%) were given prophylaxis with intravenous 1.4% sodium bicarbonate (the $NaHCO_3$-hydrated subgroup), and 24/155 (15.5%) were given no prophylaxis (the no-prophylaxis subgroup; see table 5.1 for details). Reasons for deviating from standard prophylaxis and giving intravenous $NaHCO_3$ hydration were heart failure (42%), logistics (33%), dyspnoea (17%), and diabetic renal failure (8%). Reasons for deviating from standard prophylaxis and giving no prophylactic intravenous hydration were aortic valve stenosis (57%), fluid overload (17%), heart failure (9%), logistics (9%), renal function (4%), and in 1 case no reason was recorded (4%).

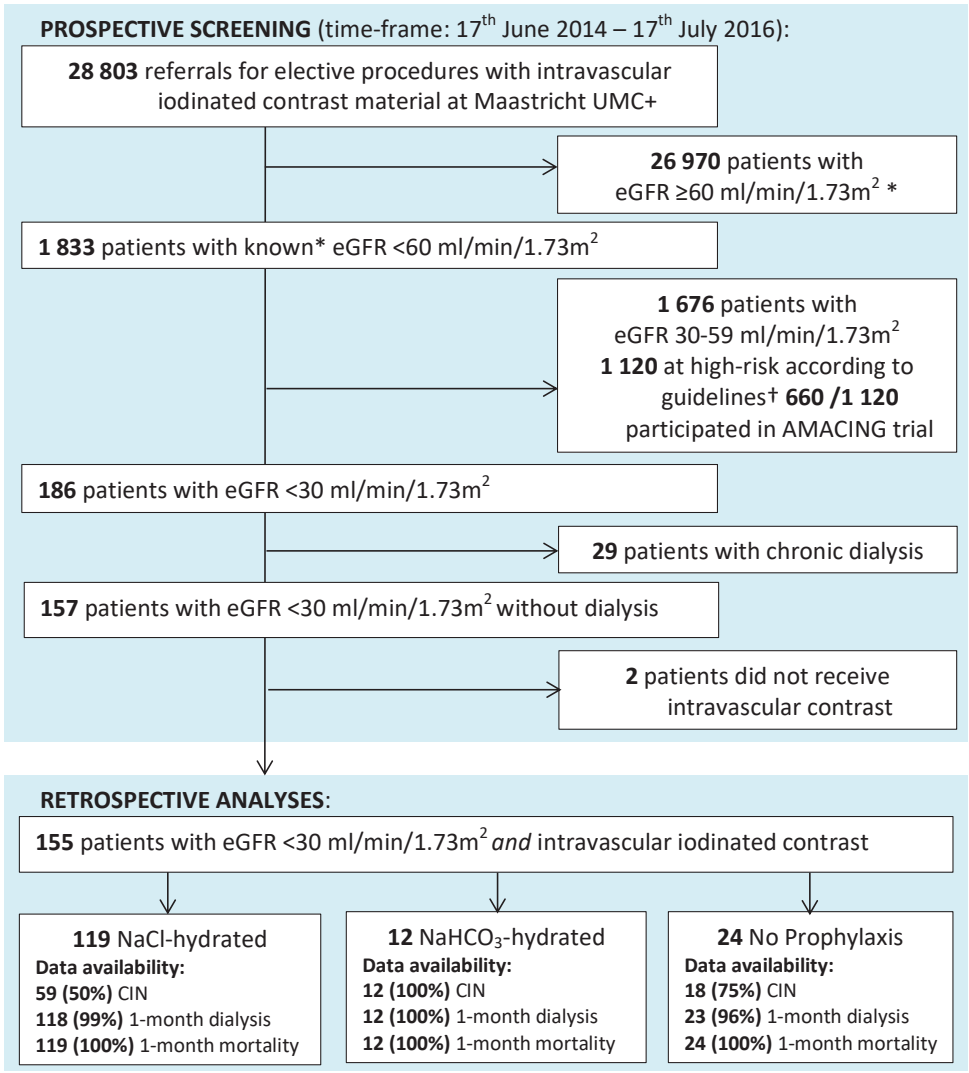

Figure 5.1. eGFR <30 ml/min/1.73m^2 population screening and inclusion profile

UMC+= University Medical Centre; AMACING =A MAastricht Contrast-Induced Nephropathy Guideline trial; eGFR=estimated glomerular filtration rate. *renal function is assessed only if ≥1 predefined risk factor is present (age >60 years, diabetes, use of nephrotoxic medication, urological/nephrological history, hypertension, peripheral vascular or cardiac disease, lymphoplasmacytic lymphoma/ multiple myeloma). †i.e. eGFR 30-45ml/min/1.73m^2; or lymphoplasmacytic lymphoma/ multiple myeloma with small chain proteinuria; or eGFR 45-59 ml/min/1.73m^2 with diabetes or with ≥2 predefined risk factors (age >75 years; anaemia; cardiovascular disease; NSAID or diuretic nephrotoxic medication).

Table 5.1. Baseline characteristics

	Population included in the AMACING trial: at risk of CIN with eGFR 30-59 ml/min/1.73m^2 (n=660)	**Patients with eGFR <30 ml/min/1.73m^2** and elective intravascular iodinated contrast (n=155)	**p value**
Men	407 (62%)	83 (54%)	0.0669
Age	72 (9.3)	74 (10.0)	0.0229
Inpatient	57 (9%)	62 (40%)	<0.0001
Intra-arterial contrast	319 (48%)	97 (63%)	0.0008
Interventional procedure	103 (16%)	39 (25%)	0.0083
Renal function (from referral)			
eGFR (ml/min/1.73m^2)	47.45 (7.98)	23.70 (4.26)	<0.0001
serum creatinine (µmol/l)*	118.24 (26.13)	217.32 (52.11)	<0.0001
Guideline risk factors			
Baseline eGFR <15	0 (0.0%)	7 (5%)	<0.0001
Multiple myeloma/ l.lymphoma	3 (1%)	1 (1%)	1.0000
Diabetes	215 (33%)	65 (42%)	0.0343
Age >75 years	286 (43%)	83 (54%)	0.0133
Prescribed diuretic medication	307 (47%)	113 (73%)	<0.0001
Prescribed NSAID	319 (48%)	64 (41%)	0.1162
Anemia †	184 (28%)	90 (59%) ‡	<0.0001
Cardiovascular disease	493 (75%)	104 (67%)	0.0424
Administered volumes (ml)			
30 mg iodine/ml contrast	91 (41)	81 (45) §	0.0126
intravenous 0.9% NaCl (for H+)	1637 (950)	1604 (575) #	0.9178
Prophylaxis received			
Intravenous 0.9% NaCl	328 (50%)	119 (77%)	-
Intravenous 1.4% $NaHCO_3$	0 (0%)	12 (8%)	-
None	332 (50%)	24 (16%)	-

Data are presented as n (%) or mean (SD). *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. ‡2 unknown ; §3 unknown ; #n=117, 2 unknown. CIN = contrast-induced nephropathy; eGFR, estimated glomerular filtration rate.

Data on 2- to 6-day serum creatinine were available for 59/119 (50%) of NaCl-hydrated patients, for 12/12 (100%) $NaHCO_3$-hydrated patients, and for 18/24 (75%) no-prophylaxis patients. Data for 35-day dialysis were available for 118/119 (99%) NaCl-hydrated patients, for 12/12 (100%) $NaHCO_3$-hydrated patients, and for 23/24 (96%) no-prophylaxis patients. Data on 35-day mortality were available for all 155 (100%) patients. Data for complications of prophylactic intravenous hydration were available for 119/119 (100%) NaCl-hydrated patients.

Contrast-induced nephropathy occurred in 8/59 (13.6%) NaCl hydrated patients, in 1/12 (8.3%) $NaHCO_3$-hydrated patients, and in 1/18 (5.6%) no-prophylaxis patients. Dialysis within 35 days post contrast exposure occurred in 1/118 (0.85%) NaCl-hydrated patients, in 1/12 (8.3%) $NaHCO_3$-hydrated patients, and in 0/23 (0.0%) no-prophylaxis patients. Death within 35 days post contrast exposure occurred in 11/119 (9.2%) NaCl-hydrated patients, in 0/12 (0.0%) $NaHCO_3$-hydrated patients, and in 0/24 (0.0%) no-prophylaxis patients.

Because of the small numbers in the $NaHCO_3$-hydrated and no-prophylaxis subgroups, outcomes of post contrast adverse events are reported without statistical analyses of the differences between subgroups. Furthermore, only patients having received standard prophylactic intravenous hydration with 0.9% sodium chloride were included in statistical analyses. For the same reason, only data from NaCl-hydrated patients of both the eGFR <30 ml/min/1.73m^2 and AMACING were used in between-population comparisons.

Comparing NaCl-hydrated eGFR <30 ml/min/1.73m^2 with NaCl-hydrated AMACING trial patients, incidences of unfavourable outcomes following intravascular contrast administration were CIN 13.6% versus 2.7% (p=0.0019); 35-day dialysis 0.9% versus 0.0% (p=0.2646); and 35-day mortality 9.2% versus 0.0% (p<0.0001; figure 5.2). Complications of prophylactic intravenous hydration occurred in 5.9% (7/119) NaCl-hydrated eGFR <30 ml/min/1.73m^2 versus 5.5% (18/328) NaCl-hydrated AMACING patients (p=0.8529; figure 5.2).

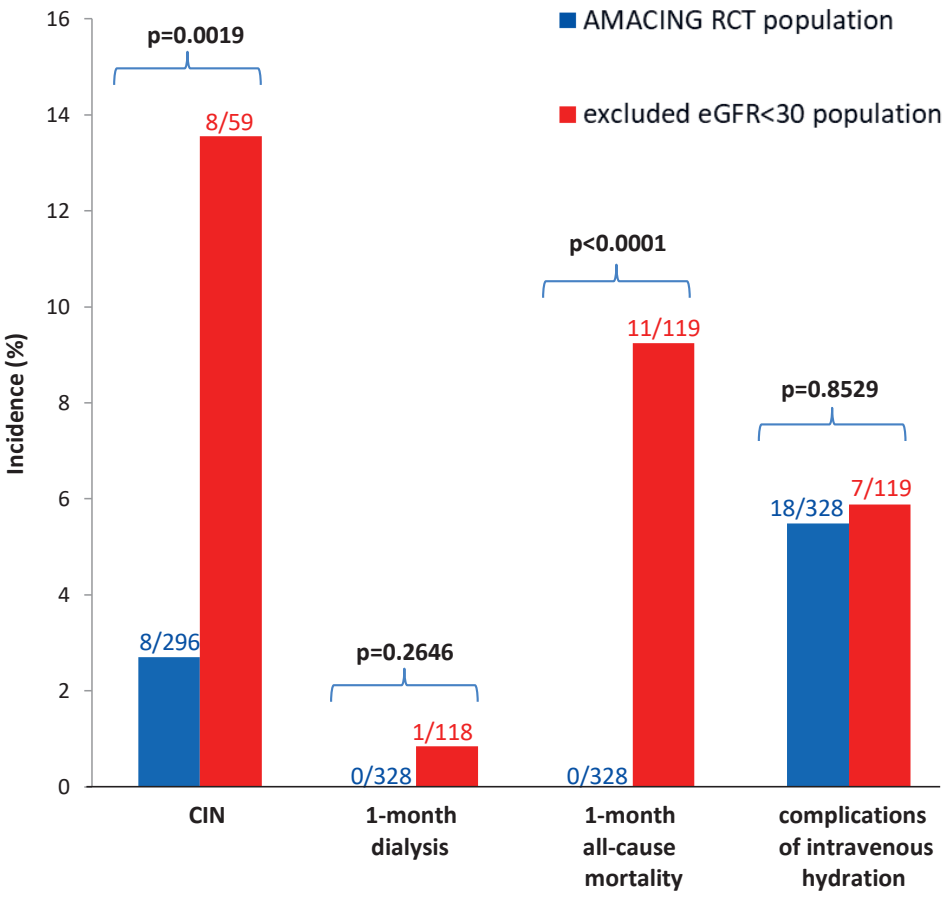

Figure 5.2. Incidences of adverse evens in subgroups with standard prophylactic intravenous 0.9% NaCl hydration.

RCT indicates randomised controlled trial; eGFR, estimated glomerular filtration rate.

The distributions of percentage change in serum creatinine from baseline 2- to 6-day post contrast exposure in both NaCl-hydrated eGFR <30 ml/min/1.73m^2 and NaCl-hydrated AMACING trial populations centre around a change close to zero. Median change was 1.90% for NaCl-hydrated patients with eGFR <30 ml/min/1.73m^2 versus 0.0% for NaCl-hydrated patients of AMACING (p=0.6090). The distribution for eGFR <30 ml/min/1.73m^2 patients shows more variance, and the frequency of more extreme changes is higher. Levene test for equality of variances was found to be significant (p≤0.0001, figure 5.3).

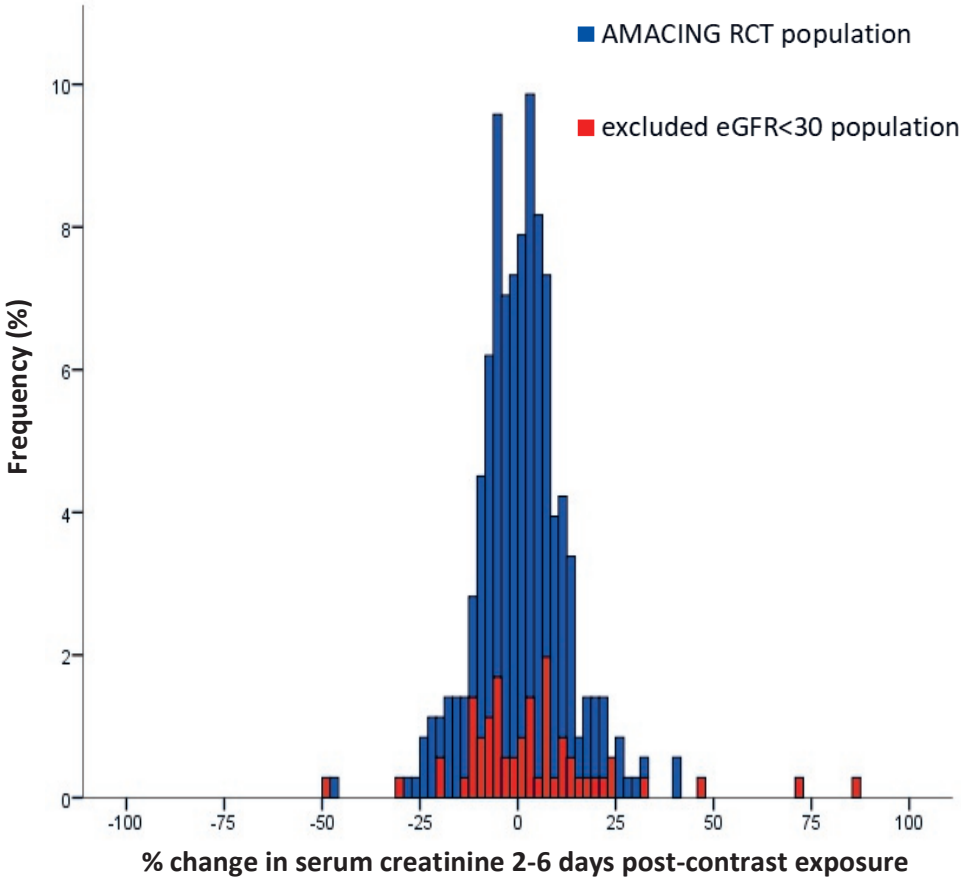

Figure 5.3. Distribution of the changes in serum creatinine from baseline in subgroups with standard prophylactic intravenous 0.9% NaCl hydration.

RCT indicates randomized controlled trial; SD, standard deviation.

Discussion

From the baseline characteristics (table1), we can conclude that the population with eGFR <30 ml/min/1.73m^2 referred for an elective procedure with intravascular iodinated contrast material is significantly more burdened with comorbidities than the former high-risk population with eGFR 30 to 59 ml/min/1.73m^2.

The population with eGFR <30 ml/min/1.73m^2 shows a significantly higher incidence of CIN and a greater variance in changes in serum creatinine from baseline, even after prophylactic intravenous hydration. At 35 days post contrast incidences of dialysis are very low and not significantly different between the populations, but the eGFR <30 ml/min/1.73m^2 population has significantly higher mortality rates.

These data support the first implicit assumption underlying the updated guideline recommendation for prophylaxis, patients with eGFR <30 ml/min/1.73m^2 are at higher risk of post contrast unfavourable outcomes, than former high-risk patients with eGFR ≥30 ml/min/1.73m^2. The baseline characteristics of the 2 populations were significantly different, however, which raises the question whether the greater risk of post contrast renal function decline and mortality is a consequence of intravascular iodinated contrast administration, or inherent to the eGFR <30 ml/min/1.73m^2 population.

Whether prophylactic intravenous hydration mitigates the risk of CIN, dialysis and mortality in the eGFR <30 ml/min/1.73m^2 population cannot be evaluated due to lack of a sufficiently large control group without prophylactic intravenous hydration. Estimated glomerular filtration rate <30 ml/min/1.73m^2 patients have at least as much risk of complications of prophylactic intravenous hydration as the AMACING trial population.

The current study includes all elective procedures over a 2-year period at the Maastricht University Medical Centre (MUMC+): 63% of the eGFR <30 ml/min/1.73m^2 procedures and 48% of the AMACING trial procedures used intra-arterial contrast administration. Clinical practice was recorded for all nonrandomised aspects: oral fluid consumption and contrast parameters were not influenced.

The data on the eGFR <30 ml/min/1.73m^2 population is retrospective, which precludes standardisation or preselected control groups; however, to the best of our knowledge, this is the first report of post contrast outcomes in this well-defined cohort. Furthermore, the study characteristics ensure that results are representative of daily clinical practice.

The study provides an estimate of the incidence of CIN after prophylactic intravenous hydration in patients with eGFR <30 ml/min/1.73m^2, which enables calculation of the required sample size for future efficacy studies in this population. It also provides the expected incidence of complications of prophylactic intravenous hydration, which can help in determining an acceptable non-inferiority margin.

The incidences of CIN in both populations were based on a single serum creatinine measurement within 2 to 6 days post contrast exposure, as opposed to a smaller time window or sequential measurements from which the maximum change in serum creatinine can be identified. However, post contrast serum creatinine has been shown to peak at 4 to 5 days post contrast on average,[120] and only very transient changes in serum creatinine would have been missed by our method. Transient changes are of questionable clinical relevance, as only persistent CIN is associated with increased long-term adverse events.[159]

Although the term CIN implies 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. Contrast-induced nephropathy or CI-AKI is a correlative diagnosis, and therefore the term PC-AKI, post contrast acute kidney injury, would perhaps be more accurate.[71,76,78] However, we chose to use the term CIN because it is what the guidelines aim to prevent, and the term is still the one most widely known and used in literature.

Most published incidences of CIN are either retrospective or done in the acute setting. In both cases, there is considerable bias toward sicker hospitalised patients with unstable renal function, and as a consequence some reported incidences are

comparatively high. The incidence of CIN found in the AMACING trial is similar to those found in other elective patient populations.[160-163] For elective patients with eGFR <30 ml/min/1.73m^2, there are fewer examples of incidences of CIN in literature, but a large retrospective study in outpatients receiving standard prophylaxis and computed tomography yielded a 10.8% CIN incidence (27/250).[151] Many factors must be taken into consideration when planning a procedure with intravascular iodinated contrast material, and guideline recommendations on safe use of intravascular contrast material are much broader than the recommendation of prophylactic intravenous hydration alone.[70,71,73,76,136]

The focus of the current study lies on the recommendation of prophylactic intravenous hydration for patients with eGFR <30 ml/min/1.73m^2, not on the specific protocol. Whereas the recommendation of intravenous hydration as prophylaxis is found in most guidelines, specific protocols vary across guidelines and over time.[70,71,73, 75,76,79,136] Taking together the facts that the AMACING trial found not giving prophylaxis to be non-inferior to prophylactic intravenous hydration with sodium chloride, and that large-scale studies find no benefit of sodium bicarbonate over sodium chloride,[164,165] it may well be possible that neither prophylactic strategy is effective at reducing the risk of post contrast adverse outcomes.

The Dutch and European safety guidelines for the prevention of CIN have been considerably modified, and the population considered at high risk of CIN and targeted for prophylaxis has been drastically reduced.[76,79] The current recommendations for prophylactic intravenous hydration of patients with eGFR <30 ml/min/1.73m^2, still, are not based on robust evidence. It has been said that AMACING trial results lead us to be suspicious of expert opinion and to object to quality measures not backed by randomised trial data.[134] Ideally then, the new guideline recommendation would be subjected to a sufficiently powered and robust randomised controlled trial comparing the recommended prophylaxis to no prophylaxis.

That incidences of post contrast adverse outcomes in the eGFR <30 ml/min/1.73m^2 population are significantly higher than those in the population for which prophylactic

intravenous hydration no longer applies, even in the elective setting, makes further research pertinent. The substantial risk of complications of the prophylactic treatment found further increases the import of acquiring evidence for net efficacy in the prevention of CIN and other post contrast adverse outcomes.

Carrying out prospective studies to provide this evidence, however, may be a demanding and costly task. The AMACING trial, in which 28 803 referrals were prospectively screened, required considerable logistic and financial input (the costs to date amount to more than €500,000). Patients with eGFR <30 ml/min/1.73m^2 undergoing elective procedures with intravascular iodinated contrast administration are scarcer than high-risk patients with eGFR 30 to 59 ml/min/1.73m^2. A retrospective report on outpatients referred for computed tomography (CT) screened 446 672 CT scans, found 250 patients with eGFR <30 ml/min/1.73m^2, translating to a prevalence of 0.06%.[151] Another study screened patients from 27 hospitals undergoing diagnostic cardiac catheterisation, and (elective or emergency) percutaneous coronary intervention, and found 129 patients with eGFR <30 ml/min/1.73m^2 in 993 procedures.[145] This translates to a prevalence of 13% in the setting of intra-arterial procedures, but this may be an overestimation as emergency procedures were included in this study. A retrospective study including all intravenous and intra-arterial procedures over a 2-year period found 6/2817 (0.2%) patients with eGFR <30 ml/min/1.73m^2.[166] In the AMACING trial, a prevalence of 0.5% was found (157/28803).[104] Similar prevalence (0.4%–0.5%) is reported for the general population.[130,167,168]

The estimate of CIN incidence in patients with eGFR <30 ml/min/1.73m^2 having received prophylactic intravenous hydration represents important information. This expected CIN incidence in the intravenously hydrated population, a p0 of 13.6%, is necessary for the calculation of the required sample size for a trial evaluating the efficacy of prophylactic intravenous hydration in the prevention of CIN in patients with eGFR <30 ml/min/1.73m^2 referred for elective procedures with intravenous or intra-arterial iodinated contrast material administration. Using this value and keeping the AMACING trial non-inferiority design with a non-inferiority margin of 2.1%, 6 594

patients would be required (3 297 + 3 297 patients randomised to either receive prophylaxis or not), to be 80% sure that the limits of a one-sided 95% confidence interval will exclude the pre specified difference in CIN (one-tailed alpha 5%).

Given the low prevalence, including such a large number of eGFR <30 ml/min/1.73m^2 patients in a trial would be a mammoth task. Consider for example the fictitious situation in which all of the Netherlands participates in a trial comparing prophylactic intravenous hydration according to the guidelines to no prophylaxis in patients with eGFR <30 ml/min/1.73m^2. An estimated 0.5 to 1 million procedures with intravascular contrast material are carried out in the Netherlands each year. An estimated 0.5% of those procedures will involve patients with eGFR <30 ml/min/1.73m^2. This means there would be an estimated 2 500 to 5 000 procedures eligible for inclusion. If 60% give informed consent, as in the AMACING trial, a maximum of 1 500 to 3 000 patients could be included each year. Achieving the sample size of 6 594 patients would then require 2 to 5 years of sustained national effort.

The importance given to sample size in current trial design and publication makes guideline evaluation an unattractive prospect. Indeed, if we only have few patients or are looking for very small effects, it is unlikely that the required sample sizes are feasible. Should we, then, forego robust evidence in such cases and rely solely on expert opinion?

In absence of robust evidence one way or the other, it appears that the choice is often made for defensive medicine. Since guidelines are assumed to increase safety, adherence is taken to reflect quality of care, and is subsequently monitored by accreditation programs. The focus then is so much centred on preventing a single disease entity, or, in the case of CIN, a biochemical diagnosis, that complications of preventive strategies are overlooked. Following a standard protocol for prophylaxis may thus give a false sense of security. On the whole, we may ask ourselves whether it is appropriate to dictate clinical practice with generalised guidelines, as opposed to allowing a more tailored approach based on the knowledge guidelines provide.

Whereas the guideline committee expert consensuses are essential for up-to-date clinical practice, to our mind accreditation programs are overshooting the mark when compelling general implementation.

It is the task of experts to aid us in optimising clinical practice when evidence is lacking, but it is the task of scientific researchers to find ways to evaluate their recommendations, even when those recommendations are universally accepted, or when evaluation appears to be a mission impossible. After all, smaller sample size trials, if methodologically sound and properly reported, are a much better choice than having no data at all.[169]

Post contrast incidences of CIN and mortality at 35 days are significantly higher in the population with eGFR <30 ml/min/1.73m^2 than in the former high-risk population with eGFR 30 to 59 ml/min/1.73m^2, even after prophylactic intravenous hydration. The risk of complications of prophylactic intravenous hydration is similar and substantial in both populations. Obtaining evidence from a randomised trial that efficacy of prophylactic intravenous hydration outweighs the risk of complications is important but may not be feasible.

Conundrum continued…

Contributors

E.C.N. had full access to the data and takes responsibility for the integrity of the data and accuracy of the analysis. E.C.N. and P.J.N. did the statistical analysis. E.C.N. and J.E.W. drafted the report. P.J.N., R.J.R., and G.V.O. critically revised the report.

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CHAPTER 6

every therapy or medicine represents a balancing act between positive and negative effects

6. Prophylaxis in Patients with eGFR <30 ml/min/1.73m^2, Get The Balance Right

Nijssen EC, Nelemans PJ, Rennenberg RJ, Theunissen RA, van Ommen V, Wildberger JE. Prophylaxis in high-risk patients with eGFR <30 ml/min/1.73m^2: get the balance right. *Investigative Radiology* 2019;54:580-8.

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Key Points

- Because randomised trials of sufficient power are not readily feasible in this population, the study aim was to gain insight into positive and negative effects of prophylaxis by retrospectively comparing elective patients with eGFR <30 ml/min/1.73m^2 who did and did not receive prophylaxis.
- All 55 474 elective procedures with intravascular iodinated contrast carried out at Maastricht UMC+ between May 17, 2014 and May 17, 2018 were screened for inclusion: 4-year observational data on post-contrast outcomes in elective eGFR <30 ml/min/1.73m^2 patients was collected.
- The inclusion period reflects the maximum available complete years during which the in-house protocol for the prevention of CIN was fully implemented and remained the same for elective eGFR <30 ml/min/1.73m^2 patients.
- Primary outcome was CIN; secondary outcomes at 1-month were change in eGFR, ≥5 ml/min/1.73m^2 eGFR decline, dialysis, mortality, and prophylaxis complications. Results were stratified by contrast procedure type and corrected for confounders.
- Adjusted odds ratios were non-significant and <1 for all post-contrast renal outcomes (CIN, dialysis, eGFR decline), indicating lower risk after prophylaxis.
- Adjusted odds ratios were non-significant and >1 for mortality within 1 month post-contrast, indicating higher risk after prophylaxis.
- **Conclusion**: Based on this study no standard recommendation with regard to giving or withholding prophylaxis can be given. In this setting, benefits and risks of prophylaxis must be carefully weighed and cardiac parameters assessed for each individual patient.

Prophylaxis in high-risk patients with eGFR <30 ml/min/1.73m^2: get the balance right

Estelle C Nijssen, Patty J Nelemans, Roger J Rennenberg, Ralph A Theunissen, Vincent van Ommen, Joachim E Wildberger

Abstract

Objectives Clinical guidelines recommend prophylactic intravenous fluids for patients with estimated glomerular filtration rate (eGFR) less than 30 ml/min/1.73m^2 to prevent adverse post contrast outcomes. These patients represent a small minority of the population receiving intravascular iodinated contrast material, and data are not readily available. The current study aim is to gain insight into positive and negative effects of prophylaxis by comparing post contrast outcomes in high-risk patients who did and did not receive prophylaxis.

Materials and Methods Observational data were gathered over 4 years. Inclusion criteria were age 18 years or older, eGFR less than 30 ml/min/1.73m^2, and elective intravascular iodinated contrast administration. Exclusion criteria were dialysis and nonstandard peri-procedural prophylaxis. Primary outcome was post contrast acute kidney injury (>25% or >44 µmol/l serum creatinine increase within 2–5 days). Secondary outcomes were change in eGFR, 5 ml/min/1.73m^2 or greater eGFR decline, dialysis, and mortality at 1 month post contrast including primary cause, as well as complications of prophylaxis. Results were stratified by contrast procedure type and corrected for potential confounders.

Results Of all 55 474 elective procedures with intravascular contrast administration, 362 patients met the inclusion criteria: 281 (78%) received standard 0.9% NaCl prophylaxis and 81 (22%) received no prophylaxis. Prophylaxis versus no prophylaxis adjusted odds ratios were nonsignificant and less than 1 for post contrast renal outcomes (post contrast acute kidney injury, eGFR decline, dialysis), indicating a trend toward a protective effect of prophylaxis. For mortality, adjusted odds ratios were

nonsignificant and greater than 1, indicating a trend toward higher mortality risk after prophylaxis. Of the primary causes of death analysed in prophylaxis patients, 24% (5/21) were related to prophylaxis. Among 281 prophylaxis patients, 18 (6.4%) complications of prophylaxis occurred: 15 heart failures and 3 arrhythmias.

Conclusions Based on this study, no standard recommendation with regard to giving or withholding prophylaxis can be given. Prophylactic fluids may confer some protection against post contrast renal adverse events but may also contribute toward increased risk of short-term death. In this setting, benefits and risks of prophylaxis must be carefully weighed and cardiac parameters assessed for each individual patient.

Key Words contrast media, acute kidney injury, renal insufficiency, intravenous infusion, sodium chloride, glomerular filtration rate, chronic kidney failure, contrast-induced nephropathy, post contrast acute kidney injury, eGFR less than 30 ml/min/1.73m^2

Introduction

The number of diagnostic and interventional procedures with iodinated contrast material continues to grow steadily. The benefits of such procedures, computed tomography (CT) for example, are obvious, but some risk is incurred by intravascular injection of the contrast material. Such injections have been associated with acute kidney injury, which in some cases progresses to further renal function decline, dialysis, and mortality. [18-21,25,126,127,142] Physicians from most specialties are confronted with weighing the benefits against the risks of contrast procedures.

Although in the general population the risk is small, especially after CT scans,[170] patients with pre-existing chronic kidney disease are especially vulnerable to the risk of renal adverse events. To improve safety, clinical guidelines on the use of intravascular iodinated contrast material have been issued and implemented in hospitals the world over.[70,71,73,74] The main recommendation for prevention are peri-procedural prophylactic intravenous (IV) fluids for high-risk patients.

Both what constitutes the high-risk population, and the prophylaxis itself, are subjects of debate and research. Until recently, prophylaxis was recommended for most patients with estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73m^2.[70] Large retrospective studies comparing patients with varying stages of chronic kidney disease have concluded that the highest risk of iodinated contrast material administration exists when eGFR is less than 30 ml/min/1.73m^2.[13,148,150,151,171] Several other studies found no benefit of prophylactic IV fluids over no prophylaxis for patients with eGFR of 30 ml/min/1.73m^2 or greater.[100,102,104,105]

Almost all current guidelines have been updated to reflect these findings, and prophylactic IV fluids are now recommended for patients with eGFR less than 30 ml/min/1.73m^2 only.[71,73,76,78] These patients represent 0.1% to 0.5% of the general population[130,167,168] and 0.05% to 1.8% of patients undergoing elective contrast procedures.[128,147,151,166] The estimated incidences of post contrast adverse events in this population combined with the low availability of patients makes randomised trials with sufficient power unrealistic.[128] Unsurprisingly therefore, very little data and no rigorous randomised trials comparing prophylaxis to no prophylaxis are available in literature. Guidelines are perforce largely based upon expert opinion and studies in patients with eGFR of 30 ml/min/1.73m^2 or greater.

A few observational studies on post contrast outcomes in patients with eGFR less than 30 ml/min/1.73m^2 were recently published, however, and these may offer some insight. First, from a clinical perspective, it seems that patients with eGFR less than 30 ml/min/1.73m^2 represent a different, more vulnerable population than those with eGFR of 30 ml/min/1.73m^2 or greater. Incidences of post contrast adverse events are substantially higher, and there seem to be more outliers with extreme post contrast increases in serum creatinine in the eGFR less than 30 ml/min/1.73m^2 population.[76,128,173] Second, the net effect of prophylaxis is unclear. In a study on post contrast outcomes after percutaneous coronary intervention in patients with eGFR less than 30 ml/min/1.73m^2, the comparison of patients with and without post contrast acute kidney injury (PC-AKI) shows that patients with PC-AKI had significantly less often

received prophylactic IV fluids than those without PC-AKI.[173] On the other hand, complications of prophylaxis occur (symptomatic heart failure, arrhythmias).[76,128]
The aim of the current study is to gain insight into positive and negative effects of prophylactic IV hydration in high-risk patients with eGFR less than 30 ml/min/1.73m^2 by comparing adverse outcomes between patients with and without prophylaxis.

Methods

Study Design and Participants

Observational data were gathered from patient electronic files over a 4-year period from May 17, 2014, to May 17, 2018. At the start of the inclusion period, the in-house protocol for the prevention of contrast-induced nephropathy (CIN) was fully implemented, and it remained the same throughout the inclusion period. All patients, aged 18 years or older with eGFR of less than 30 ml/min/1.73m^2, who received IV/intra-arterial (IA) iodinated contrast material during an elective procedure (such as CT scans, coronary angiographies and interventions, trans catheter valve implantation, and peripheral angiographies and interventions), were eligible for inclusion. No repeat inclusion of unique patients occurred. Patients receiving dialysis or prophylactic peri-procedural IV fluids other than according to standard prophylaxis protocol (see details later) were excluded.

The Maastricht University Medical Centre (Maastricht UMC+) Medical Research Ethics Committee approved the study and waived the requirement to obtain informed consent for use of the data.

Procedures

The protocol at Maastricht UMC+ for use of iodinated contrast material in patients with eGFR of less than 30 ml/min/1.73m^2 remained the same during the entire 4-year inclusion period. Standard prophylaxis protocol was according to the current guidelines[75]: IV 0.9% NaCl, 3 to 4 ml/kg per hour, 4 hours before and 4 hours after contrast administration; or IV 0.9% NaCl,1 ml/kg per hour,12 hours before and 12hours after contrast administration. If deemed necessary, a physician could deviate from the standard protocol for medical reasons.

When prophylactic IV fluids were first introduced as standard protocol, some serious problems were encountered in patients who could not handle the fluid administration due to impaired cardiac function (e.g., severe aortic stenosis, severe chronic heart failure). As a consequence, such patients have not been given prophylactic fluids at our institution since the year 2014 based on the judgment of the treating specialist.

All patients received pre-warmed (37°C) intravascular non-ionic, monomeric, low-osmolar iodinated contrast material (300 mg iodine/ml iopromide; Ultravist, Bayer Healthcare, Berlin, Germany). The Maastricht UMC+ uses personalised parameters (P3T, Certegra; Bayer) for optimal individualised contrast volume and flow rate.

Outcomes and Definitions

Patients with eGFR less than 30 ml/min/1.73m^2 having received standard IV prophylactic fluids (prophylaxis group) were compared with those having received no prophylaxis (no-prophylaxis group). Data on incidence and timing of outcomes were retrospectively collected from electronic patient files. Primary outcome serum creatinine was measured 2 to 5 days post contrast; secondary outcomes were recorded within 30 days post contrast; for renal function, a maximum time window of 30 to 90 days was allowed.

The primary outcome was incidence of PC-AKI, traditionally known as CIN or contrast-induced acute kidney injury. It is defined as greater than 25% or greater than 44 µmol/l serum creatinine increase within 2 to 5 days post-contrast from baseline. Secondary outcomes were change in eGFR, 5 ml/min/1.73m^2 or greater eGFR decline, dialysis, and all-cause mortality within 1 month post-contrast exposure, including primary causes of death. In addition to these secondary outcomes, complications of prophylaxis were recorded (see later for details). Characteristics of patients suffering such complications were inventoried and compared with hydrated patients without complications, to determine whether predisposition for complications of prophylactic treatment could be identified.

Data Collection

The following data were obtained from electronic patient files:

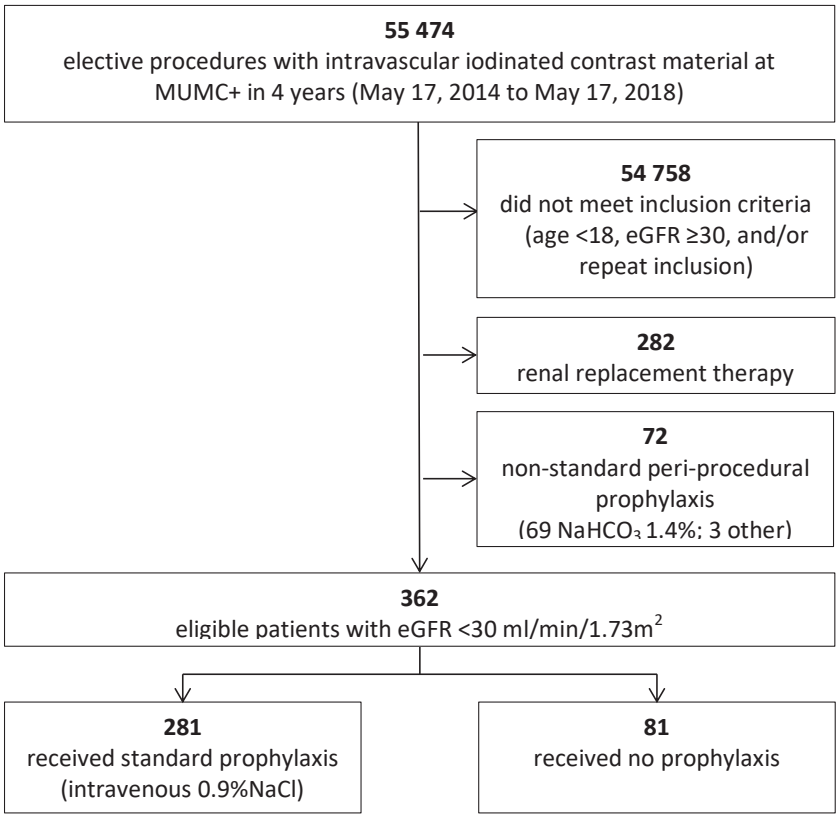
1. Baseline data: sex, age, length, weight, inpatient versus outpatient status, eGFR (the value closest to and before the time of the contrast procedure was taken as baseline; eGFR was calculated using the Modification of Diet in Renal Disease Study equation),[173] serum creatinine, diabetes, anaemia, cardiovascular disease, and prescribed diuretics and/or NSAIDs (non-steroidal anti-inflammatory drugs).

2. Contrast procedure and prophylaxis details: contrast administration route, diagnostic or interventional procedure, contrast volume, and prophylactic fluids volume. At Maastricht UMC+, all patients receive the same 300 mg iodine/ml contrast agent.

3. Post contrast adverse outcomes: 2 to 5 day serum creatinine, 1 month eGFR (time-window, 30–90 days post contrast), 30-day dialysis and mortality, including primary cause. Two experienced physicians from the departments of internal medicine and cardiology, blinded to whether prophylaxis was administered, independently reviewed primary causes of death and plausibility of a causal relationship with administration of IV fluids. A third independent adjudicating senior specialist reviewed the cases about which these two physicians disagreed.

4. Complications of prophylaxis: patient records were retrospectively searched for mention of complications of prophylactic IV fluids administered around the time of the contrast procedure (symptomatic heart failure, hypernatremia, hyponatremia, and arrhythmias), or for mention of an uncomplicated procedure/discharge. An event was registered as complication if a physician judged there to be a causal relationship at the time of the event. For this study, information on complications was gathered up to the time at which they were resolved or up to a maximum of 1 month post contrast, or until dialysis or death followed.

1A



1B

DATA AVAILABLITY	
mortality	
281 (100%)	81 (100%)
dialysis	
281 (100%)	81 (100%)
change in eGFR	
172 (61%)	61 (75%)
post-contrast acute kidney injury	
150 (53%)	58 (72%)
complications of prophylaxis	
281 (100%)	-

Figure 6.1. A, Screening and inclusion profile. B, Data availability.

MUMC+ = Maastricht University Medical Centre; eGFR = estimated glomerular filtration rate.

Statistical Analysis

Continuous data are reported as mean, standard deviation (SD), or as median, interquartile range (IQR). Categorical data are presented as absolute numbers and percentages. To compare categorical baseline characteristics between prophylaxis and no-prophylaxis groups, χ^2 test was used to test for statistical differences. Differences in continuous baseline characteristics were assessed using Student t test for independent samples or the nonparametric Mann-Whitney U test (as appropriate). Distributions of continuous variables were visually checked for normality by a histogram, and kurtosis and skewness were evaluated.

Results were stratified by contrast procedure type. For between group comparison of dichotomous outcomes (PC-AKI, eGFR decline, dialysis, and mortality), multivariable logistic regression models were used. Unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CIs) were derived from the logistic regression models. Fully adjusted models included type of prophylaxis (standard IV 0.9% NaCl and none) and relevant baseline characteristics. The group that received no prophylaxis was used as reference group. P values of less than 0.05 were considered to indicate statistical significance. Analyses were done with IBM SPSS Statistics for Windows (version 23; IBM Corp, Armonk, NY) and STATA (version 13.1; Stata Corp, College Station, TX).

Results

All 55 474 elective procedures with IV or IA iodinated contrast material administration carried out between May 17, 2014, and May 17, 2018, at Maastricht UMC+ were screened (figure 6.1A).

Three hundred sixty-two patients were identified as eligible for inclusion. Of these, 281 (78%) received standard prophylactic IV fluids with 0.9% NaCl (prophylaxis group) and 81 (22%) received no prophylaxis (no-prophylaxis group). Reasons for not giving prophylactic fluids were as follows: 33 (41%) heart failure, 29 (36%) severe aortic valve stenosis, 8 (10%) poor renal function, 7 (9%) not specified, 2 (2%) dyspnoea, and 2 (2%) other.

Baseline Characteristics

Baseline characteristics in the prophylaxis and no-prophylaxis groups are shown in table 6.1.

Because the prophylaxis and no-prophylaxis groups significantly differ with respect to contrast procedure type, we used subgroups stratified by contrast procedure type for further analyses. Baseline characteristics stratified by contrast procedure type are shown in table 6.2.

Comparative analyses for the calculation of ORs with 95% CIs were stratified by IV or IA contrast administration route procedures only. Although outcome incidences are reported for all groups including the trans catheter aortic valve implantation (TAVI) and percutaneous trans luminal angioplasty (PTA) subgroups, these latter procedures were left out of the comparative risk analyses, because no TAVI patient and all PTA patients received prophylaxis (table 6.1).

There were three significant differences in baseline characteristics in the IV and IA contrast procedure subgroups (table 6.2).

For IV contrast procedures, the percentages with cardiovascular disease ($p<0.0001$) and with diuretics ($p=0.01$) were significantly lower in the prophylaxis subgroup compared with those in the no-prophylaxis subgroup. This may reflect the fact that physicians more often decide to withhold prophylactic fluids in these patients.

For IA contrast procedures, the percentage of inpatients was significantly lower in the prophylaxis subgroup compared with that in the no-prophylaxis subgroup ($p=0.01$).

Table 6.1. Baseline Characteristics per Prophylaxis Group

	Prophylaxis group n=281	No prophylaxis group n=81	p-value
Men	162 (58%)	45 (56%)	0.75
Age	75 (±10)	77 (±9)	0.11
BMI (kg/m^2)	27 (±5)	28 (±5)	0.11
Inpatient at referral	**98 (35%)**	**41 (51%)**	**0.01**
Renal function			
eGFR(ml/min/1.73m^2)	23.5 (±4.8)	24.7 (±4.5)	0.05
Serum creatinine (µmol/l)*	221 (±66)	207 (±59)	0.09
Baseline eGFR<15ml/min/1.73m^2	22 (8%)	3 (4%)	0.22
Risk factors			
Diabetes	**180 (64%)**	**31 (38%)**	**<0.0001**
Age >75 years	160 (57%)	55 (68%)	0.08
Prescribed diuretic medication	**175 (62%)**	**67 (83%)**	**0.0004**
Prescribed NSAID	112 (40%)	36 (44%)	0.08
Anaemia†	157 (56%)	40 (49%)	0.52
Cardiovascular disease	**167 (59%)**	**76 (94%)**	**<0.0001**
Contrast procedure			
Procedure with intervention	**39 (14%)**	**28 (35%)**	**<0.0001**
Intravenous contrast procedure	**154 (55%)**	**25 (31%)**	**<0.0001**
Intra-arterial coronary procedure	93 (33%)	33 (41%)	0.18
PTA & peripheral angiography	34 (12%)	0 (0%)	-
TAVI	0 (0%)	23 (28%)	-
Contrast material (ml) ‡	82 (±42)	88 (±54)	0.29
Prophylaxis			
Intravenous 0.9%NaCl (ml)	1710 (±505)	0	-

Data are n (%) or mean (SD). Values in boldface indicate significant difference (p<0.05). *To convert to mg/dl, divide by 88.4. †Hematocrit <0.36 l/l for women and <0.39 l/l for men. ‡iopromide at 300 mg iodine/ml. BMI=body mass index; eGFR= estimated glomerular filtration rate; NSAID = nonsteroidal anti-inflammatory drugs (including antiplatelet therapy); PTA= percutaneous transluminal angioplasty (including peripheral angiography procedures); TAVI= transcatheter aortic valve implantation.

Table 6.2. Baseline Characteristics Stratified by Contrast Procedure Type

	Intravenous contrast		Intra-arterial contrast		PTA	TAVI
	Prophylaxis	No prophylaxis	Prophylaxis	No prophylaxis	All prophylaxis	None prophylaxis
	n=154	**n=25**	**n=93**	**n=33**	**n=34**	**n=23**
Men	89 (58%)	14 (56%)	53 (57%)	22 (67%)	20 (59%)	9 (39%)
Age (years)	75 (±9)	74 (±12)	74 (±10)	77 (±7)	74 (±13)	82 (±5)
BMI (kg/m^2)	26 (±5)	28 (±6)	28 (±5)	29 (±5)	27 (±5)	25 (±3)
Inpatient	46 (30%)	10 (40%)	**39 (42%)**	**22 (67%)**	13 (38%)	9 (39%)
eGFR	24.1 (±4.3)	24.1 (±5.2)	23.3 (±4.8)	25.0 (±3.6)	21.0 (±6.2)	24.9 (±5.1)
Serum creatinine (µmol/l)*	214 (±55)	219 (±80)	221 (±57)	204 (±33)	257 (±110)	199 (±62)
eGFR <15	9 (6%)	1 (4%)	6 (6%)	0 (0%)	7 (21%)	2 (9%)
Diabetes	47 (31%)	7 (28%)	36 (39%)	16 (49%)	18 (53%)	8 (35)
Age >75	89 (58%)	12 (48%)	54 (58%)	22 (67%)	17 (50%)	21 (91%)
Diuretics	**88 (57%)**	**21 (84%)**	62 (67%)	25 (76%)	25 (74%)	21 (91%)
NSAID	57 (37%)	8 (32%)	46 (50%)	20 (61%)	9 (27%)	8 (35%)
Anaemia	87 (57%)	11 (44%)	48 (52%)	19 (58%)	22 (65%)	10 (44%)
Cardio-vascular disease	**74 (48%)**	**23 (92%)**	71 (76%)	30 (91%)	22 (65%)	23 (100%)
Contrast ‡ (ml)	87 (±38)	100 (±52)	72 (±45)	89 (±63)	88 (±50)	75 (±36)
Prophylactic fluids (ml)	1817 (±437)	0	1494 (±577)	0	1823 (±393)	0

Data are presented as n (%) or mean (SD). Values in boldface indicate significant difference between prophylaxis and no-prophylaxis subgroups (P < 0.05). *To convert to mg/dl, divide by 88.4. †Hematocrit <0.36 l/l for women and <0.39 l/l for men. ‡ Prewarmed (37°C) intravascular nonionic, monomeric, low-osmolar iodinated contrast (iopromide at 300 mg iodine/ml).

Postcontrast Adverse Outcomes

The primary and secondary outcomes were evaluated within 2 to 5 days and 1 month post contrast administration respectively. Observed incidences, unadjusted OR, and adjusted ORs with 95% CIs (prophylaxis vs no prophylaxis) are detailed in table 6.3, stratified by procedure type. Figure 6.2 visualises the adjusted OR results.

Adjustment was made for the potential confounders sex, age, inpatient/outpatient status, baseline eGFR, diabetes, medication (diuretic and NSAID), anaemia, cardiovascular disease, and contrast volume.

Post Contrast Acute Kidney Injury

Data on serum creatinine within 2 to 5 days post contrast exposure were available for 150/281 (53%) prophylaxis and 58/81 (72%) no-prophylaxis patients (figure 6.1B). Serum creatinine was measured at a median of 3 days (IQR, 3–4) post contrast.

PC-AKI occurred in 20/208 (9.6%) patients: 13/150 (8.7%) prophylaxis patients and 7/58 (12.1%) no-prophylaxis patients (p=0.46; table 6.3).

In the IV contrast procedure subgroup, observed incidences of PC-AKI were 4/69 (5.8%) prophylaxis versus 3/16 (18.8%) no prophylaxis (p=0.11).
In the IA contrast procedure subgroups, observed incidences of PC-AKI were 6/61 (9.8%) prophylaxis versus 4/21 (19.0%) no prophylaxis (P=0.27; table 6.3).

For both IV and IA contrast procedure subgroups, the adjusted ORs for risk of PC-AKI are less than 1 (figure 6.2): IV contrast procedures OR=0.23 (95% CI, 0.03–1.82; p=0.16); IA contrast procedures OR=0.20 (95% CI, 0.02–1.68; p=0.14).

The point estimate indicates a trend toward a protective effect of prophylaxis against PC-AKI.

Table 6.3. Adverse post-contrast outcomes and odds ratios by contrast procedure type

	OBSERVED INCIDENCES n (%)			**ODDS RATIOS: Prophylaxis vs No prophylaxis** OR (95% CI; *p-value)*	
	Prophylaxis	No prophylaxis	p	Unadjusted	Fully Adjusted
PC-AKI*					
Total group	13/150 (8.7%)	7/58 (12.1%)	0.46	-	-
PTA	3/20 (15.0%)	-	-	-	-
TAVI	-	0 /21 (0.0%)	-	-	-
Intravenous	4/69 (5.8%)	3/16 (18.8%)	0.11	0.27 (0.05–1.34;*0.11*)	0.23 (0.03–1.82;*0.16*)
Intra-arterial	6/61 (9.8%)	4/21 (19.0%)	0.27	0.46 (0.12–1.84;*0.27*)	0.20 (0.0 –1.68;*0.14*)
≥5 unit eGFR decline†					
Total group	18/172(10.5%)	11/61(18.0%)	0.13	-	-
PTA	3/23 (13.0%)	-	-	-	-
TAVI	-	2/16 (12.5%)	-	-	-
Intravenous	11/88 (12.5%)	4/18 (22.2%)	0.29	0.50 (0.14-1.80;*0.29*)	0.59 (0.09–3.98;*0.59*)
Intra-arterial	4/61 (6.6%)	5/27 (18.5%)	0.10	0.31 (0.08-1.26;*0.10*)	0.36 (0.05–2.51;*0.30*)
1-month dialysis					
Total group	6/281 (2.1%)	1/81 (1.2%)	0.60	-	-
PTA	3/34 (8.8%)	-	-	-	-
TAVI	-	0/23 (0.0%)	-	-	-
Intravenous	2/154 (1.3%)	1/25 (4.0%)	0.35	0.32 (0.03–3.62;*0.35*)	0.37 (0.03–4.40;*0.43*)
Intra-arterial	1/93 (1.0%)	0/33 (0.0%)	0.57	-	-
1-month mortality					
Total group	24/281 (8.5%)	4/81 (4.9%)	0.28	-	-
PTA	3/34 (8.8%)	-	-	-	-
TAVI	-	1/23 (4.3%)	-	-	-
Intravenous	17/154 (11.0%)	2/25 (8.0%)	0.65	1.43 (0.31–6.59;*0.65*)	2.10 (0.36–12.08;*0.41*)
Intra-arterial	4/93 (4.3%)	1/33 (3.0%)	0.75	1.44 (0.16–13.35;*0.75*)	4.02 (0.16–99.31;*0.40*)

*Data on 2-5 day serum creatinine were available for 150/281 (53%) prophylaxis and 58/81 (72%) no-prophylaxis patients. †Data on eGFR within 1-3 months post-contrast were available for 172/281 (61%) prophylaxis and 61/81 (75%) no-prophylaxis patients. CI indicates confidence interval.

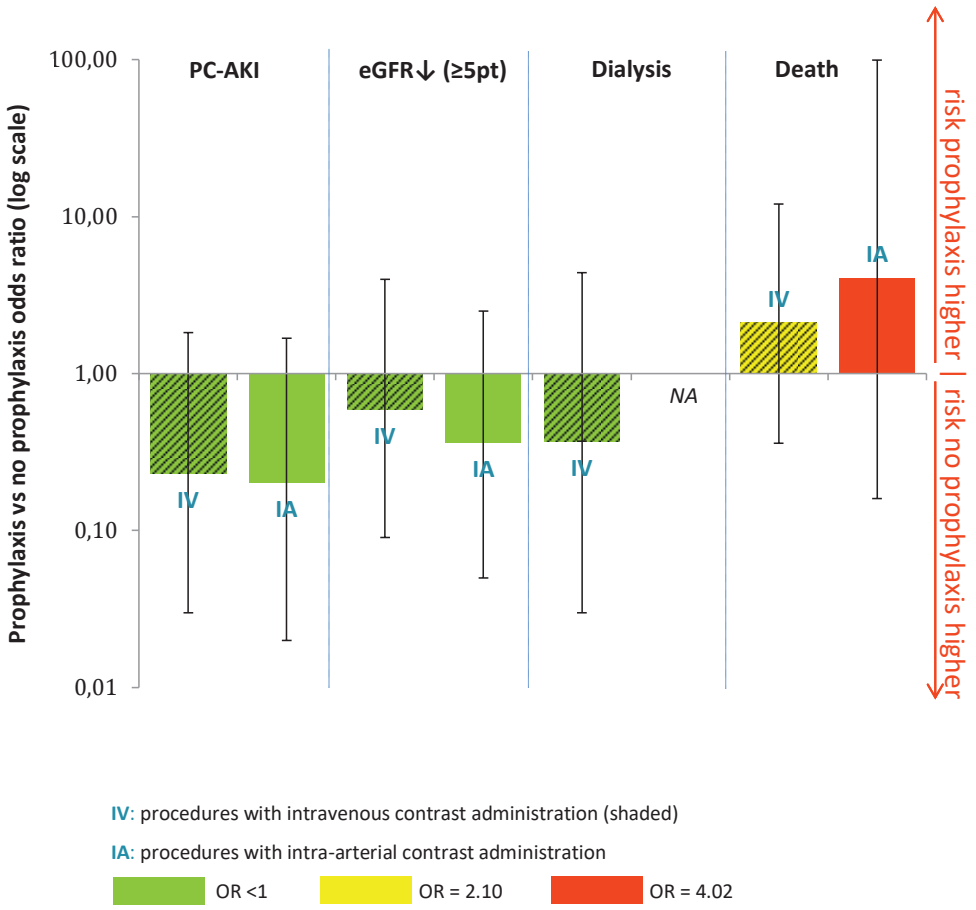


Figure 6.2. Post contrast adverse outcomes: prophylaxis versus no prophylaxis odds ratios.

Bars indicate 95%confidence intervals. PC-AKI indicates post contrast acute kidney injury. eGFR↓ (≥5 pt) indicates decline in estimated glomerular filtration rate with more than 5 ml/min/1.73m^2; eGFR decline was recorded up to 90 days post contrast.

Dialysis and death were recorded up to 1month post contrast. NA indicates not available: there were no instances of dialysis in the no-prophylaxis IA contrast subgroup, therefore comparative analysis could not be done for IA procedures.

Change in eGFR and Incidences of ≥5ml/min/1.73m^2 eGFR Decline

Data on change in eGFR were available for 172/281 (61%) prophylaxis patients, and for 61/81 (75%), no-prophylaxis patients (figure 6.1B).

A time-window of 30 to 90 days post contrast was allowed, and median time of serum creatinine measurement was 36 (IQR, 30–53) and 36 (IQR, 31–50) days post contrast exposure, respectively.

The distribution of the changes in eGFR from baseline in prophylaxis and no-prophylaxis patients is shown in figure 6.3. Median change in eGFR was 0.0 ml/min/1.73m^2 (IQR,-2 to 3) in the prophylaxis group (n=172), and 1.0 ml/ min/1.73m^2 (IQR, -2 to 6) in the no prophylaxis group (n=61; p=0.42).

A ≥5 ml/min/1.73m^2 eGFR decline occurred in 29/233 (12.4%) patients: 18/172 (10.5%) prophylaxis patients and 11/61 (18.0%) no prophylaxis patients (p=0.13; table 6.3).

In the IV contrast procedure subgroup, observed incidences of GFR decline were 11/88 (12.5%) prophylaxis versus 4/18 (22.2%) no prophylaxis (p=0.29). In the IA contrast procedure subgroups, observed incidences of eGFR decline were 4/61 (6.6%) prophylaxis versus 5/27 (18.5%) no prophylaxis (p=0.10; table 6.3).

For both IV and IA contrast procedure subgroups, the adjusted ORs for risk of eGFR decline are less than 1 (figure 6.2): IV contrast procedures OR=0.59 (95% CI, 0.09–3.98; p=0.59); IA contrast procedures OR=0.36 (95% CI, 0.05–2.51; p=0.30).

The point estimate indicates a trend toward a protective effect of prophylaxis against eGFR decline.

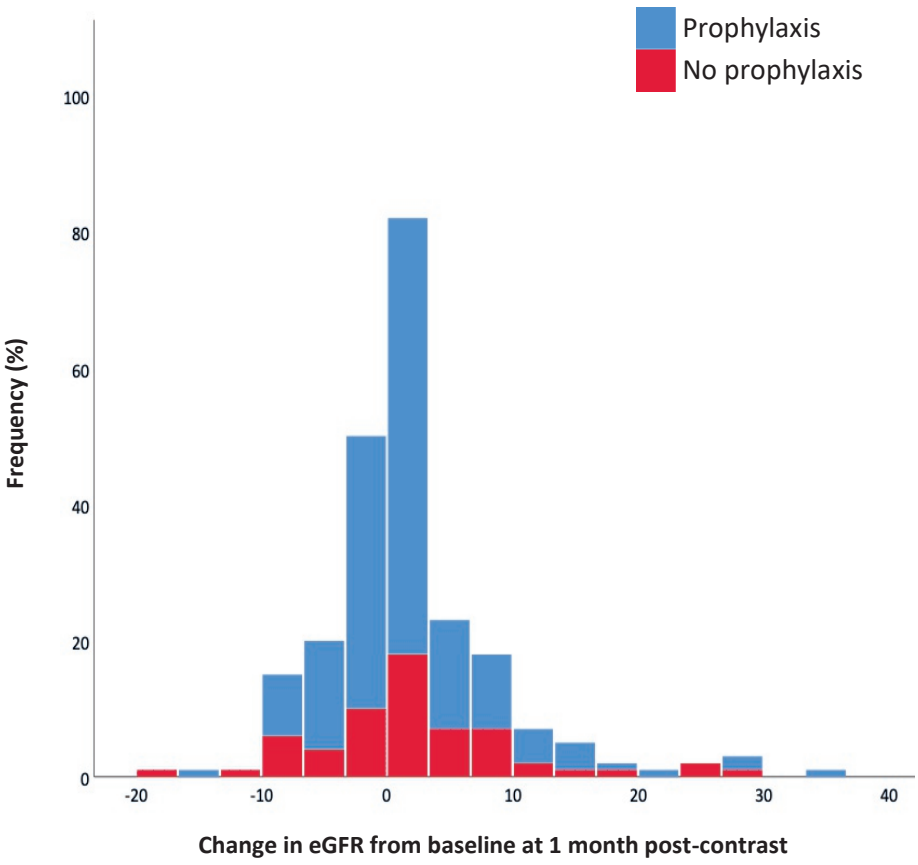


Figure 6.3. Distribution of the changes in eGFR from baseline in prophylaxis and no-prophylaxis patients.

Prophylaxis: median change in eGFR = 0.0 ml/min/1.73m^2 (IQR, -2 to 3; n=172). No prophylaxis: median change in eGFR = 1.0 ml/min/1.73m^2 (IQR, -2 to 6; n=61; p=0.42).

Dialysis

Data on dialysis were available for all patients (figure 6.1B). Dialysis within 1 month post contrast was recorded for 7/362 (1.9%) patients: 6/281 (2.1%) prophylaxis patients and 1/81 (1.2%) no-prophylaxis patients (p=0.60; table 6.3).

For the IV contrast procedures subgroup, there were 3 instances of dialysis within 1 month: 2 prophylaxis versus 1 no prophylaxis (p=0.35; table3). The adjusted OR is less than 1: OR=0.37 (95% CI, 0.03–4.40; p=0.43; figure 6.2).

The point estimate indicates a trend toward a protective effect of prophylaxis compared with no prophylaxis against dialysis, but event rates are too low to draw a definite conclusion.

In the IA contrast procedures subgroup, there was one instance of dialysis within 1 month in the prophylaxis subgroup, and none in the no-prophylaxis subgroup (p=0.57; table 6.3). Therefore, a comparative analysis could not be done for IA contrast procedures.

Incidences of All-Cause Mortality

Data on mortality were available for all patients (figure 6.1B). In total, 28/362 (7.7%) patients died within 1 month post contrast: 24/281 (8.5%) prophylaxis patients and 4/81 (4.9%) no-prophylaxis patients (p=0.28; table 6.3).

In the IV contrast procedure subgroup, 19/179 (10.6%) patients died within 1 month: 17/154 (11.0%) prophylaxis versus 2/25 (8.0%) no-prophylaxis patients (p=0.65).

In the IA contrast procedure subgroup, 5/126 (4.0%) patients died within 1 month: 4/93 (4.3%) prophylaxis versus 1/33 (3.0%) no-prophylaxis patients (p=0.75; table 6.3).

Adjusted ORs for risk of death are greater than 1 for both IV and IA contrast procedures (figure 6.2): IV contrast procedures OR=2.10 (95% CI, 0.36–12.08; p=0.41); IA contrast procedures OR=4.02 (95% CI, 0.16–99.31; p=0.40).

The adjusted ORs account for the observed differences in baseline characteristics between prophylaxis and no prophylaxis subgroups. Confidence intervals are wide, especially for the IA contrast subgroup in which only a few events were recorded. However, the point estimates indicate a trend toward higher risk of death for prophylaxis compared with no prophylaxis.

Primary Causes of Death

Primary causes of death in the IV and IA contrast procedure subgroups were as follows: 42% cardiovascular (10/24), 42% cancer (10/24), 13% sepsis (3/24), and 4% other (1/24). Cardiovascular disease deaths were distributed over the subgroups as follows: 6 prophylaxis IV versus 0 no prophylaxis IV; 3 prophylaxis IA versus 1 no prophylaxis IA. Cancer deaths occurred solely in the prophylaxis IV subgroup.

The blinded physicians reviewing primary causes of death relationship to IV fluids independently agreed on 17 of 24 cases: 5 related and 12 unrelated. They differed on 5 cases and were uncertain about 2 cases (Cohen's k=0.54, moderate agreement), which were adjudicated by the third physician as 5 unrelated, and 2 uncertain.

According to adjudication, 5 deaths were caused by heart failure related to IV fluids (4 prophylaxis IV and 1 prophylaxis IA). All occurred within a few days to 2 weeks post contrast and in prophylaxis patients, representing 24% of deaths in the IV and IA prophylaxis subgroups (5/21).

Although these results do not explain the large difference in risk of short-term death between prophylaxis and no-prophylaxis groups, they indicate that prophylaxis might have contributed toward mortality in prophylaxis patients.

Complications of Prophylaxis

Data on complications of prophylaxis were available for all prophylaxis patients (see data availability overview in figure 6.1B). Complications occurred in 18/281 prophylaxis patients (6.4%): 15 symptomatic heart failures (including the 5 deaths mentioned previously) and 3 arrhythmias.

Baseline characteristics of prophylaxis patients with and without complications of IV fluids are given in the Supplementary Appendix Table.The group of 18 patients with complications significantly differed from patients without complications in the following: inpatient status at time of referral for the contrast procedure (56% vs 33%; p=0.047), age older than 75 years (83% vs 55%; P=0.02), use of diuretics (89% vs 60%; p=0.01), and cardiovascular disease (94% vs 57%; p=0.002). In the prophylaxis group, the risk of complications is approximately 10 times higher for patients with pre-existing cardiovascular disease (17/167= 10.2%) than for those without (1/114=0.8%; p=0.002).

An explorative analysis of the records of patients with complications showed the following as frequently present:

1. specific diuretic medication (bumetanide, furosemide, eplerenone, and/or spironolactone; 16/18, 89%)
2. pre-existing heart failure (15/18, 83%; 10 had New York Heart Association classification III–IV)
3. barely adequate/poor functional capacity (17/18, 94%)
4. prior clinical indicators of fluid retention (13/18, 72%)

Mean volumes of administered IV fluids did not differ much between patients with and without complications. Volumes were 1528 ml (SD, 642 ml) for patients with complications and 1721 ml (SD, 495 ml) for patients without complications (p=0.14; see Supplementary Appendix Table).

These results suggest complications of prophylaxis may be predicted if certain patient characteristics are individually considered.s

Discussion

Adjusted ORs for post contrast risk of contrast-induced acute kidney injury, eGFR decline, and dialysis are all lower than 1.These ORs were not significant, but the point estimates indicate a trend toward a protective effect of IV prophylactic fluids over no prophylaxis against post contrast renal function decline. For dialysis, event rates are too low to draw a definite conclusion.

Analysis of all-cause mortality within 1 month post contrast yielded adjusted ORs greater than 1. Although confidence intervals are wide, the point estimates indicate a trend toward higher risk of short-term mortality after prophylaxis as compared with no prophylaxis.

Part of the excess mortality in the prophylaxis group might be explained by the 5 cardiovascular deaths, which according to adjudication, were causally related to administration of prophylactic IV fluids. Complications of the prophylaxis might thus have contributed toward an increased risk of short-term mortality, and 24% of deaths in the analysed prophylaxis patients were related to IV fluids. On the other hand, other differences between the groups may have contributed to the higher risk of mortality seen in the prophylaxis group. Differences in recorded baseline characteristics (such as inpatient status, age, diabetes, and so on) were captured by the multivariate logistic regression models, but it is likely that there were other, unrecorded reasons for referring patients to prophylaxis or no prophylaxis. Also, 10 of 24 deaths in the prophylaxis group were due to cancer, suggesting that in this group the percentage of patients with cancer may have been higher than in patients referred to the no-prophylaxis group. All the above may in part explain the excess mortality in the prophylaxis group. Nevertheless, it remains the case that 5 patients died of heart failure precipitated by IV fluids in the prophylaxis group, a situation which did not occur in the no-prophylaxis group.

Prophylaxis was safe for 93.6% of patients; serious complications occurred in 6.4% of patients.The comparison of baseline characteristics and inventory of more details regarding cardiovascular health and medication showed that patients with and without

complications differ in identifiable ways. For example, 94% of patients with complications had pre-existing cardiovascular disease, and risk of complications was approximately 10 times higher for patients with pre-existing cardiovascular disease than for those without. These data suggest that serious complications could be avoided if cardiac function parameters were given extra and individual attention before deciding whether to administer prophylaxis to high-risk patients with eGFR less than 30 ml/min/1.73m^2.

The main limitations of the current study are its observational nature, the retrospective data collection, and limited sample size. The multivariable logistic regression accounts for the observed differences in baseline characteristics between groups, and stratification accounts for different contrast procedure types. However, even after stratification and adjustment, we cannot be sure that there is no residual confounding due to factors that were not captured in the multivariable models. Potential confounding by indication is a problem common to comparative observational studies.

In the current study, data on serum creatinine were missing for 47% prophylaxis and 28% no-prophylaxis patients. This is likely a result of noncompliance to guidelines in the clinical setting, which is a known and serious problem, considering the vulnerable population affected.[128,163] On the other hand, patients in whom post contrast renal function was checked might represent a selected group in which PC-AKI is overrepresented or underrepresented. However, the observed total incidence of PC-AKI in the current study (20/208, 9.6%) is similar to those 2 other retrospective studies found in patients with eGFR less than 30ml/min/1.73m^2 (10.8% after computed tomography and 9.7% after percutaneous coronary intervention).[151,173] There were no missing data on death and complications of prophylaxis.

The current results concern IV prophylactic hydration with normal saline. Guidelines recommend various protocols, with differing durations and flow rates and some with IV 1.4% sodium bicarbonate ($NaHCO_3$) instead of normal saline.[76,79] Patients with and without complications received similar prophylactic volumes, and total volumes of IV normal saline administered in the current study are similar to those reported

elsewhere.[165,174] Furthermore, the rate of complications after IV sodium bicarbonate prophylaxis seems to be similar to that after normal saline.[76,165] Finally, large-scale studies fail to find significant differences between sodium bicarbonate and sodium chloride prophylaxis.[164,165]

The definition used for PC-AKI in this study is under debate, and updated guidelines recommend using the general definition for acute kidney injury as defined by the KDIGO work group (an increase in serum creatinine greater than 26.5 µmol/l or to 1.5 times the baseline value).[19,76,78,79] Although using the KDIGO definition may increase incidences of PC-AKI due to the lower threshold, differences between subgroups remain similar and ORs remain below 1, thus conclusions are not altered. We chose to use the traditional definition of PC-AKI (an increase in serum creatinine >44 µmol/l or >25%) for continuity and comparability with other studies, and restricted ourselves to one definition in the manuscript to limit complexity.

Sample size is limited, which limits power to detect small but relevant effects. The present study was based on available data over a 4-year period, a formal sample size was not calculated, and it must therefore be considered exploratory. Barring a massive international effort, however, sample sizes similar to ours are probably as much as we can hope for in this setting. First, one may encounter 1 patient in every 200 elective contrast procedures on average, and this may be as low as 1 in 2 000 in some settings.[128,147,151,166] Second, low inclusion and adherence are relevant problems.[128,163]

Two physicians independently adjudicated primary causes of death to determine whether a causal relationship with prophylactic IV fluids was plausible and a third adjudicated cases on which they did not agree. The number of deaths analysed was small, and such adjudication does not equal proof, however. Also, there was moderate agreement between the 2 physicians, who disagreed on a relationship with prophylaxis in 5 of 24 cases.

To the best of our knowledge, this is the first report to compare prophylaxis to no prophylaxis in patients with eGFR less than 30 ml/min/1.73m^2. In absence of

randomised trials and in view of the paucity of available data in literature, this may provide valuable information for physicians to help in their decision-making on prophylaxis for high-risk patients.

Based on this study, no standard recommendation with regard to giving or withholding prophylaxis can be given. The current data indicate that prophylactic IV fluids may confer some protection against post contrast renal adverse outcomes, but may also contribute toward increased short term mortality risk. The results further suggest that serious complications of prophylaxis may be avoided if cardiac function parameters are given extra attention when contemplating prophylaxis for this vulnerable population. In other words, both benefits and risks of prophylaxis must be carefully weighed for each individual high-risk patient with eGFR less than 30 ml/min/1.73m^2.

Conflicts of interest and sources of funding

The authors declare no conflicts of interest. The study was funded by Stichting de Weijerhorst.

Supplementary Appendix Table.

Baseline characteristics of prophylaxis patients with/without complications

	Complications & in the prophylaxis group **(n=18)**	**No complications** & in the prophylaxis group **(n=263)**	**p-value**
Men	9 (50%)	153 (58%)	0.51
Age (years)	78 (±9)	74 (±10)	0.06
BMI (kg/m^2)	28 (±7)	27 (±5)	0.57
normal weight (19-25)	9		
overweight (BMI >25-30)	4		
obesity (BMI >30-35)	3		
severe obesity (BMI>35-40)	0		
morbid obesity (BMI>40)	2		
Inpatient status at referral	10 (56%)	88 (33%)	**0.05**
Baseline renal function			
eGFR	23.5 (±4.9)	23.5 (±2.3)	0.97
serum creatinine (µmol/l)*	208 (±28)	222 (±67)	0.37
eGFR < 15	1 (6%)	21 (8%)	0.76
Contrast procedure			
Intravenous contrast procedure	9 (50%)	145 (55%)	0.68
Intra-arterial coronary procedure	7 (44%)	86 (33%)	0.34
PTA & peripheral angiography	2 (11%)	32 (12%)	0.90
Indication procedure	4 persistent heart failure 4 ischemia of extremities (fontaine 4) 3 cancer diagnosis or progression 2 suspected coronary insufficiency 2 chest pain 2 pain upper abdomen (obstruction?) 1 suspected pulmonary embolism	*NA*	
Risk factors			
Diabetes type II	11 (61%)	169 (64%)	0.80
Age >75 years	15 (83%)	145 (55%)	**0.02**
Prescribed diuretics (all loop-diuretics)	16 (89%)	159 (60%)	**0.01**
Prescribed NSAIDs	6 (33%)	106 (40%)	0.56
Anemia†	11 (61%)	146 (56%)	0.68
Cardiovascular disease	17 (94%)	150 (57%)	**0.002**

	Complications & in the prophylaxis group **(n=18)**	**No complications** & in the prophylaxis group **(n=263)**
Prescribed B-blockers	15 (83%)	
Atrial fibrillation/pacemaker	9 (50%)	
Hypertension	12 (67%)	
Heart failure	15 (83%)	
Heart failure NYHA III-IV	10 (56%)	
Significant heart valve stenosis	5 (28%)	
(N)STEMI in case history	6 (33%)	
TIA/CVA in case history	3 (17%)	*NA*
Admission via cardiac emergency	8 (80% of inpatients)	
Patient functional capacity	1 adequate 12 barely adequate 5 poor	
Physical indicators of fluid retention	13 (72%)	

Data are n (%) or mean (±SD). NA = data not available for the current study. BMI=body-mass index. eGFR= estimated glomerular filtration rate in ml/min/1.73m^2. PTA=percutaneous transluminal angioplasty. NSAID=non-steroid anti-inflammatory drugs. NYHA=New York Heart Association Classification. (N)STEMI=(non) ST-elevation myocardial infarction. TIA=transient ischemic attack. CVA=cerebrovascular accident. *To convert to mg/dL, divide by 88.4. †Anemia is defined as hematocrit value <0.36 l/l for women and <0.39 l/l for men.

CHAPTER 7

CIN no more?

"The fundamental question of AMACING was not about the risk, origin or meaning of CIN. The knowledge gap we aimed to fill was the efficacy of guideline-recommended prophylaxis in the prevention of CIN compared with not giving prophylaxis, in the population targeted by the guidelines."

7. AMACING Discussion & Conclusion

The study object of this dissertation is the recommendation for prophylactic hydration in clinical practice guidelines on the use of intravascular iodinated contrast material.

The aim of the guidelines is to prevent post-contrast adverse outcomes: contrast-induced nephropathy (CIN), long-term renal function decline, dialysis, and mortality.

The aim of AMACING was to evaluate whether the main recommendation of the guidelines, i.e. administering peri-procedural prophylactic intravenous hydration to a predefined high-risk population, is safe and (cost) effective.

The initial studies of this dissertation thus concern the population considered high-risk and eligible for prophylaxis at the time of the AMACING trial (chapters 2 & 3), with eGFR 30-59 ml/min/1.73m^2 and risk factors.[46] As is described in chapter 4 guidelines were updated following the publication of the AMACING trial results, which changed the study object.[76-79]

The eGFR 30-59 ml/min/1.73m^2 population is currently no longer eligible for prophylaxis according to the guidelines, and the population for whom the guidelines recommend prophylaxis now only includes patients with eGFR <30 ml/min/1.73m^2. The latter patients were excluded from our trial for safety reasons. However, A MAastricht Contrast-Induced Nephropathy Guideline evaluation was continued beyond the guideline updates: study focus shifted to elective intravascular iodinated contrast procedures in patients with eGFR <30 ml/min/1.73m^2 (chapters 5 & 6).

This Discussion chapter, in which key findings, strengths, limitations, conclusions, pertinence, and future directions of research are discussed, is structured in four parts. First the key findings of the AMACING randomised controlled trial and of the observational studies on patients with eGFR <30 ml/min/1.73m^2 are summarised, followed by their separate strengths and limitations. Next, conclusions and pertinence of the sum total of the studies are detailed, and finally, areas of future research are explored.

7.1 To hydrate or not to hydrate? Lessons learned from AMACING

Any therapy or medicine represents a balancing act between positive and negative effects. In the case of prophylactic intravenous hydration, neither effect was properly investigated before its introduction as standard care. Guideline committees acknowledged that randomised trials comparing prophylactic intravenous hydration to a proper control group without prophylaxis were not available, but stated that carrying out such trials would be ethically unacceptable given the current understanding of CIN.[28] At our centre, based on our daily practice, we were not convinced that these extensive guidelines were the best approach. Nor did we agree that such a trial would be unethical: we had already encountered some serious complications of the prophylactic treatment such as symptomatic heart failure and arrhythmias. Based on these and other deaths deemed avoidable in retrospect, the Commissie Onderzoek Overleden Patiënten of Maastricht UMC+ (COOP: a committee which investigates all in-hospital deaths) opened the discussion on burdens of interventions that exceed the coping ability of fragile patients, and sometimes lead to serious complications and death.[92] Taking all the above into consideration, not knowing whether the benefits of the treatment outweighed this risk was, to our minds, unacceptable.

The CIN group started with a short explorative retrospective analysis of in-house data to determine the ipact of implementing the newly issued guidelines.[80] 419 consecutive patients who underwent an elective coronary angiography or intervention were screened, and 47 of these met the guideline criteria for high-risk patients. In accordance with the in-house protocol at the time, only 9 of the 47 patients had received prophylactic intravenous fluids, and 38 received none. Only one in 47 (2.1%) at risk patients developed CIN. This incidence of CIN was much lower than incidences which had been reported in literature (ranging from 2% - 50% or more).[111] Furthermore, renal function normalized within a few weeks, and no clinically relevant consequences were observed.

This set the stage for the AMACING trial.[103] The aim of the trial was to evaluate the clinical-effectiveness and cost-effectiveness of prophylactic hydration according to the guidelines, by comparing patients at risk of CIN who received prophylaxis to those who

did not. For the randomised controlled trial a non-inferiority design was chosen, because although not giving prophylaxis might be expected to increase CIN incidence, it would also reduce patient burden, hospital burden, and health care costs. Furthermore, although sometimes associated with longer-term morbidity and mortality, CIN usually resolves without clinically relevant consequences. Lastly, not giving prophylaxis would mean avoiding complications of intravenous hydration.

For the AMACING trial we prospectively screened all 28 803 elective procedures requiring iodinated contrast material carried out over a two-year period at our centre.[104] 1 120 patients met the inclusion criteria (i.e. elective high-risk patients according to the guidelines with eGFR <60 ml/min/1.73m^2 combined with risk factors for CIN).[70,75] 660 patients (59%) agreed to participate in the trial, and these were randomised 1:1 to either standard prophylactic hydration according to the guidelines or no prophylaxis. In view of patient safety, we excluded patients with severe chronic kidney disease from the trial, i.e. those with eGFR <30 ml/min/1.73m^2. After these exclusions, the included population still represented approximately 90% of patients to whom the guideline recommendation of standard prophylaxis was applicable.

Primary results showed that not giving prophylaxis was non-inferior to standard prophylaxis with normal saline in the prevention of CIN. CIN incidences were 8/296 (2.7%) in the standard prophylaxis group versus 8/307 (2.6%) in the no prophylaxis group (absolute difference in proportions, no prophylaxis group minus prophylaxis group, -0.10%, 95%CI -2.25 to 2.06, p=0.4710). The upper limit of the one-sided 95% confidence interval excludes an increase in CIN of 2.1% or more; in other words, the results exclude an unacceptable increase in CIN in absence of prophylaxis (the non-inferiority margin). No dialysis or related deaths occurred within 1 month. However, 5.5% of intravenously hydrated patients suffered complications from the prophylactic treatment (13/328 symptomatic heart failure, 4/328 arrhythmia, 1/328 hyponatremia). Finally, costs per patient were almost twice as high for prophylaxis patients than for no prophylaxis patients (mean difference 663 euro per patient).

The AMACING data led to the conclusion that, assuming optimal contrast media administration, withholding prophylaxis for patients with eGFR ≥30 ml/min/1.73m^2 might be considered without compromising patient safety.

Secondary outcomes of the trial included incidences of adverse outcomes up to one year post-contrast. The one-year AMACING follow-up data showed no clinically relevant differences in one-year dialysis, one-year mortality, long-term change in serum creatinine from baseline, or renal events between the no prophylaxis and intravenously hydrated groups.[105] The observed differences between no prophylaxis and prophylaxis groups were consistently small and not significant. This confirmed the earlier conclusion that prophylaxis could safely be withheld for this population.

The AMACING trial prompted an amendment to several guidelines. The guideline committees of the Netherlands (NVvR)[76] and the United Kingdom (NICE)[77] carried out exceptional reviews in order to incorporate the findings into their guidelines: that routine use of prophylactic intravenous hydration in high-risk patients with eGFR 30-59 ml/min/1.73m^2 may not be beneficial and may inadvertently cause harm through fluid overload.[76-79]

Currently clinical guidelines have been updated to recommend prophylactic intravenous hydration for patients with eGFR <30 ml/min/1.73m^2 only.[76-79] The change is undoubtedly a net improvement, as implementation will mean avoiding unnecessary complications of prophylactic treatment, a considerable reduction in hospital and patient burdens, and health care budget savings of €50-100 million a year in the Netherlands (with ca. 17 million Dutch residents in 2017); extrapolating the AMACING results to possible consequences worldwide leads to an estimation of health care savings of roughly €2 billion or more each year worldwide.[104] However, the new prophylaxis threshold at eGFR <30 ml/min/1.73m^2 has not been chosen because of (new) evidence that these patients may profit from prophylactic intravenous hydration. Indeed, very little data and no rigorous randomised trials evaluating prophylaxis are available in literature.

Ideally, the new guidelines would be subjected to a sufficiently powered and robust randomised controlled trial, comparing the recommended prophylaxis to no prophylaxis in patients with eGFR <30 ml/min/1.73m^2. However, such an endeavour may not be as simple as it sounds.

A retrospective analysis of patients with eGFR <30 ml/min/1.73m^2 excluded from the AMACING trial showed that these patients represent a different, more vulnerable population to those with eGFR 30-59 ml/min/1.73m^2 included in the trial.[128] Incidences of post-contrast adverse events were substantially higher in the eGFR <30 ml/min/1.73m^2 population compared to those in the AMACING trial population: CIN 13.6% versus 2.7% (p=0.0019); 1 month dialysis 0.9% versus 0.0% (p=0.2646); and 1 month mortality 9.2% versus 0.0% (p<0.0001). Furthermore, more outliers with extreme post-contrast increases in serum creatinine were observed in the eGFR <30 ml/min/1.73m^2 population.

eGFR <30 ml/min/1.73m^2 patients, then, appear to indeed be truly high-risk. However, the low prevalence of eGFR <30 ml/min/1.73m^2 (0.4% - 0.5% in the general population, and 0.06% - 0.5% in the setting of elective iodinated contrast administration) combined with a relatively small non-inferiority margin (only a small increase in CIN would be deemed acceptable), makes randomised trials of sufficient power unrealistic.[128,151,166-168] Based on our observational data it may take an estimated 2-5 years and the participation of all centres in the Netherlands.[128]

In a second, larger observational study, all 55 474 elective contrast procedures carried out over a 4-year period at our centre were retrospectively screened.[135] The aim was to gain some insight into the positive and negative effects of prophylactic treatment in high-risk patients with eGFR <30 ml/min/1.73m^2, by comparing adverse outcomes between patients with and without prophylaxis. This was possible because treating specialists may decide not to give prophylaxis to patients at risk of complications of intravenous hydration, with aortic stenosis or severe chronic heart failure for example. Differences between prophylaxis and no prophylaxis groups were corrected for observed differences in baseline characteristics.

The resultant adjusted odds ratios for risk of CIN, eGFR decline, and dialysis within 1 month were all lower than 1. Though not significant, the point estimates indicate a trend toward a protective effect of intravenous prophylactic fluids over no prophylaxis for post-contrast renal function decline. Adjusted odds ratios for all-cause mortality within 1 month post-contrast were higher than 1, however, with point estimates indicating a trend toward higher risk of short-term mortality after prophylaxis as compared to no prophylaxis.

Because the study was observational, confounding by indication may partly be responsible for the observed increased risk of short-term mortality, but complications of the prophylaxis contributed towards the risk. Amongst 281 prophylaxis patients, 18 (6.4%) complications of prophylaxis occurred: 15 heart failures including 5 deaths, and 3 arrhythmias. Of all 21 deaths in the analysed prophylaxis patients, 24% (5/21) were considered to be related to intravenous fluids.

An exploration of differences in baseline characteristics between patients with and without complications suggested that serious complications can be avoided if cardiac function parameters are given extra and individual attention before deciding whether to administer prophylaxis to high-risk patients with eGFR <30 ml/min/1.73m^2.[135]

This conclusion has potential consequences for guidelines and daily clinical practice. Physicians from all specialties are confronted with weighing the benefits against the risks of procedures with iodinated contrast material. To date most focus on protecting renal function; our data indicate that cardiac parameters should also be considered.

The high incidences of post-contrast adverse outcomes in patients with eGFR <30 ml/min/1.73m^2 compared to AMACING trial participants indicate that the updated guidelines now better define the patient at 'high-risk of CIN'. Prevalence of eGFR <30 ml/min/1.73m^2 is low, but we are still talking about an estimated 15 000 high-risk patients a year in the Netherlands, and at least 375 000 patients a year worldwide, who are confronted with the risks of contrast administration and prophylaxis.

Prophylaxis may offer some protection against renal function decline, and looks to be without complications for 93.6% of patients, but serious complications do occur, and when they do they may be fatal. In absence of randomised controlled trials, which as we have seen may not be readily feasible, many questions remain open on the subject of prophylaxis in patients with eGFR <30 ml/min/1.73m^2. We recommend a thorough individual evaluation, and deliberation on whether to hydrate or not to hydrate in this, truly high-risk, population.

AMACING taught us that prophylaxis was not beneficial for patients with eGFR 30-59 ml/min/1.73m^2, and that patients with eGFR <30 ml/min/1.73m^2 warrant extra and individual attention in this setting. It also taught us that it pays to scrutinise our daily clinical practice, to be wary of quality measures not backed by randomised trial data, and to dare to put expert opinion to the test.[133,134]

7.2 Praise, Criticisms, Strengths & Limitations

7.2.1 AMACING trial: Praise, Criticisms, Strengths & Limitations

Any study questioning the status quo can expect extra scrutiny and criticisms. It is testimony to the inherent strength of the AMACING trial that although an amazing amount of comments were written on the trial (no pun intended – see list and QR access codes/links in Appendix I), most authors discussed consequences and generalisability of the findings (see, for example, the letters in section 2.3 and Appendix III), and contained praise for the trial.

Dr. Mandrola, wrote on Medscape (Appendix I, nr. 14):[134] "**The strengths of AMACING outnumber its weaknesses. A principal strength is its relevance to clinical practice. Investigators enrolled patients who were similar to the population for which guidelines recommend hydration. Three-quarters of the cohort had cardiovascular disease, nearly half were on NSAIDs, and almost one-third had diabetes. And this representative sample underwent varied types of contrast procedures; nearly half had intra-arterial contrast.**

The trialists also mirrored good clinical practice by using minimum volume, prewarmed, low-osmolar, monomer, non-ionic contrast material. That may lessen the chance of CIN (lower event rates) and thus reduce the benefit-to-harm ratio of hydration. But that's the point of pragmatic and contemporary research. IV hydration may have been useful in another era."

Limitations are discussed in the articles and letters detailed in chapters 2 and 3. Below, some of the more pertinent points and issues are addressed.

Trial design

One editorial contained criticisms on trial design and execution.[175] This accompanying commissioned editorial for the Lancet was also the first and last virulent criticism of the AMACING trial. The commissioned editorial focuses mainly on the appropriateness of the trial, the choice for a non-inferiority design, and the non-inferiority margin. Here, we will address the main issues raised by the authors.

The authors wrote (see Appendix I, nr. 8):[175] **"In our view this field is not ready for non-inferiority trials until we have a reference standard intervention that is agreed upon as proven, and thus can be positioned as the control group and be compared with novel treatment or strategy."**

This is exactly why we began the AMACING trial. The prophylactic treatment *was* standard care in most countries; it *was* the reference standard treatment agreed upon; it was *not* a treatment that had been proven; yet it *was* consistently positioned as the control group. Perhaps the myriad studies published over the last decades – in which the standard prophylactic treatment is positioned as the control group and is compared with novel treatments – can be considered premature.

The search 'Contrast Induced Nephropathy OR Contrast Induced Acute kidney Injury' yields at least 8 000 publications in PubMed, hundreds of which concern randomised controlled trials comparing the standard prophylaxis to another strategy. None compared standard prophylaxis to not giving any prophylaxis. To our minds the field was more than ready for such a trial. Given the fact that the guideline recommendation

carried such enormous impact in its implementation, and that this unproven prophylaxis is being given to patients the world over every day, such a trial was perhaps even long overdue.

The situation in the Netherlands was more acute than in other countries. Adherence to guidelines varies per country,[163] but in the Netherlands guideline recommendations were strictly imposed. Adherence was even used as one of the indicators for hospital quality and safety by accreditation institutions (https://www.vmszorg.nl/).

So why choose a non-inferiority design? Non-inferiority trials are designed to show that the effect of a new treatment is not worse than that of an active control by more than a specified margin.[176] By definition therefore the new treatment may be worse and still be called non-inferior. Such a situation is acceptable if other aspects of the new treatment, such as patient burden or side effects, are demonstrably better.

In the context of CIN and prophylaxis there are many unknowns, making a non-inferiority design the only choice for this evaluation:

1. CIN is a biochemical marker by definition, and direct health effects are absent. There is uncertainty surrounding CIN and its clinical effects.[83]
2. Incidences of long-term post-contrast adverse effects are very low, and the cause-effect relationship with iodinated contrast has not been shown to exist.[18,20,21]
3. Significant patient burden, logistic burden, and health care costs incurred by giving prophylaxis are certain, whereas beneficial effects in protecting renal function have not been adequately shown.

It is understandable why some might consider the AMACING trial unconventional, because some aspects are topsy-turvy compared to the 'standard' randomised controlled trial.[176] First, the control group is the group that *received* the treatment, because it was the standard care. Second, the intervention group received *no treatment*, because what happens to high-risk patients who receive intravascular contrast without prophylaxis was unknown, since it had never been adequately tested.

Commissioned editorial:[175] **"The method of computation of the non-inferiority margin and the revision of this statistical approach was unconventional and in the end had the assumptions that the contrast-induced acute kidney injury rate in the normal saline group would be 2.4% and the rate in the no saline prophylaxis group could be as high as 4.5% with relative risk or hazard ratio of less than 1.88 to meet non-inferiority."**

It is surprising that the choice of non-inferiority margin was criticized. The non-inferiority margin was set at 2.1% based on the assumption that CIN incidence in the control group receiving standard care (prophylaxis group) would be 2.4%, the incidence published in a then recent Dutch paper.[93]

Due to the nature of the problem it was not possible to follow formal rules for the setting of a non-inferiority margin.[176] In a situation where the effectiveness of the standard treatment has never been proven, it is not possible to choose the non-inferiority margin in such a way that at least half of the effectiveness of standard treatment is retained. Another formal approach is to base the non-inferiority margin on meta-analysis estimates. However, estimates of the difference in proportions of contrast-induced nephropathy with 95% confidence intervals were simply not available in literature.

A non-inferiority margin of 2.1% was considered acceptable, because CIN is usually a transient change in serum creatinine, resolving within two weeks, and with no lasting effects. Although CIN can be associated with increased morbidity and mortality, clinically relevant consequences are reported to occur in fewer than 1% of cases.[18,20,21] The true long-term consequences of CIN in terms of renal dysfunction and related morbidity and mortality are unknown,[177] and research into renal damage biomarkers, which might elucidate the underlying mechanisms, is only just emerging.[178] In addition, although an association between increased risk of mortality and dialysis and CIN has been reported in literature, there is no evidence of a causal relationship, and CIN might be a marker only.[83,177] Importantly, prior to the AMACING trial it had not been shown whether standard care prophylactic hydration reduces the risk of long-term effects.

The authors of the commissioned editorial continue:[175] **"The upper bound of the 95% confidence limit for this construction is about 4.50, which exceeds all conventions for non-inferiority trials. In other words, could one be comfortable accepting the non-inferior result knowing that withholding standard-of-care volume expansion could result in 4 to 5-fold increased hazard of contrast-induced acute kidney injury? Clearly this is questionable and represents an example on how clinical trials can go awry with hypothesis testing."**

A non-inferiority margin is subjectively chosen before a trial in absence of data: it is impossible to calculate a 95% confidence interval around a non-inferiority margin. The implication that we accepted a 4 to 5-fold increase in risk of CIN is misleading and not substantiated by any available statistical method.

To be clear: we deemed a maximum increase of 2.1% incidence in the biochemical diagnosis CIN to be acceptable, which, as the authors correctly stated earlier, translates to a maximum hazard ratio of 1.88 for our study design. We never allowed for acceptance of a higher increase in risk.

In a non-inferiority trial, the null hypothesis states that the alternative treatment (withholding prophylaxis) is worse than the standard treatment (giving prophylaxis) by more than an acceptable difference, which is defined by the non-inferiority margin.[176] The type 1 error in a non-inferiority trial, i.e. erroneously rejecting the null hypothesis, means *missing an unacceptably large difference* between groups and falsely concluding non-inferiority.

Conventionally, in a non-inferiority trial a one-sided type I error (α) of 5% is chosen and interpretation depends on the one-sided 95% confidence interval around the absolute difference between groups. If this confidence interval excludes the non-inferiority margin, the null hypothesis, that there is a difference greater than what is determined to be acceptable, can be rejected.

In the AMACING trial the primary outcome was the absolute difference in CIN incidences between randomised groups, which was found to be -0.10%. The upper limit

of the 95% confidence interval for this result was lower than 2.1% excluding the non-inferiority margin and indicating no prophylaxis to be non-inferior. There is only a 5% chance that the true difference between groups is greater than that suggested by the limit of the confidence interval. This chance is considered as acceptably small by regulators.[179]

In answer to the question whether one could be comfortable accepting the non-inferiority result: there is no reason to expect, nor did we observe, large differences in risk of CIN. Indeed, the primary study results show no difference in CIN incidence, no inkling of differences in persisting renal problems, and no differences in progression to the clinically relevant adverse outcomes dialysis or death. The pertinent question in view of these outcomes is whether one could be comfortable continuing to give a treatment that is unproven, carries proven risks, confers significant burden upon patient and hospital, and is so costly.

In conclusion, the commissioned editorial failed to put the trial into perspective and raised several invalid points. Dr. Mandrola wrote on Medscape:[134] **"In an accompanying editorial, three authors took exception to the non-inferiority trial design. Their argument does not persuade me. I'm no statistician, but primary-outcome rates of 2.7% and 2.6% are essentially the same and 18 vs. 0 adverse events are lopsided in favor of no hydration. That's the beauty of elegant simple experiments: you don't need fancy statistics or composite end points to explain the results."**

C.Wyatt et al., Kidney International (see Appendix I, nr. 9):[131] …**"the AMACING trial was rigorously designed and conducted"…**

Primary outcome

An active discussion exists in the medical community on terminology, definition and existence of CIN.[76,78,95,129,162,180] Some argue that the term CIN is misleading. Most object to the 'Nephropathy', because it indicates a disease or damage to the kidney, whereas this context implies acute renal insult. Others object to the 'Contrast-Induced'

because this implies a causal link and, in practice, it is not often possible to distinguish between renal function decline caused by contrast administration and that caused by another aetiology.

Alternate names suggested include contrast-induced acute kidney injury (CI-AKI), contrast-associated nephropathy (CAN), contrast-associated acute kidney injury (CA-AKI), and post-contrast acute kidney injury (PC-AKI).[76,78] We support the introduction of the strictly more correct term PC-AKI (as it least implies a causal relationship), and it is likely that it will be predominantly used in future studies. This term is also the one recommended in updated clinical practice guidelines.[76,78] Furthermore, when using the KDIGO definition for general acute kidney injury (see below)[19] and taking into account the uncertainty surrounding the causal relationship with iodinated contrast, PC-AKI does indeed seem the most appropriate term.

In this dissertation, however, the term CIN is used because it is what the guidelines aim to prevent and it is still the most widely used term in literature (table 7.1).

Table 7.1. Prevalence of terms for post-contrast renal function decline in literature.

	PubMed search February 19, 2019	**Results (count)**
CIN	"contrast-induced nephropathy" OR "contrast induced nephropathy"	1855
CI-AKI	"contrast-induced acute kidney injury" OR "contrast induced acute kidney injury"	568
CAN	"contrast-associated nephropathy" OR "contrast associated nephropathy"	26
CA-AKI	"contrast-associated acute kidney injury" OR "contrast associated acute kidney injury"	22
PC-AKI	"post-contrast acute kidney injury" OR "post contrast acute kidney injury"	5

The >25% or >44µmol/l increase in serum creatinine definition for CIN is also under fire.[22,24-26,76,78] According to several authors it is a sensitive but wildly nonspecific surrogate. Again, we used the definition as stated in the evaluated guideline, and this definition of CIN is and has been the most widely used in literature.[23] In the updated guidelines, the KDIGO definition for acute-kidney injury is advised (an increase in serum creatinine of >26.5µmol/l from baseline or to >1.5 x the baseline value).[19,76,78] For the AMACING trial, using the KDIGO definition does not change the conclusion: the number of CIN cases increases from 8 to 10 in both randomised arms which translates to incidences of 3.4% (was 2.6%) and 3.3% (was 2.7%). The absolute difference between groups (no prophylaxis minus prophylaxis) remains unchanged at minus 0.1%.

In the eGFR <30 ml/min/1.73m^2 population KDIGO-defined incidences similarly increase (for example in the intravenous contrast administration subgroups incidences increase from 5.8% and 18.8%, to 13% and 37.5%). However, odds ratios for risk of CIN all remain below 1, and point estimates still indicate prophylaxis may have a protective effect.

Importantly, clinically relevant outcomes such as longer-term eGFR outcomes, dialysis, and mortality, play a large part in the analyses and conclusions, and these are not affected by which definition of CIN is used.

Sample size[169]

A comment made by some authors is that we should strive for much larger trials,[175, 181,182] but the AMACING trial is the largest trial of its kind. The final sample size was smaller than planned: the feasible inclusion target had to be revised from 1 300 to 660 halfway through the inclusion period.[104] Some reviewers saw reason to question whether the study had sufficient power, but such a conclusion reflects a lack of understanding as to what constitutes the null hypothesis in a non-inferiority trial.[183]

Whereas the type 1 error (α) depends only on the one-sided 95% confidence interval around the absolute difference between groups (see above),[176] the type II error (β) and the power (1-β) may potentially be affected by the smaller than originally planned

sample size of the AMACING trial. However, in a non-inferiority trial the type II error (and power) relates to the chance that the one-sided 95% confidence interval around the absolute difference between groups does *not* exclude the non-inferiority margin, when in fact the alternative intervention (withholding prophylaxis) is truly non-inferior. The type II error (and power) is typically referred to as the "sponsor's" risk.[184] When the power is low, the sponsor runs the risk that a truly non-inferior alternative treatment is not recognized as non-inferior to standard care. However, in the AMACING trial non-inferiority of withholding prophylaxis to standard care with prophylaxis could be concluded despite the limited power.

Missing data

A limitation of the AMACING trial is that post-contrast serum creatinine measurements were not available for all patients: serum creatinine within 2-6 days post-contrast was missing for 32/328 (9.8%) prophylaxis and 25/332 (7.5%) no prophylaxis patients.[104]

Absence of serum creatinine values was unrelated to the study intervention, and it is reassuring that baseline characteristics of patients with and without 2-6 day serum creatinine values were similar. However, because the attrition rate for the primary outcome (ca. 9%) is higher than the observed incidences of CIN (2.6% and 2.7%), it could be argued that a small number of undocumented CIN events could have changed the study results. This is possible in theory, but seems unlikely.

Could the nearly identical rates of CIN have occurred by chance? However unlikely, there is always a possibility. This is where trial replication may be helpful (more on that in section 7.3). Regardless, validity of the conclusion for clinically relevant effects is assured because data on dialysis and mortality were available for all patients, including any patients in whom CIN may have gone undetected. The results therefore reliably reflect efficacy of prophylaxis in reducing clinically relevant adverse post-contrast outcomes.

7.2.2 Observational Studies in Patients with eGFR<30 ml/min/1.73m^2: Strengths & Limitations

The main limitations of the observational studies are due to their observational nature, and are discussed in the articles detailed in chapters 5 and 6.[128,135] Below, some of the more pertinent points are addressed.

In the first of the two observational studies all patients excluded from the AMACING trial because they had eGFR <30 ml/min/1.73m^2 were studied. The largest subgroup of these eGFR <30 ml/min/1.73m^2 patients received standard prophylaxis, and baseline characteristics and incidences of post-contrast adverse outcomes in this subgroup were compared to those of eGFR 30-59 ml/min/1.73m^2 patients in the prophylaxis arm of the AMACING trial. The baseline characteristics of the eGFR <30 ml/min/1.73m^2 and the AMACING trial populations were significantly different, which raises the question whether higher incidences of renal function decline and mortality are a consequence of greater susceptibility to toxic effects of intravascular iodinated contrast administration, or whether these are inherent to the eGFR <30 ml/min/1.73m^2 population.

Because both groups used in the comparison received prophylaxis – the subgroup of the eGFR <30 ml/min/1.73m^2 population not receiving prophylaxis was too small (n=24) to enable a meaningful comparison - this study could not answer the question whether standard prophylaxis is effective in preventing CIN and other adverse outcomes in patients with eGFR <30 ml/min/1.73m^2. This question was explored in the second study comparing patients with eGFR <30 ml/min/1.73m^2 who received standard prophylaxis according to the guidelines to patients who did not receive prophylaxis.

The main limitations of this second study are the retrospective data collection and, despite the 4-years' worth of data, the limited sample size. Even after stratification by contrast procedure type and adjustment for potential confounders one cannot be sure that there is no residual confounding due to factors that were not captured in the multivariable models. Potential confounding by indication is a problem common to comparative observational studies.

In the 4-year study on prophylaxis versus no prophylaxis in eGFR <30 ml/min/1.73m^2 patients, data on CIN were missing for 47% prophylaxis and 28% no prophylaxis patients. Although this is likely a result of non-compliance in the clinical setting, the patients in whom post-contrast renal function was checked might represent a selected group in which CIN is over- or underrepresented. However, the observed incidence of CIN (20/208, 9.6%) is similar to those which two other retrospective studies found in patients with eGFR <30 ml/min/1.73m^2 (10.8% after computed tomography and 9.7% after percutaneous coronary intervention).[151,172] Furthermore, the conclusion was for the largest part based on incidences of death and complications of prophylaxis for which there were no missing data.

One of the major conclusions of the 4-year study relied on independent adjudication of primary causes of death by three physicians. Upon translating these results to practice one must remember that the number of cases analysed was small, and such adjudication does not equal proof.

The study was based on all available data over a 4-year period, but sample size is limited, which limits power to detect small but relevant effects. A formal sample size was not calculated, and the study must therefore be considered exploratory. Barring a massive international effort, however, sample sizes similar to the 4-year study are probably as much as can be hoped for in this setting. First, one may encounter 1 patient in every 200 elective contrast procedures on average, and this may be as low as 1 in 2 000 in some settings.[128,130,147,151,166] Second, low inclusion and adherence to protocol are relevant problems.[128,163]

The main strength of the observational studies is that they provide a complete picture of daily clinical practice. All elective procedures during the study periods at Maastricht University Medical Centre (Maastricht UMC+) were screened, and clinical practice was recorded for all aspects; oral fluid consumption and contrast parameters, for example, were not influenced.

To the best of our knowledge, the studies in patients with eGFR <30 ml/min/1.73m^2 are the first reports of post-contrast outcomes in this well-defined cohort, and the larger

study is the first to compare prophylaxis to no prophylaxis in this population. In absence of randomised trials and in view of the paucity of available data in literature, this provides valuable information for physicians to help in their decision-making on prophylaxis for high-risk patients with eGFR <30 ml/min/1.73m^2.

The studies also provide estimates of the incidences of CIN and other adverse outcomes after prophylactic intravenous hydration in patients with eGFR <30 ml/min/1.73m^2, which will facilitate calculation of the required sample size for future efficacy studies in this population. It also provides the expected incidence of complications of prophylactic intravenous hydration, which can help in determining an acceptable non-inferiority margin.

7.3 AMACING Conclusions and Pertinence

7.3.1 Conclusions & Translation to Clinical Practice

The most distinct conclusion is the one based on the AMACING trial results: withhold prophylaxis for elective patients with eGFR 30-59 ml/min/1.73m^2. Guideline committees have come to the same conclusion, and prophylaxis is now no longer recommended for this population.[70,71,73,76,77,79]

It was not AMACING alone that led to abolishing prophylaxis for patients with eGFR 30-59 ml/min/1.73m^2, extensive reviews of all available relevant literature form the basis for that decision.[76,79] However, the AMACING trial is the only large randomised controlled trial providing data on efficacy of prophylaxis versus no prophylaxis in the setting of elective intravascular iodinated contrast administration.[76] Normally, scientific rigour would demand the trial be replicated before such drastic changes are made in clinical practice. No matter how good the trial, one is still only one. However, in this the AMACING trial deviates.

First of all, it would be surprising if this trial were replicated. The AMACING trial was intense and costly, and in the interim no prophylaxis has become standard care. Given the non-existent difference intravenous hydration made in the incidence of CIN, the

5.5% patients that had serious complications of intravenous hydration, and the growing uncertainty of the clinical relevance of CIN in current practice, medical research ethics committees are likely to frown upon a trial administering abolished prophylactic intravenous hydration. Furthermore, publication opportunities for replicated trials are not very good, making the required cost and effort even less appealing.

Second, acting upon the results was probably the only ethical choice to make. The alternative would have been to continue giving a treatment that is unproven, carries proven risks, and confers significant burden upon patient, hospital, and health care budgets. The burden of proof has now correctly been laid at the feet of prophylaxis, as it should have been from the start.

In view of the above, it is interesting that the practice of administering prophylaxis is perpetuated in patients with eGFR <30 ml/min/1.73m^2.[70-74,76,77,79] The burden of proof has not shifted for this population, despite absence of evidence. Why perpetuate the practice?

The observational studies in patients with eGFR <30 ml/min/1.73m^2 detailed in chapters 5 and 6 were published after the guideline updates.[128,135] They provide the first data for this population in this setting, but establish the uncertainty surrounding prophylaxis. The results cannot exclude the possibility that the cure may sometimes be more harmful than the disease, drawing attention to the fact that efforts to prevent CIN may in some cases lead to fatal consequences. The main conclusion of the observational studies on eGFR <30 ml/min/1.73m^2 patients is that prophylactic strategy needs to be individualised in order to minimise risk of complications.

There are several reasons perpetuating prophylaxis for eGFR <30 ml/min/1.73m^2 patients may have been seen as the only option at the time of the guideline updates. First, some studies have shown benefits of intravenous hydration in acute settings.[99,101] Arguably patients with eGFR <30 ml/min/1.73m^2 are similarly vulnerable and perhaps also less stable, and may therefore similarly benefit. Second, without the renal capacity to compensate, any loss in renal function will quickly lead to dialysis for these patients.

Because there are convincing physiological arguments as to why intravenous hydration could mitigate risk of renal injury,[66] the choice for defensive medicine may be considered valid despite the risk of complications and the chance of inefficacy.

7.3.2 Pertinence: What Cannot Be Concluded from the Available Data

This dissertation is not about fundamental research into contrast-induced nephropathy (CIN). It does not delve into or shed light upon questions cause, physiological pathway, consequences, existence or relevance of CIN, nor about who is at risk. Rather, it is 'on the evaluation of guideline-recommended prophylaxis to prevent contrast-induced nephropathy' and therefore very much daily practice-oriented.

The recommendations in question, and thus the studies in this dissertation, entail substantial consequences for millions of patients, hospitals, and health care budgets the world over, true. However, the central theme of this thesis is the evaluation of a specific recommendation by a specific clinical practice guideline: peri-procedural prophylactic intravenous hydration with normal saline for the prevention of CIN after elective iodinated contrast material administration.

Other settings

The AMACING trial was done amongst patients eligible for standard prophylaxis according to the guidelines, and results may not be generalizable to other settings. Considering the many comments and questions on this topic, it is pertinent to emphasize that emergency and intensive care status were amongst the exclusion criteria, and acute patients are beyond the scope of this dissertation. In any case, standard prophylaxis recommendations in the guidelines do not apply to emergency situations, where many other factors play a role.[70-74,76,77,79]

Other contrast administration protocols

As described in section 1.1, not all iodinated contrast materials were created equal. Furthermore, nor are contrast protocols: administered contrast material volumes and total iodine loads may vary. The conclusions contained in this dissertation assume optimal contrast administration. In other words, the use of low-osmolar, non-ionic,

monomeric contrast with appropriate (low) iodine concentration; pre-warming contrast to body temperature before injection; and optimising overall volumes for each individual patient.

Other prophylaxis protocols

The current results concern intravenous prophylactic hydration with normal saline. In the last guideline updates, the choice of standard intravenous fluids has shifted along with the high-risk population.[76,79] Instead of intravenous 0.9% NaCl, 4-12 hours before and after contrast administration, now the standard is intravenous 1.4% sodium bicarbonate ($NaHCO_3$) 1 hour before and 6 hours after contrast administration.

There are several potential benefits to this change. The first is the 1-hour pre-hydration, which is an obvious burden relief for hospital logistics and hospitalisation. The second benefit is the potential reduction in total volume administered, from roughly 1.5 litres 0.9% NaCl to 750 ml 1.4% $NaHCO_3$ on average. The third potential benefit is in slightly different physiological effects of bicarbonate: sodium bicarbonate theoretically has all the same beneficial influences as normal saline, with the added potential benefits of substantial renal tubule alkalinisation and free radical clearing.[66]

Taken together with the lower volumes administered one might expect better net results from $NaHCO_3$ prophylaxis. However, in our studies total volumes administered in patients with and without complications did not differ much.[135] Furthermore, the rate of complications after $NaHCO_3$ prophylaxis appears to be similar to that after normal saline.[76] Finally, large-scale studies consistently fail to find a benefit of sodium bicarbonate over sodium chloride prophylaxis with respect to adverse post-contrast outcomes.[164,165]

In short, the AMACING trial results showed that doing nothing was non-inferior to administering intravenous sodium chloride in the bulk of patients, and the current results cannot give direct insight into efficacy of sodium bicarbonate prophylaxis. However, in literature notable differences between intravenous sodium chloride and sodium bicarbonate prophylactic treatments are not reported, despite many and very

large trials. This leads to the speculation that neither prophylactic strategy is effective at reducing the risk of post-contrast adverse outcomes, at least in patients with eGFR 30-59 ml/min/1.73m^2.

Meaning of CIN and safety of iodinated contrast

"People have foolishly called the AMACING trial as the last nail in the coffin for CI-AKI. Really? All it showed was that intravenous (IV) fluid expansion does not prevent a soft definition of AKI from happening in low to intermediate risk patients. Like Mark Twain, one has to conclude that the reports of the death of CI-AKI have been greatly exaggerated."[185]

CIN is what the guidelines aim to prevent, therefore studies evaluating efficacy must have CIN as primary outcome.[70-74,76,78,79] However, the AMACING trial was not about (the risk of) CIN, but about guideline efficacy. Whether CIN is synonymous to renal damage and whether all renal damage is reflected in CIN incidence cannot be answered from the current data.

The meaning of CIN is unclear, the more so because serum creatinine is a non-specific surrogate and imperfect marker for renal function.[186] It is influenced by factors such as muscle mass, diet, hydration, and activity, it shows diurnal and seasonal fluctuations, and is often unstable in patients with health issues.[187,188] Several retrospective studies have shown that fluctuations equal to those used to define CIN are seen in absence of contrast administration, the incidences of which can equal or exceed reported incidences of CIN (1.3 – 19.8%).[95,162,180] Thus it may be that measuring post-contrast change in serum creatinine yields mostly noise, with only a few instances of acute kidney injury.

The implications of the often transient and acute rise in serum creatinine that represents CIN are also unclear. Several studies have shown correlations between CIN and increased morbidity and mortality risk, but whether CIN is a marker or part of a causative process is not known and cannot be deduced from our data.[18,20,21,83,177]

Several reviewers asked us to perform analyses comparing patients who had CIN and those who did not in the AMACING trial. We did not do so because the aim was to evaluate efficacy of intravenous hydration and we did not wish to confuse the issue. Also, the trial was not designed for a comparison between CIN and no CIN patients, and such a comparison would be subject to confounders.

Until more specific biomarkers are found which prove useful in distinguishing renal injury from other causes of serum creatinine increases, the meaning of CIN will remain unclear. In order to ensure clinical relevance a primary outcome CIN must therefore always be accompanied by hard endpoints such as long-term persistent renal function decline, dialysis, and death.

7.4 Future research

Three main topics form areas of future research in this context:

1. effectiveness of standard prophylaxis in eGFR <30 ml/min/1.73m^2 patients
2. the meaning of CIN and its link with renal damage
3. the link between CIN/renal damage and intravascular iodinated contrast.

7.4.1 AMACING II

Considering the fact that the situation with regards to the guideline recommendation for prophylactic intravenous hydration remains unchanged, in that there is no robust scientific evidence to back the recommendation, the immediate impulse is to advocate AMACING II; i.e. a randomised controlled trial of no prophylaxis versus prophylaxis in patients with eGFR <30 ml/min/1.73m^2. Indeed, if such a trial were readily feasible it would already be under way.

However, as addressed in chapter 5, including the required number of patients will be a mammoth task.[128] Assuming 60% of patients will consent to participate at Maastricht UMC+, it would take up to 75 years for us to include the required 6 594 patients at our centre.

A solution would be multi-centre collaboration, but the required sample sizes would be hard to achieve even then. Furthermore, such a trial would be confronted with large logistic challenges and would have to contend with disparities in procedures and contrast media use. Another solution may lie in the choice of primary outcome: an outcome with lower incidences combined with a reasonable non-inferiority limit leads to smaller required sample size.[184] However, a primary outcome must be clinically relevant.

Some authors have relied on mean change in serum creatinine and used the standard deviation of the mean change as starting point for sample size calculation.[102] This approach has the advantage that considerably smaller sample sizes are required, but seems ill advised considering the very limited clinical relevance of the outcome in this setting. Whereas such an outcome can give an indication of a shift towards more favourable outcomes in a group of patients, an average serum creatinine increase will not detect acute renal function decline occurring in a few patients. The latter is what prophylactic intravenous hydration aims to prevent.

Perhaps trials should aim at novel biomarkers of renal damage. Unfortunately, this area of research is only just coming out of its infancy, expected incidences are not readily available, and it is not entirely clear which marker has sufficient specificity and sensitivity for this setting.[178] Furthermore, patients with eGFR <30 ml/min/1.73m^2 will likely have a baseline presence of damage markers. As with serum creatinine, therefore, a damage marker primary outcome must be in the form of a threshold increase from baseline, which must first be established. At this time, there is no obvious candidate for an alternative, meaningful primary outcome for AMACING II.

Perhaps we should acknowledge that such a trial is not readily feasible, and also that our attention may be better spent considering the previous step which has been passed over. In other words, the question should perhaps be whether in the current clinical setting there is still a need for a standard prophylaxis to protect renal function from intravascular iodinated contrast administration.

7.4.2 The Meaning of CIN and its Link with Renal Damage: CIN in Absence of Iodinated Contrast

As described in section 7.3.2, the meaning of CIN is uncertain. Two main questions arise: (how often) is the serum creatinine increase that defines CIN a direct result of iodinated contrast administration, and (how much of) CIN is a reflection of renal damage?

CIN in absence of iodinated contrast has been shown to occur, and incidences of such 'pseudo' CIN are sufficient to eclipse those of CIN.[95,162,180] No prospective studies on incidences of CIN in absence of contrast have been done, however, and data on eGFR <30 ml/min/1.73m^2 patients in general is rare in literature.

It would be interesting to prospectively determine how often patients with eGFR <30 ml/min/1.73m^2 have CIN – or rather, 'pseudo CIN' – in absence of contrast administration. Furthermore, it would be pertinent to evaluate whether CIN or 'pseudo CIN' reflect acute kidney injury. The answer to the latter question would lie in alternate ways of measuring renal injury.

Many biomarkers have been studied over the last decades, and although there is still not one ultimate marker with high sensitivity and specificity for acute renal injury, there are several promising markers that have persisted in literature over the last decade.[178,189]

7.4.3 The Link between Renal Damage and Intravascular Iodinated Contrast

As described in section 1.1, many advances have been implemented since CIN and associated long-term risk were first reported.[64] We currently operate in a new, safer era of iodinated contrast administration, and contrast administration is not what it once was.[190] Contrast toxicity in clinical practice can be expected to likewise have changed.

The question at this time, therefore, is whether iodinated contrast administration still induces renal damage in the current clinical setting. More specifically, once the reliability of a marker for renal damage is more or less established, the question is whether, how often, and in which patients concentrations of such a marker increase after iodinated contrast. These questions would best be answered by randomised controlled trials comparing patients receiving iodinated contrast versus a placebo injection. If it were reliably demonstrated that 'pseudo-CIN' accounts for most of the CIN seen in clinical practice, such randomised controlled trials would be the logical next step. They could first be done in healthy volunteers, and if results are favourable, in patients with eGFR 30-59 ml/min/1.73m^2 and ultimately in patients with eGFR <30 ml/min/1.73m^2. Even then, given the current understanding of CIN, such trials may not be considered ethical at this time.

Then again, so it was for AMACING.

CHAPTER 8

The AMACING conclusions have been implemented in most countries. The result: noticeabe lightening of patient, specialist, hospital, and health care budget burdens.

8. AMACING societal and scientific impact

Every day, hundreds of thousands procedures with intravascular iodinated contrast injections are carried out the world over (CT scans, coronary angiographies, etc.).[2] Many of these procedures are performed in elderly patients with cardiovascular disease, decreased renal function, diabetes mellitus, and on nephrotoxic medication, all risk factors for post-contrast renal injury. Weighing the benefits against the risks of contrast injections is something health care professionals from all specialties are confronted with daily.

Guidelines on safe use of iodinated contrast material recommend intravenous prophylactic hydration to prevent post-contrast adverse (renal) effects.[70-73,76] The AMACING trial - an interdisciplinary collaboration between the departments Radiology, Cardiology, Internal Medicine, Clinical Epidemiology & Medical Technology Assessment of Maastricht University Medical Centre, and Epidemiology of Maastricht University - is the first and only study to show that prophylactic intravenous hydration is not (cost-) effective for the largest part of the population eligible for prophylaxis according to the evaluated guideline. The conclusions were confirmed by the 1-year follow-up data.[104,105] The consequences of the AMACING findings are profound.

The AMACING trial prompted an amendment to several guidelines: clinical practice has been demonstrably altered in the Netherlands and Europe, and the impact is felt worldwide.[70-73,76-79] The guideline committees of the Netherlands (NVvR) and the United Kingdom (NICE) carried out exceptional reviews in order to incorporate AMACING trial findings into their guidelines: that routine use of prophylactic intravenous hydration in at-risk patients with eGFR 30-59 ml/min/1.73m^2 may not be beneficial and may inadvertently cause harm through fluid overload.[76,77]

At this time most guidelines have been updated in line with the AMACING trial results. In Europe, America and Ocenia, umbrella organisations no longer recommend standard prophylaxis for patients with estimated glomerular filtration rate (eGFR) 30-59 ml/min/1.73m^2 combined with risk factors represented by

AMACING trial participants.[70,71,73,79] The chages in recommendations on standard prophylaxis in the Dutch (The Radiological Society of The Netherlands, NVvR) guidelines are detaied in table 8.1.[76] The updates have led to palpable changes for patients, hospitals and health care budgets, and has promoted a paradigm shift in the scientific discussion surrounding CIN and iodinated contrast material administration.

8.1 Local effects: Maastricht UMC+

At Maastricht UMC+ the protocol for the prevention of CIN was updated and implemented in the summer of 2017. After the in-house protocol had been updated to no longer giving prophylaxis to those patients with eGFR 30-59 ml/min/1.73m^2 formerly eligible for prophylaxis, the observational Contrast-Induced Nephropathy After Reduction of the prophylaxis Threshold (CINART) project was started (registered with Clinicaltrials.gov under NCT03227835).[191] The aim of this retrospective observational study was to evaluate consequences for clinical practice at Maastricht University Medical Centre (UMC+) in terms of patient burden (complications of prophylaxis), hospital burden (extra hospitalisations for prophylaxis), and costs.

In this project, retrospective data similar to data collected prospectively for the AMACING trial were registered on all elective procedures with intravascular iodinated contrast administration in patients *formerly* eligible for prophylaxis (with eGFR 45-59 ml/min/1.73m^2 in combination with diabetes or more than 1 risk factor, OR with eGFR 30-44 ml/min/1.73m^2)[70,75], and in patients *currently* eligible for prophylaxis (with eGFR <30 ml/min/1.73m^2).[76,78]

The data concern procedures, therefore repeat inclusion of patients was allowed. Data were retrospectively collected from patient electronic files. The Medical Research Ethics Committee Maastricht UMC+ waived the requirement for informed consent.

The primary outcome was the number of elective radiology or cardiology procedures in patients (no longer) eligible for standard prophylaxis, i.e. the number of procedures in patients *formerly* eligible for standard prophylaxis, according to guidelines before the update, and the number of procedures in patients *currently* eligible for standard prophylaxis, according to updated guidelines. Additional information concerns the proportions of outpatients, defined as the proportion of patients not hospitalised at the moment of referral for the contrast procedure.

The results were subsequently used to calculate the main results: the impact of guideline updates in terms of relative reduction in the numbers of complications, hospitalisations, and costs associated with prophylactic intravenous hydration.

Table 8.1. Clinical practice recommendations for elective patients in the Netherlands before and after guideline updates

Guideline recommendation[§]	**Before November 2017 update**	**After November 2017 update**
Patient eligible for standard prophylaxis	- eGFR <45 ml/min/1.73m^2 or eGFR 45-59 ml/min/1.73m^2 combined with diabetes or >1 risk factor[$]	eGFR <30 ml/min/1.73m^2
Standard prophylaxis	iv 0.9% NaCl 4 or 12 h before & 4 or 12 h after	iv 1.4% $NaHCO_3$ 1 h before (& 6 h after)

eGFR = estimated glomerular fitration rate. [§]Centraal Begeleidings Orgaan guideline on iodinated contrast material 2007,[75] and The Radiological Society of The Netherlands (RSTN - NVvR)[76] guideline on safe use of contrast media 2017; [$]age >75 years, anaemia, cardiovascular disease, nephrotoxic medication.

From July 1, 2017 until July 1, 2018, a total of 1 992 elective procedures with intravascular iodinated contrast material in patients formerly and currently eligible for prophylaxis were identified: 1 808 procedures in patients formerly eligible for prophylaxis (with eGFR 30-59 ml/min/1.73m^2 combined with risk factors), and 184 procedures in patients with eGFR <30 ml/min/1.73m^2 currently eligible for prophylaxis (figure 8.1).

Calculations of complications, hospitalisations, and costs associated with standard prophylaxis before and after guideline updates are detailed below and the findings are illustrated in figure 8.2.

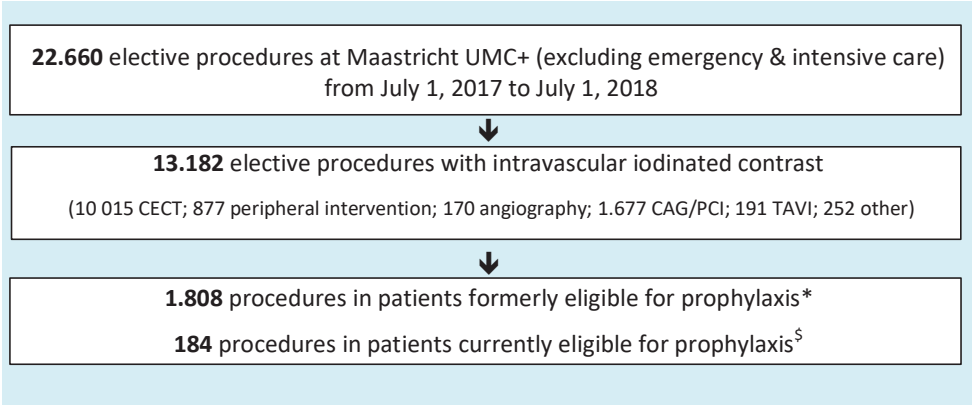


Figure 8.1. Screening and inclusion profile of the CINART study

CECT = contrast-enhanced computed tomography; CAG = coronary angiography; PCI = percutaneous coronary intervention; TAVI = transcatheter aortic valve implantation. *i.e. eGFR 30-59 ml/min/1.73m^2 combined with risk factors; $i.e. eGFR <30 ml/min/1.73m^2

CALCULATIONS

Complications of prophylaxis

The number of complications of prophylaxis was calculated based on the 5.5% rate of complications found in AMACING trial patients with eGFR 30-59 ml/min/1.73m^2 combined with risk factors (Chapter 2), and the 6.4% rate of complications found in our 4-year observational study in patients with eGFR <30 ml/min/1.73m^2 (Chapter 6).[104,135]

Total complications before update: (1 808*0.055) + (184*0.064) = 111/year

Total complications after update: 184*0.064 = 12/year

Total complications avoided after guideline update: 0.055*1 808 = 99/year (-89%)

Hospitalisation for prophylaxis

CINART registered 85.4% outpatients (1.544/1.808) in the group formerly eligible for prophylaxis, and 64.7% outpatients in the group currently eligible for prophylaxis (119/184).

Total extra hospitalisations before update: (1 808*0.854) + (184*0.647) = 1 663/year

Total extra hospitalisations after update: 184*0.647 = 119/year

Total beds freed after the guideline update: 1 808*0.854 = 1 544/year (-93%)

Costs

Cost calculations were based on the difference in costs associated with elective contrast procedures (excluding costs of the procedure itself) up to one month post-contrast as registered in the AMACING trial:[104] mean extra costs of resources used by patients receiving standard prophylaxis were €663 per procedure per patient. These costs were mostly due to hospitalisation costs.

Total extra costs before the guideline update: 1 992*€663 = €1 320 696/year

Total extra costs after the guideline update: 184*€663 = €121 992/year

Total savings after the guideline update: €1 198 704/year (-91%)

Abolishing prophylaxis for patients with eGFR 30-59 ml/min/1.73m2 combined with risk factors and administering it only to patients with eGFR <30 ml/min/1.73m2 has led to an estimated 89% reduction in the number of patients suffering complications of prophylaxis such as symptomatic heart failure (99 cases a year); 93% reduction in the number of hospitalisations for prophylaxis (1 544 a year); and 91% reduction in medical costs (€ 1.2 million a year) at Maastricht UMC+.

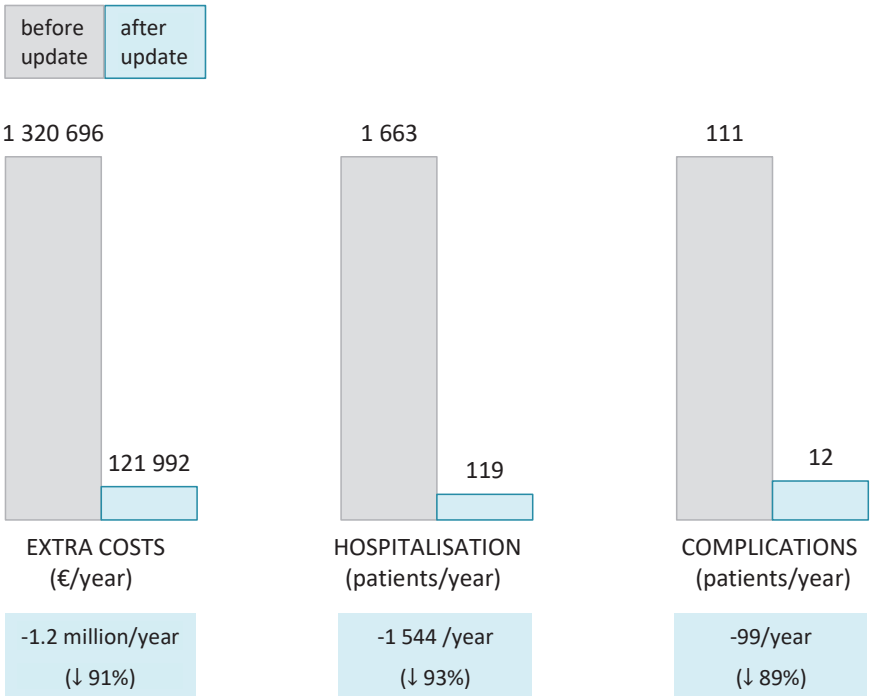


Figure 8.2. Costs, hospitalisations, and complications associated with standard prophylaxis at Maastricht UMC+ before and after guideline updates

8.2 (Inter)national effects

It is estimated that the updated recommendations for prophylaxis save up to 50 to 100 million euro each year in the Netherlands alone.[104] At the same time hospital bed occupancy has been drastically reduced and complications are avoided, relieving patient and hospital burden.

A world impact estimate can be acgueved using calculations as in CINART (detailed under section 8.1 above), although one must adjust for lower adherence to guideline recommendations. Guideline recommendations were imposed quite strictly in the Netherlands which is why adherence is close to 100%, but experience and surveys have shown that elsewhere adherence may be absent (e.g. a hospital in China and a hospital in France; personal communication) or somewhere at the level of 64-87%.[163]

Based on the estimated number of iodinated contrast injections carried out worldwide – estimated at 75 million a year in 2005[2] – and assuming a worldwide average adherence to guideline recommendations of 40% (based on the reported 64-87% adherence in Europe, Oceania and North America, and a worst-case scenario of zero adherence in Africa, South America, and half of Asia), the results estimate would be that over 225 000 patients a year no longer suffer complications such as symptomatic heart failure associated with the prophylactic treatment, that over 3.5 million patients need no longer be hospitalized for prophylaxis, and that savings for health care budgets are over €2.7 billion, each year.

[Note that in these estimations, the number of intravascular injections dates from the year 2005, and the costs are indexed to 2015.]

8.3 Scientific discussion

Besides these societal and individual effects, AMACING has rekindled and changed the scientific discussion around CIN, prophylaxis and clinical practice guidelines. The widespread interest in the subject is reflected in the myriad conference presentations and workshops that have been given by third parties on AMACING, the various editorials in prominent journals, the many medical blogs and news items, and the >1 million followers on Twitter (see Appendix I for an overview and QR access codes). Furthermore, a double publication in Dutch was requested by the Nederlands Tijdschrift voor Geneeskunde (see Appendix II for the full article), a reprint in Chinese was produced by the Lancet, and letters were written to editors of medical journals other than the Lancet, one of which invited us to respond (see keypoints and the full letter in Appendix III).

Not surprisingly, the Lancet article received much attention: PlumXmetrics has so far registered a citation index of 111, and according to Altmetric the article has received more attention than 95% of all publications they have tracked (see Appendix I, numbers 19 & 20). Three Dutch medical professional associations (the Cardiology, Internal Medicine, and Radiological Societies) have nominated AMACING for the 2019 Dutch Association of Medical Specialists Science & Innovation Research Award.

The AMACING publications have contributed toward the fact that guideline-recommendations not backed by scientific evidence are more openly questioned, risk of prophylactic intravenous hydration is given more of the recognition it deserves, and risk of elective iodinated contrast administration is re-evaluated (Appendix I gives links and QR access codes to editorials, news items, tweets, and blogs).

Dr. Mandrola, Medscape:[134] **"Results of the AMACING study force us to 1) be suspicious of expert opinion, 2) object to quality measures not backed by randomized trial data, and 3) reconsider the existence of an entire disease entity (CIN), and in doing so, think about how our brains can trick us into seeing signal when there is mostly noise."**

In the more recent publications on patients with eGFR <30 ml/min/1.73m^2 the discussion is taken even further, introducing the questions whether preventive measures may sometimes be worse than doing nothing, and whether current clinical practice gives sufficient room for individualized precision medicine.[128,135] These two papers have led to changes in clinical practice too.

8.4 Effects for eGFR <30 ml/min/1.73m^2 patients

At Maastricht UMC+ we have translated the results into a new protocol for the prevention of complications of prophylaxis and post-contrast renal events. Patients with eGFR<30 ml/min/1.73m^2 are especially vulnerable, and their relatively low numbers enable us to give them extra attention. In order to do so, a new unit has been set up in December 2018: the Contrast Voorbereidings Poli (CVP) Maastricht UMC+. The first aim of this unit is to prevent serious complications of prophylactic intravenous hydration and eliminate associated deaths. The second aim is to provide 100% post-contrast follow-up of renal function.

Thus, all elective patients with eGFR <30 ml/min/1.73m^2 are seen at the CVP before a contrast procedure, and their cardiac parameters are evaluated in order to determine whether prophylactic treatment can be given. Second, the renal function of all patients with eGFR <30 ml/min/1.73m^2, elective or emergent, who receive intravascular iodinated contrast is checked 2-5 days post-contrast.

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SUMMARY in DUTCH

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NEDERLANDSE SAMENVATTING

Nederlandse samenvatting:

Effectiviteit en kosteneffectiviteit van preventieve intraveneuze hydratie volgens geldende klinische richtlijnen ter voorkoming van contrastnefropathie

Het onderwerp van dit proefschrift is (kosten-) effectiviteit van de klinische richtlijnen voor veilig gebruik van intravasculaire jodiumhoudende contrastmiddelen, in het bijzonder effectiviteit van de geadviseerde preventieve profylactische intraveneuze hydratie.

In de introductie, **hoofdstuk 1**, wordt uitgelegd waarom deze richtlijnen wereldwijd zijn uitgebracht, en wat er voorafging aan de AMACING (A MAastricht Contrast-Induced Nephropathy) studie. Dit bevat onder andere twee eerder publicaties van de Contrast-Induced Nephropathy (CIN, of contrastnefropathie) groep van Maastricht UMC+ (Maastricht Universitair Medisch Centrum): een verkennend onderzoek dat werd gepubliceerd in het tijdschrift Medisch Contact in 2011, en een 'letter to the editor' als reactie op een Nederlandse studie over contrastnefropathie en profylaxe, gepubliceerd in Radiology in 2012. Het hoofdstuk eindigt met een omschrijving van het ontwerp van de AMACING-studie.

Moderne contrastmiddelen zijn relatief inert, toch heeft injectie mogelijk hemodynamische gevolgen. Omdat het contrastmiddel door de nieren wordt geëlimineerd zijn dit de organen die wellicht risico lopen op schade. Dit risico op contrast-geïnduceerde nefropathie (CIN) bestaat vooral voor patiënten met een chronische nierinsufficiëntie. Terwijl CIN meestal binnen een paar weken spontaan oplost, gaat het soms gepaard met een verhoogd langere-termijn risico op dialyse en overlijden.

Richtlijnen voor veilig gebruik van jodiumhoudende contrastmiddelen werden wereldwijd uitgebracht en geïmplementeerd om potentiële nadelige gevolgen van contrastmiddelen voor de nieren te voorkomen. Het hoofdadvies betreft het geven van profylactische intraveneuze hydratie aan hoog-risicopatiënten, ter voorkoming van CIN en lange-termijn morbiditeit en mortaliteit. De profylaxe vereist een ziekenhuisopname

van 8 tot 24 uur. Dit advies heeft een enorme impact op patiënt, ziekenhuis, en zorgkosten, en de profylactische behandeling zelf is niet zonder risico. Echter, er bleek niet echt een wetenschappelijke basis te zijn voor de profylactische intraveneuze hydratie.

In Nederland was de impact extra groot omdat de aanbevelingen werden opgenomen in het door de overheid uitgebrachte VMS-programma om ziekenhuisveiligheid te verbeteren. De richtlijnen werden vrij strikt opgelegd, en opvolgen van de aanbevelingen werd gebruikt als een van de indicatoren voor ziekenhuis kwaliteit en veiligheid.

De CIN-groep Maastricht UMC+ besloot een retrospectieve exploratieve studie te doen onder patiënten die een electieve coronaire angiografie of percutane coronaire interventie ondergingen. Doel was de impact van het implementeren van de door de overheid opgelegde richtlijn op de klinische praktijk te toetsen.

De data maakten meteen duidelijk dat de beddendruk enorm zou toenemen door de nodige opnames voor het geven van profylaxe: vijfmaal in de onderzochte groep. De CIN-incidentie die werd gevonden (2.1%) was echter veel lager dan de literatuur deed verwachten, zelfs onder hoog-risicopatiënten die cf het toen geldende protocol in huis geen profylaxe kregen.

Intussen werd er een Nederlandse studie gepubliceerd waarin de auteurs concludeerden dat de lage CIN-incidentie (2.4%) die zij hadden gevonden aantoonde dat profylaxe goed zou werken. Dit terwijl alle patiënten in het onderzoek profylaxe kregen. In een brief aan de editor wees de CIN-groep er op dat noch positieve noch negatieve effecten van profylaxe naar behoren waren onderzocht, en dat conclusies betreffende effectiviteit niet konden worden getrokken zonder een controlegroep de geen profylaxe kreeg. Daarnaast sprak de groep haar zorgen uit over de complicaties van de profylactische behandeling die optraden tijdens die studie, waarvoor een aantal patiënten zelfs moesten worden opgenomen op de intensive care.

De door de overheid opgelegde richtlijn, het exploratieve onderzoek, en de brief in Radiology legden de basis voor de gerandomiseerde AMACING-studie. Het doel van de studie was een evaluatie van de klinische en kosteneffectiviteit van profylactische intraveneuze hydratie volgens geldende richtlijnen. Dit werd gedaan door hoog-risicopatiënten met en zonder profylaxe met elkaar te vergelijken. Er werd gekozen voor een non-inferioriteitsonderzoek omdat, terwijl geen profylaxe wellicht zou leiden tot een hogere CIN-incidentie, het ook een forse vermindering in belasting voor patiënten, ziekenhuisdruk, en ziektekosten zou betekenen. Daarnaast zou het niet geven van profylaxe ervoor zorgen dat complicaties van de intraveneuze hydratie worden vermeden. Tenslotte, hoewel CIN wordt geassocieerd met een verhoogd risico op morbiditeit en overlijden op langere termijn, lost CIN meestal spontaan binnen een paar weken op, zonder klinisch relevante gevolgen.

Hoofdstukken 2 en 3 bevatten de publicaties van de primaire en lange-termijn resultaten van de AMACING-studie.

Voor de AMACING-studie werden alle 28 803 verwijzingen voor electieve procedures met intravasculair jodiumhoudend contrast in Maastricht UMC+ gedurende een periode van twee jaar prospectief gescreend voor inclusie. 1 120 patiënten voldeden aan de inclusiecriteria (d.w.z. hoog-risicopatiënten volgens de geldende richtlijnen met een geschatte glomerulaire filtratie-snelheid (eGFR) van 30-59 ml/min/1.73m^2 in combinatie met risicofactoren voor CIN). 660 patiënten wilden meedoen aan de studie, en zij werden 1:1 gerandomiseerd naar standaard profylactische intraveneuze hydratie volgens de richtlijnen, of naar geen profylaxe. Uitgaande van een risico op CIN van 2.4% na standaard profylaxe werd een maximale toename van de kans op CIN van 2.1% in de groep zonder profylaxe als acceptabel beschouwd (non-inferioriteitsmarge).

De primaire uitkomsten werden in 2017 gepubliceerd in The Lancet. **Appendix II** bevat de dubbelpublicatie in het Nederlands Tijdschrift voor Geneeskunde van het in 2017 gepubliceerde Lancet artikel.

Het niet geven van profylaxe werd non-inferieur bevonden ten opzichte van standaard profylaxe in de preventive van CIN; er werd geen dialyse of gerelateerd overlijden geregistreerd binnen 1 maand na contrasttoediening; bij 5.5% van de patiënten met profylaxe leidde de intraveneuze hydratie tot klinische complicaties (symptomatisch hartfalen, hartritmestoornissen, en hyponatriëmie); en kosten tot 1 maand na contrast waren ongeveer twee keer zo hoog voor profylaxe patiënten dan bij patiënten die geen profylaxe kregen.

De 1-jaars resultaten werden in 2018 gepubliceerd in het online tijdschrift van The Lancet, EClinicalMedicine. Er werden geen significante verschillen gevonden tussen de twee gerandomiseerde groepen in kans op dialyse, overlijden, verandering in serumcreatinine, of nier-gerelateerde incidenten. De lange-termijn geobserveerde verschillen tussen profylaxe en geen profylaxe waren allen klein en niet significant.

De AMACING gegevens leidde tot de conclusie dat, aannemende dat contrasttoediening wordt geoptimaliseerd, men bij patiënten met een eGFR 30-59 ml/min/1.73m^2 die een electieve procedure ondergaan kan overwegen de profylaxe achterwege te laten, zonder in te leveren op patiëntveiligheid. Hierdoor worden complicaties vermeden, lasten van medische centra en patiënten verlicht, en de ziektekosten verminderd met naar schatting 50-100 miljoen euro per jaar in Nederland.

Hoofdstuk 2 bevat ook een gepubliceerde reactie op ingezonden brieven aan The Lancet. In deze reactie werden de volgende punten benadrukt: zowel spoed/intensive care als eGFR <30 ml/min/1.73m^2 patiënten werden geëxcludeerd, en deze kaders vallen buiten de strekking van de studie; het doel van AMACING was de doelmatigheid van de aanbevelingen van klinische richtlijnen te toetsen, niet het risico van CIN peilen; in de studie werd de klinische praktijk gevolgd, en de bestudeerde populatie bevatte 90% van de patiënten die in aanmerking kwam voor standaard profylaxe volgens de getoetste richtlijnen. In antwoord op de vraag of het voorbarig zou zijn de klinische praktijk nu al te veranderen: zou het verantwoord zijn een behandeling door te zetten die onbewezen is, bewezen risico meebrengt, patiënt en ziekenhuis zo zwaar belast, en zo duur is?

Hoofdstuk 4 omschrijft de vergaande en snelle gevolgen voor de klinische praktijk, en wat die betekenden voor het AMACING project. Vrij snel na de publicatie van de AMACING resultaten werden de richtlijnen geactualiseerd. Profylaxe werd niet langer aanbevolen voor de populatie zoals geïncludeerd in de AMACING gerandomiseerde studie, maar uitsluitend nog voor patiënten met een eGFR <30 ml/min/1.73m^2.

Deze verandering in de richtlijnen werd echter niet geïntroduceerd omdat er wetenschappelijk bewijs was voor de doelmatigheid van profylaxe in deze populatie. Patiënten met een eGFR <30 ml/min/1.73m^2 zijn relatief zeldzaam, en er waren geen gegevens over deze populatie in de context van CIN in de literatuur. Omdat het doel van het AMACING project de evaluatie van profylaxe volgens geldende richtlijnen is, veranderde de focus van het onderzoek door de gewijzigde richtlijnen. Patiënten met een eGFR <30 ml/min/1.73m^2 werden de nieuwe onderzoeks-focus.

Hoofdstuk 5 bevat de publicatie uit 2018 in Investigative Radiology, van een studie waarin de 157 patiënten met eGFR <30 ml/min/1.73m^2 die werden geëxcludeerd van de AMACING gerandomiseerde studie worden vergeleken met de patiënten die meededen aan de studie. Het doel was om te kijken of eGFR <30 ml/min/1.73m^2 patiënten een hoger risico lopen op nadelige gevolgen voor de nieren na contrasttoediening, of profylaxe dit risico vermindert, en of dit effect opweegt tegen de complicaties die profylaxe soms meebrengt.

Incidenties van ongewenste klinische uitkomsten in gehydreerde eGFR 30-59 ml/min/1.73m^2 en eGFR <30 ml/min/1.73m^2 patiënten werden met elkaar vergeleken. Patiënten met een eGFR <30 ml/min/1.73m^2 hadden aanzienlijk hogere incidenties van contrastnefropathie, dialyse en mortaliteit. Dit duidt er op dat deze patiënten inderdaad als hoger-risico kunnen worden gezien. Of profylactische intraveneuze hydratie het risico vermindert kon niet worden afgeleid uit deze dataset omdat de subgroup eGFR <30 ml/min/1.73m^2 patiënten zonder hydratie te klein bleek. In de gehydreerde groep waren complicaties van hydratie aanwezig en aanzienlijk. Het hogere risico op gevolgen na contrast gecombineerd met het risico op complicaties maakt een evaluatie van de doelmatigheid van profylaxe van groot belang.

Het is echter maar de vraag of een gerandomiseerde studie zoals AMACING haalbaar is in deze populatie. Een berekening gebaseerd op de huidige resultaten leidde tot de conclusie dat alle ziekenhuizen in heel Nederland gedurende 2 tot 5 jaar zouden moeten meedoen om een dergelijk studie tot een succes te maken.

In **hoofdstuk 6** wordt de retrospectieve analyse van data van alle electieve procedures met intravasculair jodiumhoudend contrasttoediening over een periode van 4-jaar – van 17 mei 2014 tot 17 mei 2018 - in het Maastricht UMC+ beschreven (Investigative Radiology, 2019). Het doel was inzicht te krijgen in zowel de positieve als de negatieve effecten van profylactische intraveneuze hydratie in hoog-risico patiënten met een eGFR <30 ml/min/1.73m^2, door patiënten die standaard profylaxe kregen te vergelijken met diegenen die geen profylaxe kregen.

Alle 55 474 electieve procedures die gedurende 4 jaar in het Maastricht UMC+ zijn uitgevoerd werden retrospectief gescreend, en dat leverde 362 in aanmerking komende patiënten met eGFR <30 ml/min/1.73m^2 op: 281 met, en 81 zonder profylaxe. De resultaten werden gepresenteerd als odds ratios voor het risico op ongewenste klinische uitkomsten, gecorrigeerd voor potentiële verstorende factoren.

De gecorrigeerde odds ratios waren niet significant, maar puntschattingen duidden er op dat profylaxe mogelijk een beschermend effect had op nierfunctie (CIN, dialyse, en nierfunctieverandering na 1 maand). Voor overlijden binnen 1 maand was het risico verhoogd na profylaxe. Complicaties traden in 6.4% gehydreerde patiënten op, soms gevolgd door de dood. Dit laatste heeft mogelijk bijgedragen aan het verhoogde risico op korte-termijn mortaliteit.

Een vergelijking tussen gehydreerde patiënten met en zonder complicaties leidde tot de conclusie dat complicaties wellicht kunnen worden vermeden wanneer de cardiale parameters van de patiënt zorgvuldig worden geëvalueerd alvorens een besluit over profylaxe te nemen. Ons advies is de cardiale parameters van patiënten zorgvuldig te controleren voor elke procedure met intravasculair jodiumhoudend contrast.

Hoofdstuk 7 geeft een overzicht van de lessen die zijn geleerd door het gelopen AMACING traject. De hoofdbevindingen van alle studies worden doorgenomen, alsook sterke en zwakke aspecten, conclusies en relevantie. Het hoofdtsuk eindigt met ideeën over mogelijk toekomstig onderzoek.

In **hoofdstuk 8** wordt de maatschappelijke en wetenschappelijke impact van de studies besproken. De observationele studie Contrast-Induced Nephropathy After Reduction of the prophylaxis Threshold (CINART) toonde aan dat het actualiseren van de richtlijnen het aantal complicaties door profylaxe vermiderd met 89% (99 gevallen per jaar); het aantal ziekenhuis opnames voor profylaxe terugbrengt met 93% (1 544 bedden per jaar); en een besparing van 91% in medische kosten met zich meebrengt (€ 1.2 miljoen per jaar). Dit zijn de cijfers voor Maastricht UMC+.

Wereldwijd komen we uit op de volgende schattingen: 225 000 minder complicaties zoals symptomatisch hartfalen per jaar, 3.5 miljoen minder ziekenhuisopnames voor profylaxe per jaar, en een jaarlijkse besparing aan zorgkosten van meer dan 2.700.000.000 euro.

Naast deze maatschappelijke en individuele voordelen heeft AMACING ook de wetenschappelijke discussie rondom CIN, profylaxe, en richtlijnen aangewakkerd. De vele en internationale aandacht voor de AMACING studie wordt gereflecteerd in de dubbelpublicatie in het Nederlands Tijdschrift voor Geneeskunde, de door de Lancet gemaakte herdruk in het Chinees, alsook in de lange lijst van editorials, blogs, en nieuws-stukken, en in de meer dan 1 miljoen volgers uit de internationale medische gemeenschap op Twitter in de context van de AMACING publicatie in The Lancet.

De recentere studies onder patiënten met een eGFR <30 ml/min/1.73m^2 hebben ook al geleid tot veranderingen in de dagelijkse klinische praktijk in Maastricht UMC+. Er is een Contrast Voorbereidings Poli opgezet, met het doel de complicaties van profylaxe en de daarmee geassocieerde overlijdens naar nul terug te brengen, en om de opvolging van de nierfunctie van deze patiënten na contrast tot 100% op te voeren.

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I dedicate this thesis to my mother
without whom it, and indeed I, would not be

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We are very proud that three Dutch medical professional associations (the Netherlands Cardiology, Internal Medicine, and Radiological Societies) have nominated the AMACING trial for the Dutch Association of Medical Specialists Science & Innovation Research Award. Thank you for this important recognition and support of our work.

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The longer I write this acknowledgement the more I despair of being able to mention everyone. No (wo)man is an island indeed… Forgive me if your name should be here but isn't, and please know that this reflects my failings and not a lack of appreciation.

ABOUT THE AUTHOR

Biography

Estelle Claire Nijssen was born in Laren, the Netherlands, on Saturday November 7th 1970. She grew up in France, but her secondary and tertiary education was mostly British.

In 1992 she received a Bachelor of Science degree with honours in Biochemistry from Bristol University. She returned to the Netherlands, her nationality proving an insurmountable obstacle to obtaining the national funding necessary for the planned biochemical cooperation between Bristol and Cambridge universities - Europe was not what it is now. Finding similar transnational problems at laboratories in the Netherlands, she decided to start a Dutch Propedeuse in Biology at Utrecht University through evening classes in 1994. This she completed in 1996.

From 1996 to 1997 Estelle obtained a Natuur & Milieu Educatie certificate from Utrecht University, having worked in that capacity on a project for Staatbosbeheer in Driebergen. For this project she and her project partner Serge Calon received an award from the Nederlandse Vereniging Voor Didactiek in de Biologie in 1997.

In the years 1997-1998 Estelle went to the Ivory Coast for a Master thesis on primate behaviour. In the spring of 1999 she received a cum laude Master of Science degree in Biology from Utrecht University. In that same year she received two first prizes for both her research work on *Colobus polykomos* and her thesis on *Callitrichids* from the Gesellschaft für Primatologie, and she was asked to fill in for Dr E.H.M. Sterck as assistant to professor J.A.R.A.M. van Hooff for the Department of Ethology. This work included academic teaching for 2nd, 3rd and final year biology students, and for 4th year students of veterinary sciences.

In the year 2000 the Max Planck Institute for Anthropology accepted a research proposal Estelle submitted on chimpanzee behaviour. That study aimed to compare female cooperation in the chimpanzee population at Tai, Ivory Coast, to that at Kibale, Uganda. For quite a while she worked on that project, based in Leipzig and doing

fieldwork in Africa. Personal matters called her back to the Netherlands before completion of this project however, and the next 7 years were spent working in the family business.

Estelle obtained a place with professor J.E. Wildberger at Maastricht University Medical Centre (UMC+) in the summer of 2012. Her work was for and with the CIN group Maastricht UMC+, an interdisciplinary group with members from the departments of Internal Medicine, Cardiology, and Radiology, who had come together in their worry over current clinical practice guidelines. The task was to evaluate efficacy of clinical practice guidelines on the use of intravascular iodinated contrast material, in particular prophylactic intravenous hydration. This became the current PhD project. Estelle is now a non-medical staff member at the Maastricht UMC+ department of Radiology and Nuclear Medicine.

The CIN group is an interdisciplinary group at Maastricht UMC+. The founding members are from the departments of Radiology, Cardiology, and Internal Medicine. Later, an accomplished epidemiologist from the department of Epidemiology of Maastricht University was asked to join us. For the AMACING trial cost-effectiveness, a specialist from Clinical Epidemiology and Medical Technology Assessment joined the group.

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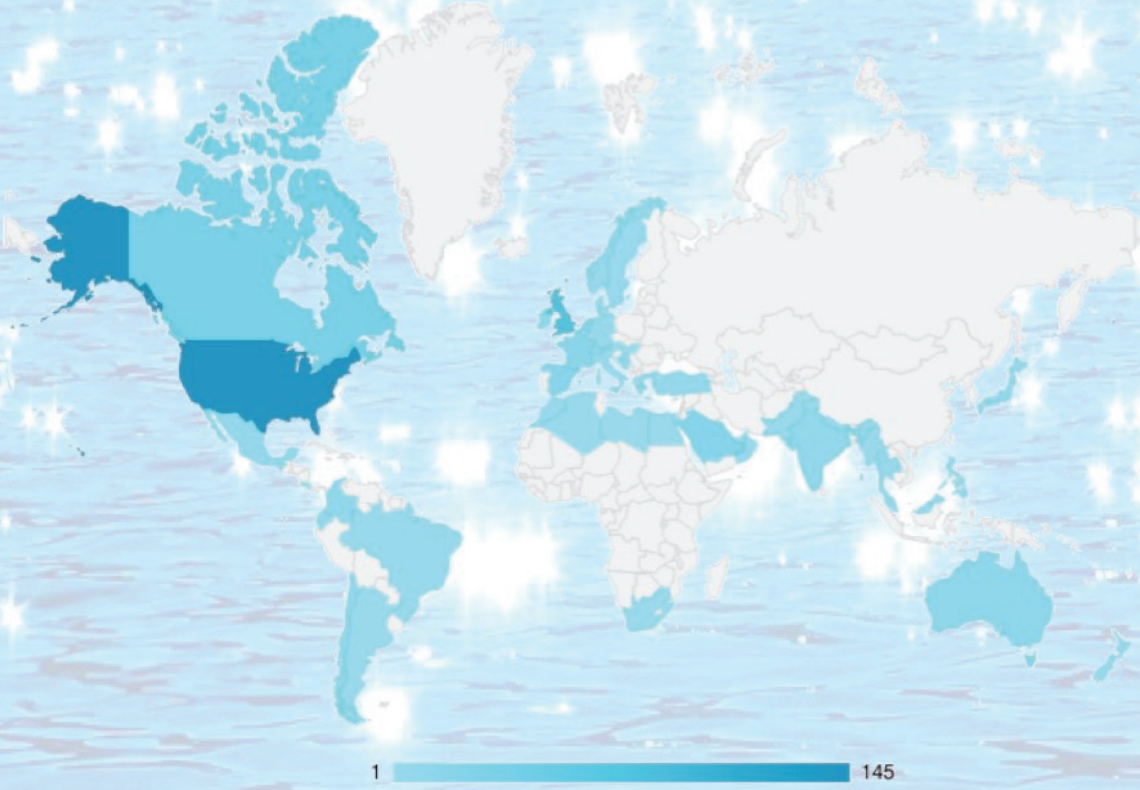
APPENDICES



Twitter demographics

Geographical representation of the attention given to the AMACING trial (source: www.altmetric.com)

APPENDICES

I. **AMACING publications, editorials, letters, guidelines, attention metrics, blogs**

II. **AMACING trial results, double publication in Dutch.** *Nederlands Tijdschrift voor Geneeskunde* 2018;162:14-19.

III. **Letters to the editor of the Journal of Thoracic Disease on the AMACING trial: authors' reply** Intravenous hydration according to current guidelines in the prevention of contrast-induced nephropathy - the AMACING trial. *J Thorac Dis* 2017;9:E656-7.

APPENDIX I.

AMACING Publications, Letters, Editorials, Guidelines, Attention Metrics, and Blogs

PUBLICATIONS OF AMACING RESULTS

1. Primary results AMACING RCT: the Lancet

   https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)30057-0/fulltext

2. Double publication in Dutch: Nederlands Tijdschrift voor Geneeskunde
   https://www.ntvg.nl/artikelen/preventieve-intraveneuze-hydratie-ter-voorkoming-van-contrastnefropathie-helpt-niet/icmje

3. 1-year follow-up results AMACING RCT: EClinicalMedicine by the Lancet
   https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(18)30044-0/fulltext

4. Comparison excluded eGFR <30 ml/min/1.73m^2 patients to AMACING RCT participants: Investigative Radiology
   https://journals.lww.com/investigativeradiology/fulltext/2018/10000/Evaluation_of_Safety_Guidelines_on_the_Use_of.7.aspx

5. Prophylaxis vs. no prophylaxis in eGFR <30 ml/min/1.73m^2 patients: Investigative Radiology

   https://www.doi.org/10.1097/RLI.0000000000000570

LETTERS TO THE EDITOR ON THE AMACING TRIAL

6. Letters to the editor of The Lancet

   https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31811-1/fulltext

   https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31812-3/fulltext

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31815-9/fulltext

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31814-7/fulltext

Authors'reply, The Lancet

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31809-3/fulltext

7. Journal of Thoracic Disease

Letters to the editor

http://jtd.amegroups.com/article/view/13849/11563

http://jtd.amegroups.com/article/view/13816/11564

Authors'reply

http://jtd.amegroups.com/article/view/14504/html

EDITORIALS ON THE AMACING TRIAL

8. The Lancet

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)30540-8/fulltext

9. Kidney International

https://www.kidney-international.org/article/S0085-2538(17)30245-4/pdf

10. Annals of Internal Medicine

http://annals.org/aim/article-abstract/2632350/adults-risk-contrast-induced-nephropathy-prophylactic-hydration-noninferior-hydration

11. American College of Cardiology

https://www.acc.org/latest-in-cardiology/clinical-trials/2017/04/11/15/18/amacing

12. Nederlands Tijdschrift voor Geneeskunde

https://www.ntvg.nl/artikelen/hydratie-ter-preventie-van-contrastnefropathie

13. National Medical Journal of India

http://www.nmji.in/article.asp?issn=0970-258X;year=2017;volume=30;issue=5;spage=272;epage=273;aulast=Bahet i

14. Medscape 1, Dr. Mandrola

https://www.medscape.com/viewarticle/876852

15. Medscape 2

https://www.medscape.com/viewarticle/876521

16. Nursing

https://www.nursing.nl/magazine-artikelen/vocht-toedienen-voor-onderzoek-met-contrast-nodig-of-niet-nodig/

AMACING TRIAL PROTOCOL

17. ClinicalTrials.gov
https://clinicaltrials.gov/ct2/show/NCT02106234

CLINICAL PRACTICE GUIDELINES WITH SPECIAL MENTION/ REVIEW OF AMACING

18. **NL:** NVvR Guideline update (AMACING: p.58-59 & p.69-70)

    https://www.radiologen.nl/kwaliteit/richtlijnen-veilig-gebruik-van-contrastmiddelen

19. **UK:** Exceptional review of AMACING trial results & NICE Guideline update

    https://www.nice.org.uk/guidance/cg169/resources/surveillance-report-exceptional-review-2017-acute-kidney-injury-prevention-detection-and-management-2013-nice-guideline-cg169-4666260925/chapter/Surveillance-decision?tab=evidence

20. **Europe:** ESUR Guideline update (AMACING: p.2859)

    https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5986837/

PUBLIC RECEPTION : ATTENTION MERICS

21. Plum X Metrics

    https://plu.mx/plum/a/?doi=10.1016%2FS0140-6736%2817%2930057-0&theme=plum-jbs-theme&hideUsage=true&display-tab=summary-content

22. Altmetric attention scores

    https://www.altmetric.com/details/16569356#score

23. Twitter attention for the Lancet article

    https://www.altmetric.com/details/16569356/twitter

MEDICAL BLOGS ON THE AMACING TRIAL

24. Think Kidneys

    https://www.thinkkidneys.nhs.uk/aki/blog/first-do-no-harm-what-now-for-contrast-induced-aki-prophylaxis/

25. RebelEM

    http://rebelem.com/the-amacing-trial-prehydration-to-prevent-contrast-induced-nephropathy-cin/

26. TCTMD

    https://www.tctmd.com/news/no-iv-hydration-contrast-nephropathy-amacing-trial-challenges-cornerstone-prophylaxis

27. PharmacoEconomics & Outcomes News

    https://link.springer.com/article/10.1007/s40274-017-3792-3

28. Fan of EM

    https://fanofem.nl/2017/04/14/amacing-het-einde-van-de-contrastnefropathie/

29. Emergency Literature

    https://www.emlitofnote.com/?p=3807

30. The Bottom Line

    http://www.thebottomline.org.uk/summaries/icm/amacing/

31. Clinical Correlations

    https://www.clinicalcorrelations.org/2018/05/16/core-im-5-pearls-on-contrast-induced-nephropathy/

32. Renal Fellow network 1

    https://www.renalfellow.org/2018/10/18/contrast-and-aki-the-plot-thickens/

33. Renal Fellow network 2

https://www.renalfellow.org/2018/03/19/chronic-kidney-disease-for-medica/

34. AJKD Blog - Nephmadness

https://ajkdblog.org/2018/03/15/nephmadness-2018-contrast-region/

35. Hindawi

https://www.hindawi.com/journals/ijn/2018/5727309/

36. Nephron power

http://www.nephronpower.com/2017/03/amacing-trial-fluids-vs-no-fluids-for.html

37. Dasfoam

https://dasfoam.org/2018/06/30/nierenversagen-durch-kontrastmittel-gibts-nicht/

APPENDIX II. AMACING Trial Results, Double Publication in Dutch.

Nijssen EC, Rennenberg RJ, Nelemans PJ, Essers BA, Janssen MA, Vermeeren MA, van Ommen GV, Wildberger JE. Preventieve intraveneuze hydratie ter voorkoming van contrastnefropathie helpt niet. *Nederlands Tijdschrift voor Geneeskunde* 2018;162:14-19.

Preventieve intraveneuze hydratie ter voorkoming van contrastnefropathie helpt niet

Estelle C Nijssen, Roger J Rennenberg, Patty J Nelemans, Brigitte A Essers, Marga M Janssen, Marja A Vermeeren, Vincent van Ommen, Joachim E Wildberger

*Dit onderzoek werd eerder gepubliceerd in The Lancet (2017;389:1312-22) met als titel '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, noninferiority trial'. Afgedrukt met toestemming.

Samenvatting

Doel Het onderzoeken van de effectiviteit en kosteneffectiviteit van de geldende klinische richtlijnen, met name preventieve profylactische intraveneuze hydratie bij hoog-risicopatiënten, ter voorkoming van potentiële nierinsufficiëntie na intravasculair gebruik van jodiumhoudende contrastmiddelen (contrastnefropathie).

Opzet Prospectief, gerandomiseerd, niet geblindeerd non-inferioriteitsonderzoek.

Methode In dit onderzoek werden hoog-risicopatiënten geïncludeerd die een electieve procedure met intravasculair contrastmiddel ondergingen en die werden doorverwezen voor preventieve intraveneuze hydratie. Hoog risico op contrastnefropathie was gedefinieerd als een eGFR 30-44 ml/min/1,73m^2 of een eGFR 45-59 ml/min/1,73m^2 in combinatie met diabetes mellitus of ≥ 2 risicofactoren (leeftijd > 75 jaar, hart- en/of vaatlijden, gebruik van nefrotoxische medicatie, anemie). Patiënten die spoedinterventies moesten ondergaan, IC-patiënten, dialyse patiënten en patiënten met een eGFR < 30 ml/min/1,73m^2 werden geëxcludeerd. De serumcreatinineconcentratie werd vooraf, 2-6 en 26-35 dagen na contrasttoediening gemeten. Contrastnefropathie werd gedefinieerd als een stijging in de serumcreatinineconcentratie van > 25% of > 44 µmol/l, 2-6 dagen na contrast-toediening. De studie werd geregistreerd bij ClinicalTrials.gov (NCT02106234).

Resultaten In de periode 17 juni 2014-17 juli 2016 werden 28 803 electieve patiënten gescreend. 660 opeenvolgende hoog-risicopatiënten werden gerandomiseerd naar geen profylaxe (H-; n = 332) of standaard intraveneuze hydratie (H+; n = 328). De incidentie van contrastnefropathie was 2.6% in de H- groep, versus 2.7% in de H+ groep (verschil: -0.10%; 95%-BI: -2.25 tot 2.06). Het achterwege laten van profylaxe was in alle gevallen kostenbesparend. Er werd geen dialyse of aan het onderzoek gerelateerd overlijden geregistreerd binnen 35 dagen na contrasttoediening. De intraveneuze hydratie leidde bij 5.5% van de patiënten tot klinische complicaties.

Conclusie Geen profylaxe werd non-inferieur en kostenbesparend bevonden ten opzichte van standaard intraveneuze hydratie volgens geldende richtlijnen ter voorkoming van contrastnefropathie.

Leerpunten

- Na het toedienen van intravasculair jodiumhoudend contrast kan een acute serumcreatininestijging optreden (contrastnefropathie).
- Patiënten met contrastnefropathie hebben verhoogde morbiditeit en mortaliteit.
- Intraveneuze hydratie wordt gegeven als profylaxe voor contrastnefropathie, maar is kostbaar en niet zonder risico, speciaal voor de hoog-risicopatiënten die er volgens de richtlijnen voor in aanmerking komen.
- Contrastnefropathie is zeldzaam bij patiënten die electieve procedures met contrasttoediening ondergaan.
- Hoog-risicopatiënten die geen intraveneuze hydratie kregen bij electieve procedures hadden geen hogere incidentie van contrastnefropathie dan de groep die de profylaxe wel kreeg.
- Bij de deelnemers aan dit prospectieve, gerandomiseerde onderzoek werden geen klinisch relevante consequenties waargenomen van het achterwege laten van preventieve intraveneuze hydratie.

Introductie

Na intravasculaire toediening van een jodiumhoudend contrastmiddel kan een stijging van de serumcreatinineconcentratie optreden.[106] Het risico op deze achteruitgang in de nierfunctie, contrastnefropathie genoemd, is groter bij patiënten die al een verminderde nierfunctie hebben.[1] Contrastnefropathie is meestal tijdelijk van aard, maar wordt in verband gebracht met een verhoogd risico op dialyse en overlijden.[106-108]

Er zijn nationale en internationale richtlijnen opgesteld om contrastnefropathie te voorkomen.[70,75] In Nederland werd dit thema in 2009 op de kaart gezet door het VMS Veiligheidsprogramma onder de titel 'Voorkomen van nierinsufficiëntie bij intravasculair gebruik van jodiumhoudende contrastmiddelen'.[75] Op geleide van deze richtlijnen moeten patiënten met een verhoogd risico op contrastnefropathie preventieve intraveneuze hydratie krijgen vóór en na contrasttoediening; hiervoor moeten zij 8 tot 24 uur worden opgenomen in het ziekenhuis. Dit betreft naar schatting jaarlijks 100 000 tot 150 000 patiënten in Nederland.[90]

Strikte naleving van dit protocol heeft grote consequenties voor de klinische praktijk van screening, opname en behandeling van patiënten, alsook voor de kosten van de zorg.[80] Naleving van het protocol is een van de kwaliteitsindicatoren op basis waarvan ziekenhuizen worden beoordeeld. De richtlijnen werden voornamelijk gebaseerd op consensus van experts, omdat er relatief weinig bekend is over de werking van intraveneuze hydratie als preventie van contrastnefropathie.[28] Ook het onderliggende mechanisme van contrastnefropathie is niet volledig duidelijk.

De effectiviteit van de preventiemaatregel werd nooit eerder vastgesteld in een gedegen gerandomiseerd onderzoek waarin de hoog-risicopopulatie waarvoor de richtlijnen werden opgesteld werd vergeleken met een groep die geen profylaxe kreeg. De incidentie van contrastnefropathie zonder profylaxe is onbekend. Verder is intraveneuze hydratie zelf niet zonder risico.[114] Dit artikel is een verkorte weergave van onze non-inferioriteitsstudie genaamd AMACING (dit staat voor: 'A MAastricht Contrast-Induced Nephropathy Guideline study'), die eerder werd gepubliceerd in The Lancet.[104]

Nederlands Tijdschrift voor Geneeskunde

In de AMACING-studie onderzochten wij of het verantwoord is de profylactische intraveneuze hydratie achterwege te laten bij patiënten die intravasculair contrastmiddel toegediend krijgen. In deze studie werd ook gekeken naar de klinische complicaties en de kosten van de profylaxe.

Methode

Studieopzet

De AMACING-studie was opgezet als een prospectieve, gerandomiseerde, niet-geblindeerde non-inferioriteitsstudie, met als doel de evaluatie van de veiligheid, effectiviteit en kosteneffectiviteit van de richtlijnen ter preventie van contrastnefropathie, met name de preventieve intraveneuze hydratie. Tot de keuze voor een non-inferioriteitsopzet kwamen wij door de aanname dat het niet geven van profylaxe weliswaar misschien zou kunnen leiden tot een hogere incidentie van contrastnefropathie, maar ook gepaard zou kunnen gaan met een vermindering van complicaties als gevolg van de intraveneuze hydratie, en van zorgkosten. Een lichte stijging in de incidentie van contrastnefropathie werd acceptabel geacht, omdat de stijging van de creatinineconcentratie in de meeste gevallen van tijdelijke aard is en gevolgen op langere termijn, zoals dialyse en overlijden, zeldzaam zijn.[20,18] Op basis van de literatuur werd geschat dat de incidentie van contrastnefropathie na contrasttoediening met intraveneuze hydratie 2.4% bedroeg; een toename in de incidentie van 2.1% werd acceptabel geacht (dit is de non-inferioriteitsmarge). De studie werd geregistreerd bij ClinicalTrials.gov (NCT02106234).

Populatie

Patiënten die werden doorverwezen voor een electieve procedure met intra-arterieel of intraveneus jodiumhoudend contrast konden worden geïncludeerd als zij voldeden aan een van de volgende criteria: eGFR 45-59 ml/min/1.73m^2 in combinatie met diabetes mellitus of ≥ 2 risicofactoren (leeftijd >75 jaar, hart- en/of vaatlijden, gebruik van nefrotoxische medicatie, anemie); eGFR 30-44 ml/min/1.73m^2 ; lijdend aan de ziekte van Kahler of de ziekte Waldenström met uitscheiding van lichte ketens in de urine. Deze criteria komen overeen met die voor hoog-risicopatiënten volgens de richtlijnen.

Exclusiecriteria waren een eGFR <30 ml/min/1.73m^2, spoed of de noodzaak tot intensive care, dialyse, geen verwijzing voor preventieve hydratie, niet kunnen afgeven van informed consent, niet kunnen meewerken aan de bepaling van de serumcreatinineconcentratie 2-6 dagen na toediening van contrast, of deelname aan een andere gerandomiseerde studie. De eGFR werd berekend met de MDRD-formule.

Randomisatie

Hoog-risicopatiënten werden 1:1 gerandomiseerd naar standaard intraveneuze hydratie volgens de richtlijnen (H+ groep) of geen profylaxe (H- groep). De randomisatie gebeurde met een computerprogramma (ALEA, v3.0.2083.212r; Formsvision BV, Abcoude) en werd gestratificeerd op wel of geen diabetes mellitus, wel of geen eGFR <45 ml/min/1.73m^2, wel of geen procedure met interventie, en op de toedieningsroute van het contrastmiddel (intra-arterieel of intraveneus).[116] De studie was niet geblindeerd, maar de serumcreatinineconcentratie – de primaire uitkomstmaat – werd gemeten door personeel dat niet op de hoogte was van de randomisatiestatus van de patiënten.

Procedures

Intraveneuze hydratie werd gegeven volgens de richtlijnen beschreven in het veiligheidsmanagementsysteem (VMS).[75] De behandelend arts kon hiervan afwijken als daar medische redenen voor waren. De tijdsduur en de snelheid van de intraveneuze hydratie werden aan het begin en einde van elke intraveneuze hydratiesessie geregistreerd. Details van contrastprocedures (tijdstip, contrasttype, contrastvolume, toedieningsroute, toegediende medicatie, ongewenste voorvallen) werden geregistreerd ten tijde van de procedure. Alle patiënten kregen voorverwarmde jopromide (37^{o}C) intravasculair toegediend (300 mg jodium/ml). De serumcreatinineconcentratie werd vooraf 2-6 en 26-35 dagen na contrasttoediening bepaald. Wijzigingen in de medicatie, ongewenste voorvallen en het middelengebruik – inclusief opname, infuuszakjes, consulten et cetera – werden systematisch geregistreerd op alle meetmomenten.

Uitkomstmaten

Omdat de richtlijnen als doel hebben contrastnefropathie te voorkomen, waren de primaire uitkomstmaten het verschil in de incidentie van contrastnefropathie tussen beide groepen en de kosteneffectiviteit van geen profylaxe vergeleken met standaard preventieve intraveneuze hydratie. Contrastnefropathie werd gedefinieerd als een stijging van de serumcreatinineconcentratie met >25% of > 44µmol/l ten opzichte van de uitgangswaarde binnen 2-6 dagen na contrasttoediening. Secundaire uitkomstmaten waren de gemiddelde verandering in de serumcreatinineconcentratie 2-6 en 26-35 dagen na contrasttoediening, en ernstige ongewenste voorvallen (overlijden, dialyse, opname op de IC, complicaties van intraveneuze hydratie, en achteruitgang van de nierfunctie). Achteruitgang van de nierfunctie werd als volgt gedefinieerd: nierfalen (eGFR < 15 ml/min/1.73m^2), een achteruitgang met >10 eGFR-eenheden, een achteruitgang tot een eGFR <30 ml/min/1.73m^2, of een combinatie van deze twee laatste criteria, op 26-35 dagen na contrasttoediening. Complicaties van intraveneuze hydratie waren symptomatisch hartfalen, hypernatriëmie of hyponatriëmie, en hartritmestoornissen.

Statistische analyse

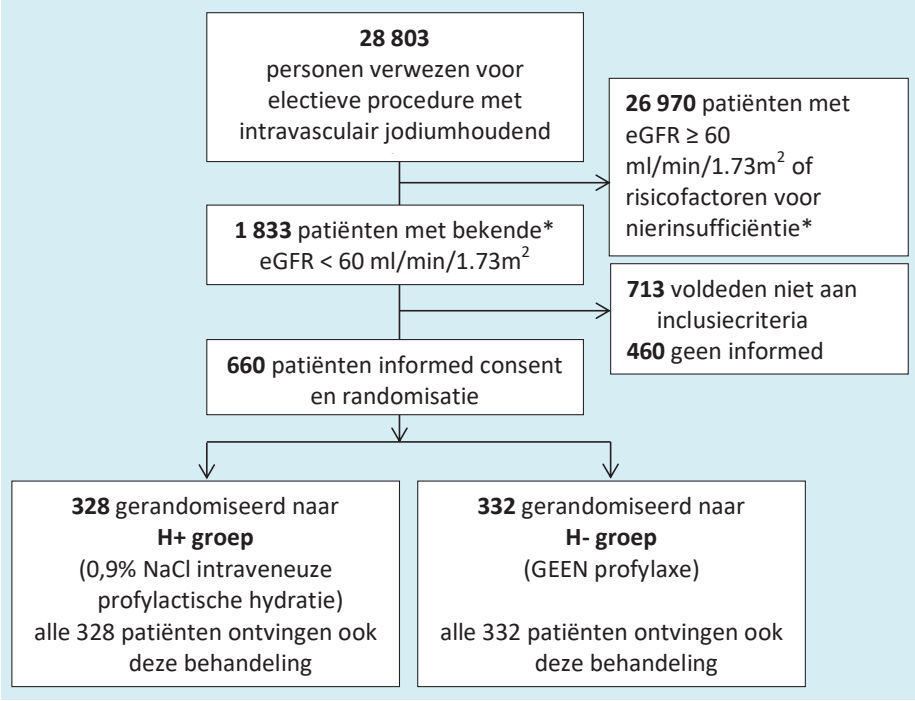
Het absolute verschil in de percentages patiënten met contrastnefropathie tussen de twee gerandomiseerde groepen (dat wil zeggen: het percentage patiënten met contrastnefropathie in de H- groep minus dat het percentage in de H+ groep) werd berekend met een eenzijdig 95% -betrouwbaarheidsinterval van het verschil.

Bij de kostenberekening werd ‘multiple imputation’ gebruikt voor ontbrekende gegevens. De ‘bootstrap’ methode (1 000 replicaties) werd gebruikt om de onzekerheid rond het verschil in gemiddelde kosten te schatten. Gebruikte kostprijzen kwamen uit de Nederlandse Kostenhandleiding of werden opgevraagd bij de ziekenhuis-administratie.[117]

De χ^2-toets en Student’s t-toets werden gebruikt voor het vergelijken van secundaire uitkomstmaten tussen de twee groepen. Een p-waarde van 0.05 of minder werd als significant beschouwd. Wij deden zowel intention-to -treat- als per-protocol-analyses.

Resultaten

In de periode 17 juni 2014 - 17 juli 2016 werden in totaal 28 803 patiënten gescreend. Bij 1 833 patiënten was de eGFR <60 ml/min/1.73m^2. 1 120 patiënten voldeden aan alle inclusiecriteria, en 660 (59%) van hen tekenden het informed consent. Deze patiënten werden gerandomiseerd naar standaard intraveneuze hydratie (n =328) en naar geen profylaxe (n = 332) (figuur). De gemiddelde leeftijd was 72.2 jaar (SD: 9.3), 407 van de 660 deelnemers (62%) waren man, 57 van de 660 (9%) waren voorafgaand aan de inclusie opgenomen in een ziekenhuis, en 215 van de 660 patiënten (33%) hadden diabetes mellitus. Het toegediende contrastvolume was gemiddeld 91 ml (SD: 41 ml).

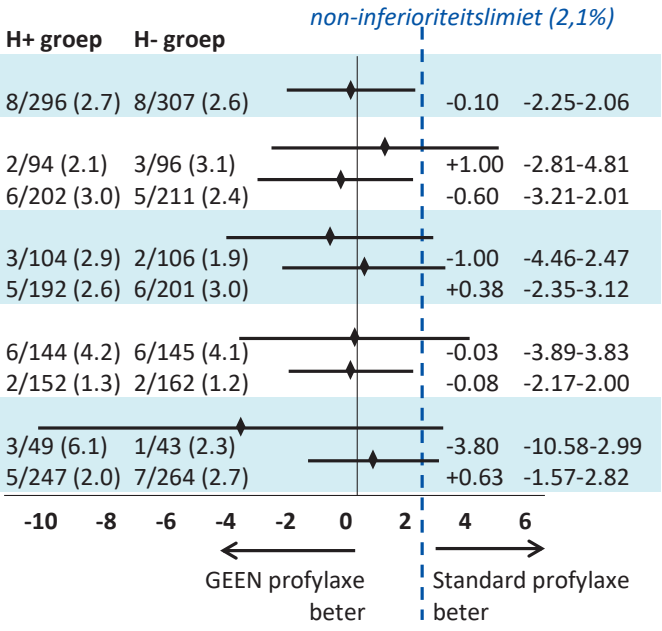


Figuur Stroomschema voor de inclusie en randomisatie van patiënten in een non-inferioriteitsstudie naar het effect van preventieve veneuze hydratie als profylaxe voor contrastnefropathie (de AMACING-studie). *De nierfunctie werd bepaald bij patiënten met ten minste 1 risicofactor voor nierinsufficiëntie, conform de CBO-richtlijn. MUMC = Maastricht University Medical Centre; eGFR = geschatte glomerulaire filtratiesnelheid.

Van 603 patiënten (91%) was de serumcreatinineconcentratie 2-6 dagen na contrasttoediening bekend. De redenen voor uitval waren vooral logistiek van aard, en niet gerelateerd aan de toegewezen behandeling. Contrastnefropathie, gedefinieerd als een stijging van de serumcreatinineconcentratie met >25% of >44 µmol/l, werd geconstateerd bij 8 van 296 patiënten (2.7%) in de H+ groep, en bij 8 van 307 patiënten (2.6%) in de H- groep (tabel). Het absolute verschil in incidentie tussen de groepen was -0.10% (H- groep minus H+ groep), met een eenzijdig 95%-BI van -2.25 tot 2.06. De bovengrens van het betrouwbaarheidsinterval (2.06%) was lager dan de vooraf bepaalde non-inferioriteitsmarge van 2.1%. Het achterwege laten van profylaxe is daarom niet inferieur aan de standaard intraveneuze hydratie. De resultaten van de vooraf geplande subgroep analyses worden weergegeven in de tabel.

Tabel Incidentie contrastnefropathie bij patiënten die wel of geen preventieve intraveneuze hydratie kregen, in de totale onderzoekspopulatie en per subpopulatie

populatie	**aantal**	**incidentie contrastnefropathie* n/N (%)**		**absoluut verschil; %**	**95%-BI**
		H+ groep	**H- groep**		
totale populatie	603	8/296 (2.7)	8/307 (2.6)	-0.10	-2.25-2.06
diabetes mellitus					
ja	190	2/94 (2.1)	3/96 (3.1)	+1.00	-2.81-4.81
nee†	413	6/202 (3.0)	5/211 (2.4)	-0.60	-3.21-2.01
eGFR< 45					
ja	210	3/104 (2.9)	2/106 (1.9)	-1.00	-4.46-2.47
nee	393	5/192 (2.6)	6/201 (3.0)	+0.38	-2.35-3.12
contrasttoediening					
IA	289	6/144 (4.2)	6/145 (4.1)	-0.03	-3.89-3.83
IV	314	2/152 (1.3)	2/162 (1.2)	-0.08	-2.17-2.00
interventie procedure					
ja	92	3/49 (6.1)	1/43 (2.3)	-3.80	-10.58-2.99
nee	511	5/247 (2.0)	7/264 (2.7)	+0.63	-1.57-2.82



De kosten per patiënt in de H+ groep waren gemiddeld 663 euro hoger dan in de H- groep (95%-BI van kosten H- groep minus H+ groep: -1234 tot -191). Het achterwege laten van profylaxe gaat gepaard met een significante kostenbesparing ten opzichte van standaard intraveneuze hydratie. De waargenomen daling in de kosten is grotendeels toe te schrijven aan een vermindering van de kosten voor dagbehandeling en ziekenhuisopname. Kosten naar aanleiding van complicaties van de intraveneuze hydratie en verlies aan productiviteit droegen in mindere mate bij aan het verschil in gemiddelde kosten. Verslechtering van de nierfunctie leidde in geen van beide groepen tot extra kosten binnen 35 dagen.

De gemiddelde verandering in de serumcreatinineconcentratie 2-6 dagen na contrasttoediening was 0.31 µmol/l (SD: 13.79) in de H+ groep, en 1.30 µmol/l (SD: 15.09) in de H- groep (p = 0.4049).

Van 520 patiënten (79%) was bekend wat de serumcreatinineconcentratie 26-35 dagen na contrasttoediening was. De uitval van patiënten was voornamelijk om logistieke redenen en hield geen verband met de toegewezen behandeling. De gemiddelde verandering in de serumcreatinineconcentratie 26-35 dagen na contrasttoediening was 1.44 µmol/l (SD: 17.10) in de H+ groep, en 1.39 µmol/l (SD: 16.12) in de H- groep (p = 0.9705).

Complicaties en ongewenste voorvallen

Nierfalen, dialyse, opname op de IC of overlijden dat gerelateerd was aan de toediening van contrastmiddel werden niet waargenomen binnen 35 dagen na de contrasttoediening. Wel overleden 3 patiënten in de H- groep aan ongerelateerde oorzaken (hartstilstand bij een terminale patiënt met kanker, ruptuur van een aneurysma, en een hartinfarct bij een patiënt die was opgenomen voor ernstige sepsis).

Een achteruitgang van de nierfunctie met >10 eGFR-eenheden werd geregistreerd bij 7/260 patiënten (2.7%) in de H+ groep en bij 11/260 patienten (4.2%) in de H- groep (p = 0.3512); een achteruitgang tot een eGFR <30 ml/min/1.73m^2 trad op bij 7/260 (2.7%)

H+ patiënten en bij 6/260 (2.3%) H- patiënten (p = 0.7881); een combinatie van deze twee maten voor de achteruitgang zagen wij bij 2/260 (0.8%) H+ patiënten en bij 2/260 (0.8%) H- patiënten.

In de H+ groep kregen 18 van de 328 patiënten (5.5%) complicaties als gevolg van intraveneuze hydratie; bij 13 van hen betrof het symptomatisch hartfalen (4.0%), bij 1 hyponatriëmie (0.3%), en bij 4 hartritmestoornissen (1.2%). Dergelijke complicaties werden niet waargenomen in de H- groep.

Beschouwing

Belangrijkste uitkomsten

De incidentie van contrastnefropathie was nagenoeg gelijk in beide groepen (2.6% versus 2.7%). Geen profylaxe werd non-inferieur en kostenbesparend bevonden ten opzichte van de standaard intraveneuze hydratie volgens de geldende richtlijnen voor de preventie van contrastnefropathie. Een maand na contrasttoediening waren de verschillen in de achteruitgang van de nierfunctie tussen de twee groepen minimaal en statistisch niet significant. Intraveneuze hydratie leidde tot complicaties bij 5.5% van de patiënten.

Vergelijking met ander onderzoek

Hoewel er veel studies over de preventie van contrastnefropathie gepubliceerd zijn, werden deze meestal in zeer specifieke klinische settings uitgevoerd. Ons onderzoek is zover wij weten de eerste gerandomiseerde studie waarin de standaard preventieve intraveneuze hydratie, zoals aanbevolen in de huidige richtlijnen, wordt vergeleken met het achterwege laten van de profylaxe bij de hoog-risicopopulatie. In tegenstelling tot andere studies werden in de AMACING-studie alle electieve procedures met intravasculair jodiumhoudend contrast meegenomen (intra-arterieel en intraveneus), en vrijwel de gehele hoog-risicopopulatie waarvoor de richtlijnen waren opgesteld.

Beperkingen

Deze studie werd uitgevoerd in één enkel ziekenhuis, maar het MUMC+ is wel een lokaal en regionaal centrum en hanteert landelijke standaarden. De studiepopulatie was kleiner dan oorspronkelijk geraamd. De bovengrens van het 95%-BI, dat de onzekerheid rond de resultaten weergeeft, ligt echter onder de non-inferioriteitsmarge van 2.1%. De bevindingen steunen daarom onze hypothese dat het achterwege laten van de profylaxe niet onderdoet voor intraveneuze hydratie. Patiënten met een eGFR <30 ml/min/1.73m^2 werden niet geïncludeerd; dit zijn de enige electieve patiënten die wel in aanmerking kwamen voor intraveneuze hydratie volgens de richtlijnen maar niet werden meegenomen in deze studie. Dit waren in totaal slechts 157 patiënten (0.5% van de totale populatie). Ook werden patiënten die met spoed onderzoek met contrasttoediening moesten ondergaan en patiënten op de IC niet meegenomen in ons onderzoek. Onze resultaten kunnen daarom niet worden gegeneraliseerd naar deze patiëntengroepen.

Consequenties voor de praktijk

De consequenties van onze bevindingen kunnen belangrijk zijn voor de praktijk. Geen profylaxe is niet inferieur aan preventieve intraveneuze hydratie, en complicaties van intraveneuze hydratie kunnen worden vermeden. Bij patiënten met een eGFR >29 ml/min/1.73m^2 die een electieve procedure ondergaan, kan men daarom overwegen de profylaxe achterwege te laten. Het achterwege laten van standaard preventieve intraveneuze hydratie kan leiden tot aanzienlijke lastenverlichting voor zowel medische centra als patiënten en tot een kostenbesparing die in Nederland naar schatting kan oplopen tot 100 miljoen euro per jaar.

Belangenconflict en financiële ondersteuning

Deze studie werd gefinancierd door een donatie van Stichting de Weijerhorst.

APPENDIX III.
Letters to the Editor of the Journal of Thoracic Disease on the AMACING Trial: Authors' Reply

Two letters were written to the Journal of Thoracic Disease in response to the AMACING Lancet publication (see Appendix I nr. 7 for QR access codes):

Sato A, Hoshi T, Aonuma K. No prophylaxis is non-inferior and cost-saving to prophylactic intravenous hydration in preventing contrast-induced nephropathy on requiring iodinated contrast material administration. *J Thorac Dis 2017;9:1440-1442* and

Raje V, Feldman G, Jovin IS. Diagnosing and treating contrast-induced acute kidney injury in 2017. *J Thorac Dis 2017;9:1443-1445*.

We were invited to respond - our response is given on the next page.

Authors' Reply: *Nijssen EC, Nelemans PJ, Rennenberg RJ, Essers BA, Janssen MM, Vermeeren MA, van Ommen GV, Wildberger JE.* Intravenous hydration according to current guidelines in the prevention of contrast induced nephropathy—the AMACING trial. *J Thorac Dis 2017;9: E656-E657*.

doi: https://doi.org/10.21037/jtd.2017.06.80

Key points

- **See comments 1-4 from the Lancet letters (section 2.3):** Similar comments were made in the JTD letters, and similar answers were given in the authors' reply.
- **Comment:** Large, multi-centre trials are required before changing standard care.
  Reply: Given the non-existent difference intravenous hydration made in the incidence of CIN, and especially given the 5.5% patients that had serious complications of intravenous hydration, we cannot agree. The burden of proof must be with intravenous prophylactic hydration and not with no-prophylaxis. We would also counter with the question whether it is ethical to continue giving a treatment that is unproven, carries proven risks, confers significant burden upon patient and hospital, and is so costly.

Intravenous hydration according to current guidelines in the prevention of contrast induced nephropathy—the AMACING trial

Estelle C Nijssen, Patty J Nelemans, Roger J Rennenberg, Brigitte A Essers, Marga M Janssen, Marja A Vermeeren, Vincent van Ommen, Joachim E Wildberger

Provenance: This is an invited Letter to the Editor commissioned by Section Editor Dr. Zhongheng Zhang (Department of Emergency Medicine, Sir Run-Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China).

Response to: Raje V, Feldman G, Jovin IS. Diagnosing and treating contrast-induced acute kidney injury in 2017. J Thorac Dis 2017;9:1443-5. Sato A, Hoshi T, Aonuma K. No prophylaxis is non-inferior and cost-saving to prophylactic intravenous hydration in preventing contrast-induced nephropathy on requiring iodinated contrast material administration. J Thorac Dis 2017;9:1440-2.

Authors' reply

We thank Vikram Raje and Akira Sato and colleagues for their interest in our work. To put the AMACING trial into perspective, the guideline on contrast-induced nephropathy (CIN) is one of ten measures to increase patient safety in the Netherlands. Since their introduction and to date, the ten measures have been imposed on hospitals quite strictly, and compliance to these is part of the annual hospital quality assessment carried out by government instances. However, the intravenous hydration to prevent CIN was introduced without its effect having been proven, and its implementation incurs risk of clinical complications as well as increased health care costs.

The aim of the AMACING trial was to evaluate the current guidelines and it was designed to that end.[104] The core question was not about the absolute risk of CIN, but rather about the clinical and cost efficacy of prophylactic intravenous hydration according to current guidelines in the prevention of CIN.

The guidelines specify prophylactic intravenous (iv) hydration for all patients with an eGFR <45 ml/min/1.73m^2, and for all patients with an eGFR <60 ml/min/1.73m^2 in combination with diabetes or >1 risk factor (age >75 years, cardiovascular disease, nephrotoxic medication or anaemia). We included exactly this patient population in the AMACING trial, except for those with an eGFR <30 ml/min/1.73m^2 (prevalence ca. 0.5%). The latter were excluded as a safety precaution because incidences of CIN in absence of prophylaxis were unknown, and not giving prophylaxis even more of a controversial topic at the time than it is now. During the two-year inclusion period of the AMACING trial we had to exclude only 157 patients because of an eGFR <30 ml/min/1.73m^2.

The best way to assure external validity is to conduct the study in a setting that is as close as possible to the one that the program would operate in in clinical routine, and to include those patients that would typically use that setting. We did not interfere with patients' drinking or aspects of daily clinical practice, other than withholding intravenous hydration in the 'no prophylaxis' randomised arm. Furthermore, we included exactly the patient population for which the guidelines recommend prophylactic intravenous hydration with normal saline.[75] We excluded all patients with an EGFR lower than 30 ml/min/1.73m^2 (n=157). Thus the population included in the AMACING trial represents 90% of the patients that receive guideline-recommended intravenous prophylactic hydration.

We found no prophylaxis to be non-inferior to standard intravenous hydration according to the guidelines, and the 95% CI reflects the strength of the results.

The CIN incidences found in our trial are considered by some to be low, however for elective procedures they fall within ranges reported in meta-analyses. For example, McDonald et al. reported post-contrast CIN incidences in the range of 2.1–19% (and 1.3–19.8% without contrast administration), Mehran and Nikolsky reported a range of 0.6–2.3% in the general population (including low risk patients), extending up to 20% in selected subgroups.[14,162] It is in specific acute clinical settings that higher incidences are reported.

We would like to emphasize that eGFR <30 ml/min/1.73m^2, emergency and intensive care status were amongst our exclusion criteria, and such patients are therefore beyond the scope of our trial.

The correspondents suggest future trials are required before changing standard care. Given the non-existent difference intravenous hydration made in the incidence of CIN [incidence in the iv hydration group minus that in the no prophylaxis group =−0.1%, one-sided (95% CI, −2.25 to 2.06), one-tailed p=0.4710], and especially given the 5.5% patients that had serious complications of intravenous hydration, we cannot agree. Any therapy must prove to have benefits exceeding the risks before being generally applied, and this is not so in the case of prophylactic intravenous hydration in the prevention of CIN. The burden of proof must be with intravenous prophylactic hydration and not with no-prophylaxis. We would also counter with the question whether it is ethical to continue giving a treatment that is unproven, carries proven risks, confers significant burden upon patient and hospital, and is so costly. If there are indications that a certain patient group might benefit from intravenous hydration, we would suggest evaluating whether the benefits outweigh the risks before general application tot that group.

Mandrola summarises on Medscape: “the most provocative aspect of AMACING is how it prompts us to re-examine the very existence of CIN. Perhaps hydration does not prevent CIN because our way of thinking about CIN is flawed. Results of the AMACING study force us to (I) be suspicious of expert opinion; (II) object to quality measures not backed by randomized trial data; and (III) reconsider the existence of an entire disease entity (CIN), and in doing so, think about how our brains can trick us into seeing signal when there is mostly noise”.[134]

Conflicts of Interest

The authors have no conflicts of interest to declare.