AMACING

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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.). 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. 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. 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. 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/1.73m² may not be beneficial and may inadvertently cause harm through fluid overload.

At this time most guidelines have been updated in line with the AMACING trial results. In Europe, America and Oceania, umbrella organisations no longer recommend standard prophylaxis for patients with estimated glomerular filtration rate (eGFR) 30-59 ml/min/1.73m² combined with risk factors represented by
AMACING trial participants.\textsuperscript{70,71,73,79} The changes in recommendations on standard prophylaxis in the Dutch (The Radiological Society of The Netherlands, NVvR) guidelines are detailed in table 8.1.\textsuperscript{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\textsuperscript{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).\textsuperscript{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\textsuperscript{2} in combination with diabetes or more than 1 risk factor, OR with eGFR 30-44 ml/min/1.73m\textsuperscript{2}\textsuperscript{70,75}, and in patients currently eligible for prophylaxis (with eGFR <30 ml/min/1.73m\textsuperscript{2}\textsuperscript{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

<table>
<thead>
<tr>
<th>Guideline recommendation§</th>
<th>Before November 2017 update</th>
<th>After November 2017 update</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient eligible for standard prophylaxis</td>
<td>- eGFR &lt;45 ml/min/1.73m² or eGFR 45-59 ml/min/1.73m² combined with diabetes or &gt;1 risk factor$^5$</td>
<td>eGFR &lt;30 ml/min/1.73m²</td>
</tr>
<tr>
<td>Standard prophylaxis</td>
<td>iv 0.9% NaCl 4 or 12 h before &amp; 4 or 12 h after</td>
<td>iv 1.4% NaHCO₃ 1 h before (&amp; 6 h after)</td>
</tr>
</tbody>
</table>

$^eGFR = \text{estimated glomerular filtration rate.}$ $^§$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; $^5$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/1.73m² combined with risk factors), and 184 procedures in patients with eGFR <30 ml/min/1.73m² 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/1.73m² combined with risk factors; ⁵i.e. eGFR <30 ml/min/1.73m²
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/1.73m² 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/1.73m² (Chapter 6).\(^{104,135}\)

Total complications before update: \( (1808 \times 0.055) + (184 \times 0.064) = 111/\text{year} \)

Total complications after update: \( 184 \times 0.064 = 12/\text{year} \)

**Total complications avoided** after guideline update: \( 0.055 \times 1808 = 99/\text{year} \ (-89\%) \)

Hospitalisation for prophylaxis

CINART registered 85.4% outpatients (1544/1808) 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: \( (1808 \times 0.854) + (184 \times 0.647) = 1663/\text{year} \)

Total extra hospitalisations after update: \( 184 \times 0.647 = 119/\text{year} \)

**Total beds freed** after the guideline update: \( 1808 \times 0.854 = 1544/\text{year} \ (-93\%) \)

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: \( 1992 \times €663 = €1,320,696/\text{year} \)

Total extra costs after the guideline update: \( 184 \times €663 = €121,992/\text{year} \)

**Total savings** after the guideline update: \( €1,198,704/\text{year} \ (-91\%) \)
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+.

<table>
<thead>
<tr>
<th></th>
<th>before update</th>
<th>after update</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXTRA COSTS (€/year)</td>
<td>1,320,696</td>
<td>1,219,992</td>
</tr>
<tr>
<td>HOSPITALISATION (patients/year)</td>
<td>1,663</td>
<td>119</td>
</tr>
<tr>
<td>COMPLICATIONS (patients/year)</td>
<td>111</td>
<td>12</td>
</tr>
</tbody>
</table>

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.\textsuperscript{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 achieved 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%.\textsuperscript{163}

Based on the estimated number of iodinated contrast injections carried out worldwide – estimated at 75 million a year in 2005\textsuperscript{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: “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/1.73m² 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/1.73m² 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/1.73m² 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/1.73m² 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/1.73m², elective or emergent, who receive intravascular iodinated contrast is checked 2-5 days post-contrast.