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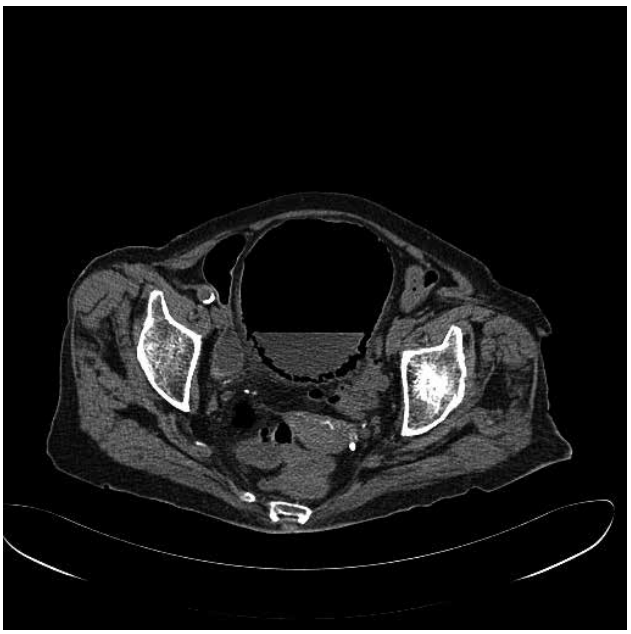

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EDITORIAL

Improving long-term outcomes of kidney transplantation: The pressure is on

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Since the first successful operation in man in 1954, kidney transplantation has evolved from an experimental therapy to the treatment of choice for patients with end-stage renal disease (ESRD). Kidney transplantation offers a significant survival benefit to patients suffering from ESRD and improves their quality of life as compared with patients who remain dependent on dialysis.[1] In children, kidney transplantation improves growth, cognitive performance, and psychosocial well-being.[2] The number of transplantations performed each year in the Netherlands has continued to grow over the past decade and increased from 587 in 2002 to 960 in 2012.[3] This expansion can largely be ascribed to the continuing success of programs for living kidney donation. Currently, in our country, more patients with former ESRD are being maintained with a functioning kidney transplant than with dialysis (9386 *versus* 6396 patients, respectively, on 1 January 2013).[3,4]

Kidney transplantation is, however, not a cure for ESRD. Kidney transplant recipients need medical follow-up and have to take immunosuppressive medication for life. Advances in immunosuppressive drug therapy have resulted in a dramatic decrease in the incidence of acute rejection over the past 30 years and have contributed to the substantial improvement of one-year kidney allograft survival which is now ≥90% in most transplant centres.[5] Unfortunately, long-term transplantation outcome has not improved to a similar degree.[6] Kidney allograft half-lives are approximately 9.5 years for deceased-donor kidney transplants and around 16 years for living-donor kidney transplants.[4,6] Many transplanted patients will therefore at some point in their lives need a second transplant or return to dialysis.

The causes of long-term kidney allograft loss are multifactorial.[7,8] In about half of successfully operated patients, kidney transplants will fail because of diverse causes including, but not limited to, chronic rejection, late acute rejection (often related to non-adherence to immunosuppressive drug therapy), recurrent primary kidney disease, BK virus infection, or nephrotoxicity of the calcineurin inhibitors tacrolimus or ciclosporin.[7,8] The other half of all graft losses occurs because the recipient dies with a functioning kidney transplant.[7,8]

Cardiovascular disease (CVD) is the primary cause of death of kidney transplant recipients and precedes infection and malignancy.[9,10] Patients with ESRD have a greatly increased risk of CVD and although this risk is reduced after a successful kidney transplantation, it remains several times higher than in the general population.[11,12] The nature of CVD among patients with ESRD and those who have undergone a kidney transplantation also differs from that of the general population. Left ventricular hypertrophy, heart failure, sudden cardiac death, peripheral artery disease, and stroke are especially common.[11,12] Hypertension is an important and modifiable risk factor for cardiovascular morbidity and mortality in the transplant population. In addition, hypertension has been shown to negatively influence kidney transplant survival.[13-15]

In this edition of *The Netherlands Journal of Medicine*, Dobrowolski and colleagues report their findings on the prevalence and treatment efficacy of hypertension among kidney transplant recipients in the Netherlands.[16] To this end, they studied data from over 5000 patients registered in the Netherlands Organ Transplant Registry (a national registry which includes data from all eight Dutch transplant centres), as well as over 500 patients who were treated at the authors' institution and for whom more detailed data were available. Their main findings are that >75% of the patients had a blood pressure above the recommended target of 130/80 mmHg and that approximately 12.5% of these patients did not receive any antihypertensive medication. Of the hypertensive patients who did receive antihypertensive therapy, 74% were prescribed sub-maximal dosages. Furthermore, the majority of patients had a sodium intake above the recommended 90 mmol per day. The authors conclude that better blood pressure control should be possible by

intensifying pharmacological treatment and providing more advice on dietary sodium restrictions.[16]

'Less salt and more pills': is that the answer to the immense burden of CVD in the kidney transplant population? Although the easy answer may be 'yes', real-life solutions are likely to be not so simple. Excessive salt intake is associated with detrimental effects on CVD.[17,18] The results of intensive programs to modify lifestyle (smoking cessation, promoting weight loss, and reducing dietary salt intake), however, have been disappointing.[19] The question therefore arises why the patients in this study were not prescribed more intensive drug therapy. Over the past decade, the awareness of the high cardiovascular risk of transplant recipients has grown. Guidelines for cardiovascular risk management have been published and the use of potentially cardioprotective medication in this population has increased.[20,21] Medical neglect is thus an unlikely explanation. This is supported by Dobrowolski *et al*. who show that the number of 'under-treated' patients in the authors' centre, a university hospital with a long tradition of caring for transplanted patients and with a research interest in hypertension, did not differ from the rest of the Netherlands.[16]

Another explanation could be that the prevalence of hypertension was overestimated in this study as only single, office-based, blood pressure measurements were recorded.[22] Moreover, the recommended target blood pressure of <130/80 mmHg is currently debated and may have been considered too strict by the attending physicians. However, even when a cut-off of 140/90 mmHg was used, 44% of the population were still classified as being hypertensive. Other studies have reported comparable findings, suggesting that the true prevalence of under-treated hypertension is indeed this high.[23] It is also conceivable that with more detailed assessments such as 24-hour ambulatory recordings, hypertension may be more prevalent because calcineurin inhibitors reduce the nocturnal drop in blood pressure.[24]

Possibly, practical limitations prevented more intensified blood pressure-lowering pharmacotherapy. Non-compliance to immunosuppressive drug therapy among transplant recipients is very common.[25] Further increasing the pill burden is unlikely to promote adherence and there may have been a trade-off between antirejection and antihypertensive treatment. Side effects of antihypertensive therapy further complicate management. For example, ACE inhibitors and angiotensin-receptor blockers may worsen hyperkalaemia caused by tacrolimus and co-trimoxazole prophylaxis. Oedema may worsen when calcium-channel or alpha blockers are given together with glucocorticoids. Changes in serum creatinine caused by diuretics may arouse suspicion of acute rejection. Concerns about overzealous blood pressure management and the risk of fall-related injuries in the elderly are justified.[26] Fear of overdosing certain beta blockers in patients with limited graft function and interactions between immunosuppressive and antihypertensive drugs may have contributed to suboptimal blood pressure control in individual cases.[27]

Despite all these practical challenges, we believe the complexity of antihypertensive therapy in kidney transplant recipients should not lead to therapeutic nihilism. Novel antihypertensive treatments, a smarter use of existing drugs and maybe prescribing fewer drugs may do the trick. Renal denervation has been heralded as an intervention with high potential. Especially in kidney transplant recipients this technique has appeal because the native kidneys contribute to hypertension, but little to kidney function. Nonetheless, the number of patients with resistant hypertension in Dobrowolski's study was limited (7.7%) and recent reports have tempered initial enthusiasm.[28,29] With regard to a better use of existing treatments, the renewed interest in thiazide diuretics is of note. Recent research has indicated that tacrolimus (the cornerstone of modern immunosuppression) causes salt-sensitive hypertension by activating the sodium chloride cotransporter in the distal convoluted tubule, which is the target of thiazide diuretics.[30,31] Prescription of these agents, therefore, seems rational but physicians appear to be reluctant to treat transplant recipients with diuretics.[32] We are currently investigating whether chlortalidone is a more effective antihypertensive drug as compared with the calcium-channel blocker amlodipine.

A further optimisation of immunosuppressive drug therapy may have the greatest potential to reduce CVD in the transplant population. Obviously, preventing rejection and deterioration of kidney transplant function is of paramount importance. Nonetheless, the number of patients treated with maintenance glucocorticoids in Dobrowolski's study was remarkably high. Glucocorticoid-sparing or withdrawal protocols may be feasible and reduce cardiovascular risk in low-immunological risk patients treated with modern immunosuppression.[33] The optimum maintenance tacrolimus target concentrations are also a matter for debate but, again, reduction may be possible without increasing rejection risk.[34] Mycophenolate mofetil may be preferable over other antimetabolites from a cardiovascular point of view.[35] The novel immunosuppressive drug belatacept arguably has the greatest potential to reduce CVD in transplantation. This drug allows for adequate immunosuppression and results in a better kidney function, less post-transplantation diabetes mellitus, and lower serum lipids and blood pressure compared with ciclosporin-based immunosuppression.[36]

Reducing the risk of CVD is an unmet need in transplantation. It appears that the tools to do so are here. Picking the right ones for an individual patient is the challenge.

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REVIEW

Recommendations for the paracetamol treatment nomogram and side effects of N-acetylcysteine

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ABSTRACT

Treatment of paracetamol intoxication consists of administration of N-acetylcysteine, preferably shortly after paracetamol ingestion. In most countries, the decision to treat patients with N-acetylcysteine depends on the paracetamol plasma concentration. In the literature, different arguments are given regarding when to treat paracetamol overdose. Some authors do not recommend treatment with N-acetylcysteine at low paracetamol plasma concentrations since unnecessary adverse effects may be induced. But no treatment with N-acetylcysteine at higher paracetamol plasma concentrations may lead to unnecessary severe morbidity and mortality. In this review, we provide an overview on the severity and prevalence of adverse side effects after N-acetylcysteine administration and the consequences these side effects may have for the treatment of paracetamol intoxication. The final conclusion is to continue using the guidelines of the Dutch National Poisons Information Centre for N-acetylcysteine administration in paracetamol intoxication.

KEYWORDS

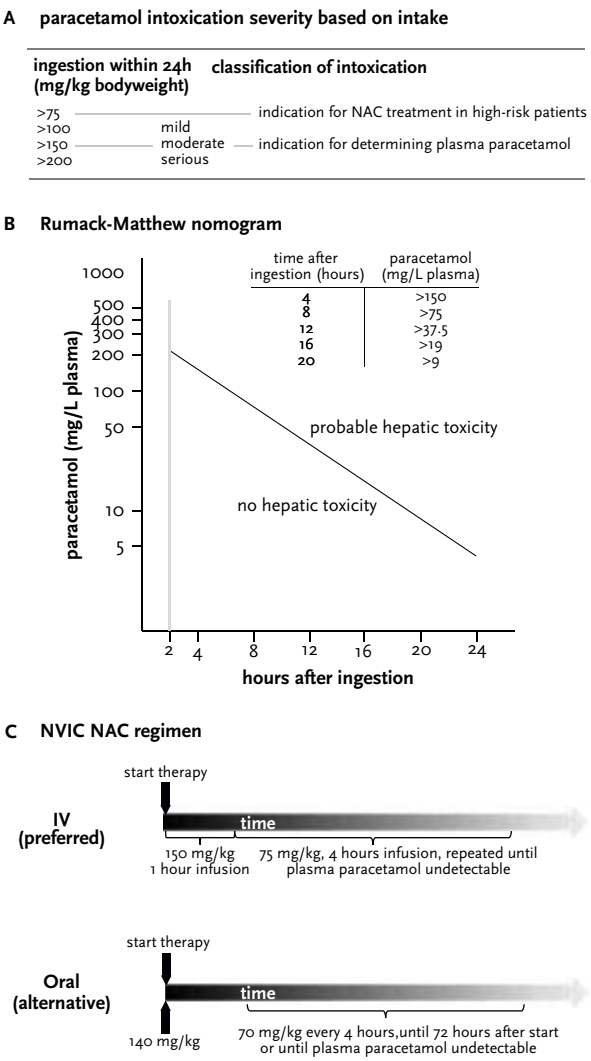
Paracetamol, acetylcysteine, adverse effects, nomogram

INTRODUCTION

In the Netherlands, overdose with paracetamol forms the largest group of medicine overdoses reported to the Dutch Poisons Information Centre (NVIC).[1] Worldwide and especially in adults, the analgesic paracetamol is often intentionally taken in overdose, potentially resulting in severe morbidity and mortality.[2] The main clinical risk of high doses of paracetamol is liver failure, due to the hepatotoxic effects of the paracetamol metabolite N-acetyl-para-benzoquinone imine (NAPQI).[3] In the US, 39-49% of all cases with acute liver failure in the period 1998-2003 were attributed to paracetamol overdose.[4] The most efficacious way to prevent paracetamol-induced hepatotoxicity is the timely administration of the antidote N-acetylcysteine (NAC). The toxic paracetamol metabolite NAPQI can normally be inactivated in the liver by conjugation with glutathione. When high amounts of paracetamol are ingested, the normal glutathione amount in liver cells is not adequate to inactivate all formed NAPQI, resulting in hepatotoxicity. NAC, an acetylated cysteine residue, is a precursor of glutathione, and NAC administration results in increased hepatic glutathione concentrations.[5] Already in the 1970s, experiments and trials with NAC showed the superiority of NAC above other cysteine derivatives, mainly in terms of less side effects. In the UK, NAC treatment started as intravenous (IV) administration, while in the US oral administration was preferred.[6] Even today studies are being performed to determine the advantages of the various administration routes in terms of drug efficacy and cost efficiency,[7] although oral administration is usually more frequently accompanied by nausea and vomiting.[8]

Treatment decision-making for acute paracetamol overdose is usually based on the Rumack-Matthew nomogram (with its subsequent adaptations). Plasma paracetamol levels above the indicated treatment line in the nomogram indicate the need for NAC treatment (*figure 1*).[9] In the US and the Netherlands this so-called treatment line in order to decide whether patients should be treated with NAC starts at a plasma paracetamol concentration of 150 mg/l at 4 hours post-ingestion. In the UK the guidelines concerning NAC administration after single acute ingestion of paracetamol have recently been adapted. The Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK now recommends NAC

Figure 1. *Regimen of NAC administration recommended by the Dutch National Poisoning Information Center (NVIC)[46]*



A) Determination of severity of paracetamol intoxication based on the amount of paracetamol ingested. B) Table of time points after paracetamol ingestion and the indicated paracetamol plasma concentrations at which NAC administration is advocated (left panel). Rumack-Matthew nomogram (right panel). C) Advocated NAC administration regimes (intravenous treatment is preferred above oral treatment).

treatment at plasma paracetamol concentrations of 100 mg/l at 4 hours post-ingestion.[10] From 1995 till 2012 two treatment lines of 100 mg/l or 200 mg/l were used with the choice of line depending on the clinical condition of the patient.[10,11] The main reasons for this change were concerns over a small number of patients who developed hepatotoxicity despite plasma paracetamol concentrations below the Rumack-Matthew treatment line and the simplification of treatment decisions and, as a consequence, risk minimisation.[10,12] Although similar cases of failure of the existing nomogram were already described in 1998,[13] the UK nomogram was only adapted in 2012. The main drawback of the new UK guideline for NAC administration in paracetamol overdose is that more patients will be treated with NAC, potentially resulting in an increased risk of adverse effects of NAC. Also, there will be a considerable increase in hospitalisation with an additional increase in health care costs.[14]

The adaptation of the Rumack-Matthew nomogram in the UK leads to the question whether Dutch clinicians should also change their treatment guidelines. In this review, we will provide an overview on the risks and benefits of NAC administration based on prospective and retrospective studies published in the last ten years. We will discuss the considerations to alter treatment guidelines in line with the new UK guidelines. Finally we will end with a recommendation of treatment guidelines for the Dutch emergency departments.

ADVERSE DRUG REACTIONS OF N-ACETYLCYSTEINE

Between 2001 and 2013 several studies were performed in order to systematically obtain an overview of the adverse drug reactions (ADRs) of NAC infusion (*table 1*). The studies used for this review all concern human exposures and the studies were performed either in a case-controlled prospective manner, or in a more observational retrospective way. In nine of these ten studies NAC was administered intravenously after ingestion of high doses of paracetamol. In one study all patients who were given NAC, irrespective of paracetamol ingestion, were analysed.[15] The studies were performed in the UK, Denmark, Malaysia and Australia. NAC infusion rates were equal in nine studies (150 mg/kg for 15 minutes, 50 mg/kg for 4 hours, 100 mg/kg for 16 hours), while in the study by Whyte *et al.*[15] the infusion rate was 300 mg/kg for 20-21 hours, with no further specification. Several symptoms appeared uniformly in these studies, including anaphylactoid symptoms such as rash, flushing and pruritus, gastrointestinal symptoms such as nausea and vomiting, and pulmonary symptoms such as shortness of breath and bronchospasm, chest pain, angioedema and hypotension (*table 1*). Strikingly, the incidence of ADRs differed highly among the studies, ranging from 9% of the NAC-treated patients[15] to 77%.[16] The variation in the relative number of each specific adverse effect was also considerable between the different studies. For instance, nausea and vomiting ranged from 3-70%, while flushing, pruritus and rash differed in range from 2-31%. An important factor in this variation is probably the difference in classification of ADRs. In the work by Pakravan *et al.*[16] a distinction is made between minimal, moderate and

Table 1. *Overview of studies on adverse reactions of NAC*

Study	Country	Type of study	n	% ADR	Symptoms reported
Yamamoto, 201328	UK	Prospective	660	12	Flushing (2%), pruritus (2%), urticaria (2%), angio-oedema (1%), breathlessness (2%), chest pain (1%), bronchospasm (1%), tachycardia (1%), nausea (3%) and vomiting (3%)
Schmidt, 201332	Denmark	Retrospective	1218	19	Flushing, pruritus and rash (31%), bronchospasm, hypotension and angio-oedema (13%), nausea and vomiting (4%)
Carroll, 201341	UK	Prospective	71	68	Rash (11%), severe anaphylactoid reaction (23%), shortness of breath (3%), nausea and vomiting (52%)
Zyoud, 201043	Malaysia	Retrospective	139	68	Flushing, rash and pruritus (16%), headache, dizziness and convulsion (34%), chest pain, bronchospasm and coughing (17%), cardiovascular reactions (7%), nausea and vomiting (39%)
Zyoud, 201044	Malaysia	Retrospective	125	68	Flushing (7%), rash (6%), headache (15%), dizziness (11%), chest pain (6%), nausea (15%) and vomiting (12%)
Pakravan, 200816	UK	Prospective	169	77	Flushing (25%), pruritus (20%), rash and urticaria (4%), wheezing and bronchospasm (7%), dyspnoea (14%), chest pain (7%), dizziness (8%), fever (5%), nausea (70%) and vomiting (60%)
Waring, 200845	UK	Prospective	362	41	Anaphylactoid reactions (15%), localised skin reactions at the infusion site (1%) and gastrointestinal reactions (25%)
Whyte, 200715	Australia	Retrospective	399	9	Anaphylactoid reactions (2%), most of the adverse drug reactions in the other patients (8%) consisted of nausea and vomiting.
Lynch, 200417	UK	Prospective	64	48	Flushing (22%), pruritus (6%), rash (30%), bronchospasm (6%), nausea and vomiting (22%)
Schmidt, 200140	Denmark	Retrospective	529	10	Flushing, rash and pruritus (8%), bronchospasm, angioedema and nausea (3%)

In this table the studies performed between 2001-2013 are listed (column 1), country where the study was performed (column 2), type of study (prospective or retrospective, column 3), number of included cases (n, column 4), percentage of cases presenting with adverse reactions (% ADR, column 5) and percentage of specific adverse reactions (column 6).

severe symptoms. Minimal symptoms represent either no reaction or mild gastrointestinal symptoms. About 60% of the patients have minimal symptoms, while 70% of the patients present with nausea, suggesting that nausea was often considered a mild symptom. It is plausible to assume that in other studies these patients were considered to be asymptomatic. It is relevant to realise that gastrointestinal symptoms such as nausea and vomiting are frequently observed in paracetamol intoxication, making a causal relation between NAC administration and gastrointestinal symptoms difficult.

ANAPHYLACTOID REACTIONS

Despite the variation in incidence of the ADRs in the different studies, it is obvious that NAC infusion may cause anaphylactoid reactions such as flushing, rash, pruritus and bronchospasms, symptoms which are usually not associated with paracetamol ingestion (*table 1*). These symptoms usually appear within 1-2 hours after starting NAC infusion. In the study by Lynch *et al.*[17] 71% of the patients show ADRs within the first 15 minutes after infusion. Lynch *et al.* used a high infusion rate suggesting that a high infusion rate, and hence a high NAC concentration, is associated with anaphylactoid reactions. It is thought that NAC induces histamine secretion by both mononucleocytes and mast cells, as has been shown by *in vitro* experiments and studies in humans.[16,18] In addition, prophylactic antihistamine treatment can abolish NAC-induced anaphylactoid reactions.[19] Interestingly, in six of the ten studies, an association has been shown between ADR severity and plasma paracetamol concentrations. Adverse effects to NAC were less frequent at higher plasma paracetamol concentrations, suggesting that plasma paracetamol protects against NAC-induced ADRs.

Treatment of ADRs induced by NAC consists of temporary or permanent discontinuation of NAC infusion and/or by administration of antiemetics, antihistamines, corticosteroids or selective β2-adrenoreceptoragonists (*table 2*). Management guidelines for discontinuation of NAC treatment after development of NAC side effects are not objective, although it has been suggested that respiratory symptoms, angio-oedema or hypotension are indications to (temporarily) discontinue NAC infusion.[20] All clinical studies discussed in this paper mention that treatment of NAC-induced ADRs is well achievable and that no patients developed serious side effects requiring intensive care. These studies indicate that there is no absolute contraindication for NAC treatment.

SEVERE AND FATAL CASES FOLLOWING THERAPEUTIC NAC DOSES AND OVERDOSES

In the literature two patients with asthma and paracetamol overdose are described with severe adverse reactions following therapeutic administration of NAC.[21,22] Both developed a respiratory arrest after NAC infusion. Treatment of these patients consisted of administration of salbutamol and corticosteroids, and respiratory support. One patient finally died due to severe hypoxic brain injury.

At supratherapeutic doses of NAC severe or fatal adverse effects may occur. Administration errors of NAC occur in the treatment of paracetamol intoxication, and might lead to supratherapeutic NAC concentrations. In the literature only a few cases are reported of patients receiving high doses of NAC and showing severe clinical symptoms, despite the treatment of millions of patients with NAC. Furthermore, in these cases direct causality between high NAC levels and the observed clinical symptoms was not obvious, as was also discussed by the presenting authors. In some cases the observed symptoms could also be attributed to the paracetamol intoxication. Clinical symptoms which were observed included severe hypotension, coagulation disorder, cardiac arrest,[23,24] seizures progressing to cerebral oedema, uncal herniation and severe brain injury.[25,26] In one specific case, initial high levels of NAC were related to an atypical haemolytic-uraemic syndrome although the time course of haemolysis was not in accordance with the NAC concentration when the NAC elimination half-life is taken in account.[27]

Table 2. *Overview of therapy provided after adverse reactions of NAC*

Study	Corr. with [paracetamol]p	Time of onset of ADRs (min.)	Infusion regime	NAC administration criterion	Therapy
Yamamoto, 2013[28]	n.a.	0 to 122 (median 32.5)	IV 150-50-100	Unknown	(Temporarily) stop NAC infusion (5%), antiemetics (5%), antihistamines (4%), corticosteroids (2%), inhaled B2 agonists (1%), adrenaline (1%)
Schmidt, 2013[32]	Yes	n.a.	IV 150-50-100	To all patients with paracetamol intoxication	Temporarily stop NAC infusion (12%), antihistamines (17%), corticosteroids (15%), switch from NAC to oral L-methionine (1%), no treatment (1%)
Carroll, 2013[41]	Yes	n.a.	n.a.	Rumack-Matthew	Unknown
Zyoud, 2010[43]	Yes	<60 minutes	IV 150-50-100	n.a.	(Temporarily) stop NAC infusion (22%), IV corticosteroids (16%), IV chlorpheniramine following skin reactions (9%), oxygen nebuliser (7%, only with bronchospasm), antiemetics (39%)
Zyoud, 2010[44]	No	15 to 60	IV 150-50-100	n.a.	(Temporarily) stop NAC infusion (21%), IV corticosteroids (14%), IV chlorpheniramine (8%, only with skin reactions), oxygen nebuliser (6%, only with bronchospasm), antiemetics (51%)
Pakravan, 2008[16]	Yes	n.a.	IV 150-50-100	n.a.	(Temporarily) stop NAC infusion (11%)
Waring, 2008[45]	Yes	50 to 112 (median 75)	IV 150-50-100	Rumack-Matthew	Temporarily stop NAC infusion and antiemetics (20%), temporarily stop NAC infusion (38%), antihistamines (14%), corticosteroids (1%), inhaled albuterol (1%)
Whyte, 2007[15]	n.a.	n.a.	IV 300	Based on dose/ symptoms	Unknown
Lynch, 2004[17]	n.a.	<60, 71% of patients <15	IV 150-50-100	n.a.	Temporarily stop NAC infusion (34%), IV chlorpheniramine (44%), corticosteroids (42%), nebulised salbutamol (6%, only with bronchospasm)
Schmidt, 2001[40]	Yes	n.a.	IV 150-50-100	To all patients with paracetamol intoxication	

In this table the same studies as in table 1 are listed (column 1). The association between adverse NAC reactions and the paracetamol plasma level is indicated (column 2), time of onset of adverse NAC reaction in minutes (column 3), NAC infusion regime provided (IV 150-50-100 = intravenous infusion, 150 mg/kg during 15 minutes, 50 mg/kg during 4 hours and 100 mg/kg during 16 hours, IV 300 = intravenous infusion, 300 mg/kg during 20 hours; column 4), criteria to infuse NAC (column 5) and percentage of cases given a specific therapy (column 5). N.a. = not available.

RATE OF INFUSION

Since most NAC ADRs appear within one hour after the start of NAC infusion, it is suggested that ADRs can be induced by high NAC infusion rates. This suggestion is underpinned by the observation that ADRs often diminish after discontinuation of NAC infusion (*table 2*) and by the fact that reducing infusion speed is used to reduce ADRs.[28] Few studies with the focus on infusion rate and adverse NAC reactions have been performed. Kerr *et al.*[29] performed a randomised prospective trial to compare the primary infusion rate of 150 mg/kg IV NAC in 15 minutes versus 60 minutes, followed by 50 mg/kg for 4 hours and 100 mg/kg for 16 hours. Although a statistically significant reduction in ADRs was not observed, there was a trend toward decreased anaphylactoid reactions in the slower infusion group. There was no difference between the two groups in terms of efficacy of paracetamol intoxication treatment. Bateman *et al.*[30] compared a NAC infusion regime of 150 mg/kg for 15 minutes, 50 mg/kg for 4 hours and 100 mg/kg for 16 hours with a regime consisting of 2 hours of 100 mg/kg and 10 hours of 200 mg/kg. Their results convincingly show that lower initial NAC levels reduce the frequency of vomiting and anaphylactoid reactions. Although these results are promising in order to reduce side effects, further studies have to be performed to evaluate whether, in paracetamol intoxication, NAC administration in a slower infusion rate is as efficacious as in the standard infusion rate.

PROPHYLACTIC TREATMENT OF NAC ADVERSE DRUG EFFECTS

Although preventing ADRs by prophylactic administration of antiemetics and/or antihistamines seems reasonable, only a few data are available regarding this treatment. In a study by Wright *et al.*[31] it was shown that only high doses of the antiemetic metoclopramide (20-50 mg IV) prevented emesis after orally administered NAC, while lower doses of metoclopramide (5-15 mg intravenously) had no effect. However, the patients treated with the high dose of metoclopramide had adverse side effects of metoclopramide, thus high-dose treatment with metoclopramide is not really a good option. In a study of Schmidt *et al.*[32] prophylactic treatment (with antihistamines with or without steroids) administered to patients with previous ADRs to NAC resulted in lower incidence of NAC-related ADRs compared with untreated patients (15% vs. 42%). Nevertheless, further studies on prophylactic treatment to prevent or attenuate ADRs are required to evaluate the efficacy of this treatment.

DISCUSSION

In order to decide how to treat patients with paracetamol overdose, the following issues should be weighed. First, the efficacy of paracetamol intoxication treatment is the most important factor. In a meta-analysis, Green *et al.* studied the efficacy of NAC treatment in paracetamol intoxication.[33] Patients treated with either IV or oral NAC before 8-10 hours after paracetamol ingestion developed hepatotoxicity in 5.7% of the cases, and hepatotoxicity in these cases was not severe. When NAC was administered late (>8 hours) after paracetamol ingestion, hepatotoxicity was more frequent and more severe. Kerr *et al.*[29] showed that NAC treatment started before eight hours after paracetamol ingestion does not result in hepatotoxicity at all. One should bear in mind that the paracetamol plasma level at a certain time after paracetamol intake is an important parameter for starting NAC treatment. The time of paracetamol ingestion is indicated by the patient or by an accompanying person and thus has some level of uncertainty in it. This may lead to an underestimation of the severity of the paracetamol intoxication based on plasma paracetamol levels at a certain time point, with an associated risk of under-treatment of the patient. Most publications on NAC administration for paracetamol intoxication do not comment on the reliability of the estimation of the time of ingestion. Medical professionals, however, should be aware of this uncertainty when treating patients with paracetamol intoxication. Bateman *et al.* state that they and others have previously reported that most episodes of hepatotoxicity occur as a result of late presentation to hospital, and this should be a target for public health intervention.[15,17,34-36] We underpin this statement. Interestingly, recent studies suggest that new biomarkers, which indicate hepatotoxicity, may become good predictors for the indication of NAC treatment in patients with a late presentation.[37]

Secondly, the prevalence and severity of adverse effects of the treatment are important for the choice of therapy. For instance, methionine can also be effective as paracetamol antidote, but it has been reported that it may be less reliable in the treatment of a paracetamol intoxication than NAC.[38] There are doubts concerning the safety of late treatment with methionine, since methionine may aggravate hepatic encephalopathy. In addition, methionine may also induce nausea and vomiting.[39] Altogether, NAC is a safer treatment of paracetamol intoxication than methionine; this is also the case for patients with a known allergy for NAC. Also the choice when to start NAC therapy effects the total number of patients with NAC ADRs. In Denmark all patients with suspected paracetamol intoxication are treated with NAC, irrespective of the paracetamol plasma concentration. This may lead to unnecessary NAC exposure and accompanying ADRs. However, in this review two studies from Denmark are included, which do not seem to show higher numbers of ADRs compared with studies in countries which strictly

follow the paracetamol plasma level for NAC treatment (*table 1*). Surprisingly, the highest rates of ADRs were observed in studies performed in the UK. This may be attributed to differences in valuing clinical symptoms or in differences in ethnic composition of patient populations. Schmidt *et al.*[32] show that in their cohort there is a difference in the rate of ADRs between people of Danish and non-Danish origin.

In order to reduce side effects of NAC administration, it is possible to adapt the NAC administration regimen for patients with increased risk for NAC ADRs. Side effects may occur more frequently in patients who are asthmatic, although only two of the ten studies mentioned in *table 1* show a significant correlation between asthma and rate of ADRs. In the study by Schmidt and Dalhoff[40] it was shown that asthmatic patients are 2.9 times more likely to develop ADRs, although there is no difference in severity of ADRs between asthmatic and non-asthmatic patients. Carroll *et al.*[41] showed an increased prevalence of anaphylactoid reactions (flushing, urticarial, angioedema or shortness of breath) in asthmatic patients. Six of the studies mentioned in *table 1* showed an inverse correlation between paracetamol plasma levels and severity of NAC ADRs. Thus, paracetamol plasma level seems to be a factor for developing NAC ADRs. The precise mechanism behind the protective capacity of high paracetamol plasma levels against NAC ADRs is not fully understood, although studies suggest that paracetamol inhibits NAC-induced histamine secretion by mast cells.[16,18] The adaptation of NAC administration regimen mainly consists of lowering the initial NAC dose, as was shown by Bateman *et al.*[30]

Thirdly, minimisation of costs is an important factor in the choice of treatment. Costs of treatment are determined by factors such as the kind of therapy provided, ADRs induced by the treatment, length of hospitalisation, and treatment efficacy. Martello *et al.*[7] compared the costs of oral versus IV NAC treatment, and came to the conclusion that patients who received IV NAC treatment had decreased health costs compared with oral treatment due to reduced length of hospital stay, while there was no difference between the efficacy of both treatments.

In the Netherlands, if we were to follow the new UK guidelines for NAC treatment (at a plasma paracetamol concentration of 100 mg/l instead of 150 mg/l at 4 hours after ingestion), this would imply an increase in the number of patients treated with NAC, and hence an increase in health costs. Furthermore, it is highly uncertain whether the number of patients with liver toxicity would decrease when the nomogram line is lowered from 150 mg/l to 100 mg/l at 4 hours post-ingestion, since the 150 mg/l line is already a safety line based on the original Rumack-Matthews 200 mg/l nomogram.[42] Recently, a study was performed in the UK where patient admission and estimated costs were compared before and after the introduction of the new UK NAC administration regime. An increase of 13.2% of NAC use in admitted patients was observed during the period of study, with an estimated annual cost increase of £ 8.3 M (€ 10 M). A life would be saved every 2.1 years, resulting in a cost-per-life saved of £ 17.4 M (€ 21 M) and this might even be higher because not all the information is available to perform a more precise calculation.[34] Unfortunately, for the Dutch situation no suitable data are available to perform an adequate cost-benefit analysis. The reason is that in Dutch hospitals the information needed for such analyses is not properly archived.

CONCLUSIONS

In view of the fact that NAC treatment has been and still is given to millions of people with a paracetamol intoxication, and the fact that adverse effects of NAC treatment are generally mild, there is no reason to avoid NAC administration in paracetamol intoxication. The seriousness of paracetamol intoxication, with life-threatening hepatotoxicity, outweighs the possibility to develop severe adverse effects from NAC administration. It is important to realise that severe adverse effects of NAC are seldom observed. Patients with increased risk for NAC ADRs are primarily severe asthmatic patients, although NAC administration is not considered a contraindication in these patients, and patients with a known allergy for NAC. In these patients, severe NAC ADRs can be minimised by prophylactic treatment with antihistamines or corticosteroids, or adjustment of the NAC infusion rate. On the other hand, over-treatment with NAC, for instance by lowering the current nomogram treatment line, is not recommended, since the 150 mg/l nomogram sufficiently discriminates between patients at risk for hepatotoxicity and patients who are not at risk. Furthermore, in the Netherlands the paracetamol concentration of 150 mg/l at 4 hours post-ingestion nomogram has already been operational for more than 30 years and has proved to be very safe. We therefore recommend the continuation of the 150 mg/l at 4 hours post-ingestion nomogram, which is in use in Dutch hospitals. When the time point of ingestion is uncertain, it is important that treatment with NAC is started until more information is gathered on the severity of the paracetamol intoxication, for example, by drawing another blood sample to evaluate whether the paracetamol concentration is increasing or that the paracetamol metabolism is already hampered by paracetamol-induced liver injury.

In *figure 1A* and *1B* the indication for NAC administration following paracetamol ingestion is provided. Patients who have taken an acute oral paracetamol dose of >150 mg/kg (or >75 mg/kg in high-risk groups) should be treated with NAC.[11] The recommended NAC administration regimen is given in *figure 1C*.

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ORIGINAL ARTICLE

Treatment efficacy of hypertension in kidney transplant recipients in the Netherlands

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ABSTRACT

Background: Hypertension in kidney transplant recipients jeopardises graft and patient survival. Guidelines suggest blood pressure targets of ≤130/80 mmHg and sodium intake <90 mmol/day.

Methods: Since the efficacy of antihypertensive treatment among kidney transplant recipients is unknown, we analysed data on office-based blood pressure and use of antihypertensive drugs from the Netherlands Organ Transplant Registry on 5415 kidney transplant recipients. Additionally, we studied dosages, prevalence of treatment-resistant hypertension and 24-hour sodium excretion in 534 kidney transplant recipients from our centre to explore possibilities for therapy optimisation.

Results: In patients registered in the Netherlands Organ Transplant Registry, median blood pressure was 134/80 mmHg (interquartile range 122-145/70-85). In 77.2%, the blood pressure was ≥130/80 mmHg; of these patients 10.4% had no registered use, 30.0% used one and 25.9% used ≥3 classes of antihypertensive agents. Parameters from our centre were comparable: 78.7% had a median blood pressure of ≥130/80 mmHg of whom 14.5% had no registered use of antihypertensives and 26.4% used ≥3 classes. Sub-maximal dosages were prescribed in 74.0% of the kidney transplant recipients with a blood pressure of ≥130/80 mmHg while using at least one antihypertensive agent. Treatment-resistant hypertension was present in 7.7%. Median 24-hour sodium excretion was 147 mmol/day (interquartile range 109-195).

Conclusions: This study suggests that therapeutic optimisation of antihypertensive treatment in kidney transplant recipients is, in theory, frequently possible by intensifying pharmacological treatment and by providing more advice on dietary sodium restrictions.

KEYWORDS

Antihypertensive treatment, hypertension, kidney transplantation

INTRODUCTION

Although kidney transplantation is the superior treatment for end-stage renal disease, kidney transplant recipients continue to have a high risk for cardiovascular morbidity and mortality. The annual risk for cardiovascular death is about 50-fold as compared with the general population and cardiovascular disease is the leading cause of morbidity and mortality in kidney transplant recipients.[1-3]

Hypertension is the foremost modifiable medical risk factor for cardiovascular disease in kidney disease. In addition, hypertension jeopardises renal allograft function, leading to graft loss.[4-7] Various studies, dating from before 2009, indicated that hypertension amongst kidney transplant recipients was prevalent in up to >90%.[4,8,9] Authoritative guidelines recommend a target blood pressure of <130/80 mmHg in kidney transplant recipients.[7,10] The efficacy of antihypertensive treatment in kidney transplant recipients has not been studied since. Against this background, we set out to study the efficacy of the current treatment of hypertension in kidney transplant recipients and to assess the number and dosages of prescribed antihypertensive drugs. Since sodium intake is a recognised determinant of blood pressure and sodium restriction is a major therapeutic antihypertensive intervention, we also surveyed the dietary sodium intake.

METHODS

We performed two separate, retrospective cross-sectional analyses: i.e. on data retrieved from the Netherlands Organ Transplant Registry (NOTR) and from the clinical files of kidney transplant recipients at our own institution, respectively.

Netherlands Organ Transplant Registry

The NOTR registry is a nationwide registry of kidney transplant recipients from the eight kidney transplant centres in the Netherlands, including our institution. The NOTR registry is managed by the Dutch Transplant Foundation and includes patient and donor characteristics and a variety of clinical parameters, such as office blood pressure and prevalent medications. In the first year after transplantation, registry follow-up is at month 3, thereafter on a yearly basis. We retrieved data on patient characteristics, kidney graft function, office-based systolic and diastolic blood pressure and the number of classes of antihypertensive drugs in the patients registered on 31 December 2011. For patients within the first year after transplantation, we included data from the latest visit. *Table 1* summarises these variables.

Table 1. *Kidney transplant recipient characteristics*

	NOTR n=5415	AMC n=534	P value
Age	48 (36-58)	54.5(43-64)	<0.001
Gender (male) (%)	59.6	56.4	0.154
Height (cm)	172 (166-180)	172 (165-179)	0.087
Weight (kg)	73 (64-83)	76 (65-88)	<0.001
Living donor (%)	44.5%	34.1%	<0.001
Time after kidney transplantation (years)	5.0 (2-11)	4.4 (1.3-9.7)	<0.001
Unilateral nephrectomy (%) Bilateral nephrectomy (%)	Unknown Unknown	6.4 5.4	- -
No diabetes mellitus (%)	91.8	72.1	<0.001
Caucasian (%) (of whom native born Dutch (%))	Unknown	76 (64)	-
Plasma creatinine (μmol/l)	126 (101-163)	143 (112-183)	<0.001
eGFR >60 ml/min/1.73m² (%)	18.2	15.2	0.485
eGFR 45-59 ml/min/1.73m² (%)	25.9	27.7	0.485
eGFR 30-44 ml/min/1.73m² (%)	34.4	34.6	0.485
eGFR 16-29 ml/min/1.73m² (%)	18.3	18.9	0.485
eGFR <15 ml/min/1.73m² (%)	3.1	3.6	0.485
Proteinuria g/l	0.11 (0.03-0.30)	0.09 (0.06-0.18)	0.831
Sodium excretion (mmol/24 h)	Unknown	147 (109-195)	-
Systolic blood pressure (mmHg)	134 (122-145)	134 (124-146)	0.171
Diastolic blood pressure (mmHg)	80 (70-85)	81 (76-88)	<0.001
Number of anti-hypertensive drugs	2 (1-2)	2 (1-3)	0.381
Diuretic (%)	21.1	31.7	<0.001
Alpha or beta blocking agent (%)	60.1	53.9	0.006
Prednisolone (%)	89.5	93.6	0.004
Prednisolone (mg/day)	Unknown	10 (5.0-10.0)	-
Tacrolimus (%)	58.2	53.4	<0.001
Cyclosporine (%)	36.9	20.8	<0.001
MMF (%)	73.8	58.1	<0.001
Azathioprine (%)	5.3	14.0	<0.001
mTOR inhibitor (%)	5.1	4.1	0.359

Interquartile ranges 25% and 75% shown. NOTR = Netherlands Organ Transplant Registry; AMC = Academic Medical Centre Amsterdam; DM = diabetes mellitus: either DM type I or II or new-onset DM after transplantation; MMF = mycophenolate mofetil; mTOR inhibitor= mammalian target of rapamycin.

Local data

To provide additional information about determinants of hypertension that could not be retrieved from the NOTR, we performed a retrospective survey on the medical files of the prevalent kidney transplant recipients at our kidney transplant centre in Amsterdam in September 2012. On average these patients visit the outpatient clinic four times per year. We collected data on patient characteristics including ethnicity, kidney graft function, office-based systolic and diastolic blood pressure and prevalent classes of antihypertensive and immunosuppressive drugs and their dosages.

In all patients 24-hour urine collections are routinely performed at each outpatient clinic visit. Therefore we were able to assess daily sodium excretion as a proxy of dietary intake parallel to the blood pressure readings. Urine sodium excretion was measured at least four weeks after adjustment or initiation of diuretic treatment. Therefore these measurements represented a steady state in which

Table 2. *Advised maximal daily dosages of antihypertensive medications in kidney transplant recipients according to the local protocol (Academic Medical Centre Amsterdam) The protocol allows higher dosages if clinically indicated*

Class	Name	eGFR 60-15 ml/min	eGFR >60 ml/min
Calcium antagonists	Nifedipine	90 mg	90 mg
	Amlodipine	10 mg	10 mg
	Barnidipine	20 mg	20 mg
Diuretics	Furosemide	120 mg	80 mg
	Bumetanide Chloro-talidone	5 mg 50 mg	2 mg 50 mg
	Hydrochloro-thiazide	25 mg	25 mg
ACE inhibitors	Enalapril	20 mg	30 mg
	Lisinopril	20 mg	40 mg
Beta blockers	Metoprolol	200 mg	200 mg
	Nebivolol	10 mg	10 mg
Alpha blockers	Doxazosine	8 mg	8 mg
Angiotensin II antagonists	Losartan	100 mg	100 mg
Central antihy-pertensives	Moxonidine	0.2 mg	0.4 mg
Central antihy-pertensives	Methyldopa	2250 mg	2250 mg

sodium intake and excretion were equal. We defined the possibility for optimisation of antihypertensive treatment as the option to initiate antihypertensive treatment or the option to increase the number and/or dosage of the prescribed antihypertensive agents up to the maximum recommended dosage in our local protocol (*table 2*).

Statistical analysis

All data were included in a master file and statistical analyses were performed using SigmaStat (Jandel Scientific Software, San Jose, California USA). Normally distributed data are represented as mean and SD; non-normally distributed data as median and interquartile ranges. Under Dutch law this retrospective, descriptive study was exempt from medical ethics review.

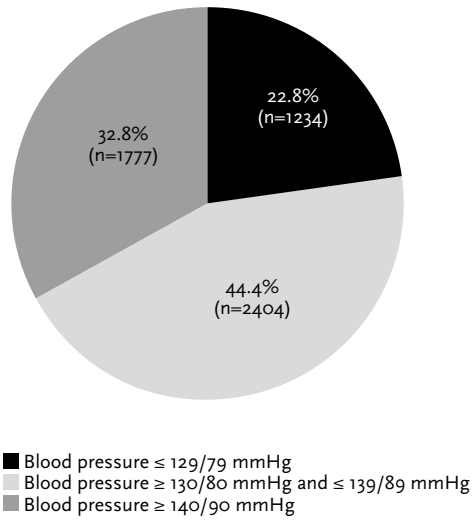
RESULTS

Netherlands Organ Transplant Registry data

On 31 December 2011, 5770 patients of 18 years and older were registered in the NOTR as living with a functioning kidney transplant. Recent blood pressure measurements were missing in 355 patients (6.2%), who were excluded from further analysis. Median age was 48 years (interquartile range (IQR) 36-58) and time after transplantation 5.0 years (IQR 2-11). Median plasma creatinine was 126 µmol/l (IQR 101-163) and proteinuria was 0.11 g/l (IQR 0.03-0.30). Most patients were treated with a calcineurin inhibitor (CNI). Tacrolimus was prescribed in 58.2% and cyclosporine in 36.9% of the patients. Prednisolone was prescribed in 89.5% of the patients, mostly in combination with a CNI. Mycophenolate mofetil (MMF) was used in addition to the CNI and/or prednisolone regimen in 73.8%. Azathioprine was given to 5.3% of the kidney transplant patients and a mammalian target of rapamycin (mTOR) inhibitor to 5.1%.

Median blood pressure was 134/80 mmHg (IQR 122-145 / 70-85). These data are summarised in *table 1* and *figure 1*. The examination of the numbers of classes of antihypertensive drugs prescribed showed that at least one class of blood pressure lowering agents was prescribed in 87.8% of the patients. Of all kidney transplant recipients with a blood pressure ≥130/80mmHg, 10.4% had no prescription for any antihypertensive drug, 30.0% used one antihypertensive agent, 33.7% used two and 25.9% used three or more different classes of antihypertensive drugs (*figure 2*).

Figure 1. *Blood pressure of kidney transplant recipients (data from the NOTR)*



Blood pressure is classified into three categories (≤ 129/79 mmHg, > 130/80 - ≤ 139/89 mmHg and ≥ 140/90 mmHg).

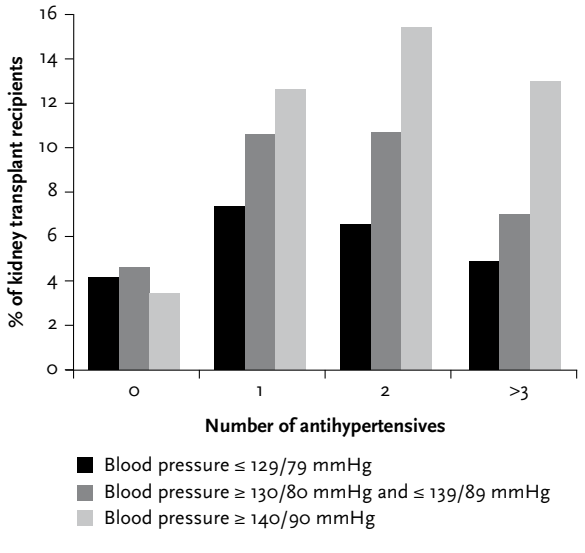
Local data

Patient characteristics are shown in *table 1*. Data on n=539 prevalent patients living with a functioning kidney transplant on 1 September 2012 were included. There were missing data on recent blood pressure in five patients. Therefore, we further analysed the data on 534 patients. There were nine patients who had missing data on 24-hour urine specimens. In this cohort, the median age of 54.5 years (IQR 43-64) was slightly higher and time after transplantation of 4.4 years (IQR 1.3-9.7) was shorter than in the NOTR survey. Ethnic diversity was broad with 76% being Caucasian and of whom 64% were of Dutch descent. Median plasma creatinine was 143 µmol/l (IQR 112-183) and proteinuria was 0.09 g/l (IQR 0.06-0.18).

The CNI tacrolimus was prescribed in 53.4% of the patients, with median dosages of 6 mg/day (IQR 4-8) and with associated plasma trough levels of 7.4 µg/l (IQR 5.5-9.2). Cyclosporine was prescribed in 20.8%, and 93.6% of the kidney transplant recipients were treated with prednisolone with median daily dosages of 10 mg (5-10 mg). In our centre, 58.1% of our kidney transplant recipients received MMF, 14.0% azathioprine and 4.1% an mTOR inhibitor.

Kidney transplant recipients had a median blood pressure of 134/81 mmHg (124-146/76-88). In 420 patients (78.6%) blood pressure was ≥130/80 mmHg, of whom 14.5% were not taking an antihypertensive drug, 29.3% used one, 29.8% two and 26.8% used three or more different classes of blood pressure lowering agents. Blood pressure ≥140/90 mmHg was found in 43.8% of our patients. Of the 420 patients with blood pressure ≥130/80 mmHg, 24.8% were taking three or more antihypertensive drugs while having their antihypertensive drugs prescribed at dosages that were lower than the highest permitted dose, as indicated by the local protocol (*table 2*). Resistant hypertension (defined as blood pressure >130/80 on either three antihypertensives including a diuretic, all in highest permitted dose, or on four antihypertensives regardless of the dose) was present in 7.7% of all our kidney transplant recipients. Median sodium intake as inferred in 24-hour urine specimens was 147 mmol/24 h (109-195).

Figure 2. *Number of classes of antihypertensive drugs prescribed (data from the NOTR)*



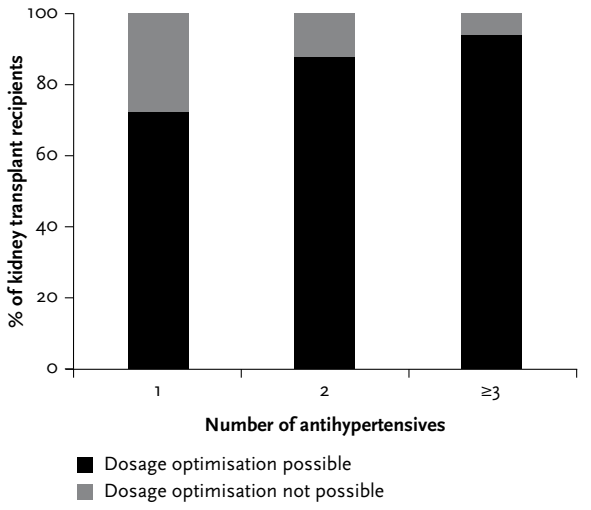
Blood pressure is classified in three categories (≤ 129/79 mmHg, ≥ 130/80 and 139/89 mmHg and ≥ 140/90 mmHg). The number of patients per group was n=659 without an antihypertensive agent and n=1650, n=1763 and n=1343 in the groups on one, two, three or more than three antihypertensive drugs respectively.

DISCUSSION

The main findings of our study include the following. Firstly, 22.8% of the kidney transplant recipients had office-based blood pressure measurements <130/80 mmHg (regardless of the use of antihypertensive drugs) while in the remaining 77.2% treatment targets are not reached. Secondly, this might be due to the prescription of too low numbers of antihypertensive drugs and/or in too low dosages. Thirdly, only 7.7% of patients fulfil the criteria of treatment-resistant hypertension. And fourthly, sodium intake targets appear not to be reached in the majority of transplant recipients.

This is the first study on the prevalence and treatment efficacy of hypertension in kidney transplant recipients in the Netherlands. Previous studies have reported prevalences of 45.5% in a kidney transplant recipient cohort studied between 1976-2002.[4] The landmark study by Opelz *et al.* analysing a large international multicentre kidney transplant recipient cohort also showed a prevalence of hypertension of ~46% at both 1 and 5 years post-transplantation.[9] In more recent studies, this prevalence has been surpassed without exception. In the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) study, 92% of 4107 American kidney transplant recipients had hypertension. Of them, 69% had a blood pressure of ≥130/80 mmHg regardless of the use of antihypertensive drugs.[8] A Spanish study showed that hypertension was more prevalent in more recent years (1994 and 1998 compared with 1990) although simultaneously a greater number of antihypertensive agents were prescribed.[11] In another ten-year follow-up study, hypertension after kidney transplantation was present in 74%.[12] A large analysis of the use of cardiovascular drugs in kidney transplant recipients, including lipid-lowering and antiplatelet agents, showed a nearly fourfold increase between 2000-2006 compared with the early 1990s.[13] These findings imply that our

Figure 3. *The possibilities for optimising the dosages of antihypertensive drugs prescribed in kidney transplant recipients with blood pressure ≥130/80 mmHg*



This chart shows the theoretical possibility to optimise dosage(s) of the class(es) of antihypertensive drugs that are prescribed in kidney transplant recipients using one, two or three or more antihypertensive drugs while having office-based blood pressure ≥130/80 mmHg (data from our cross-sectional analysis in our kidney transplant unit in Amsterdam). The number of patients per group was comparable (n= 123, n=125 and n=111 in the groups using one, two or three or more antihypertensive drugs respectively). Possibilities to optimise the dosage were based on the local protocol prescription recommendations (table 2).

results are in agreement with the data shown in literature. The prevalence of treatment-resistant hypertension is in accordance with the single published study on this topic.[14] Our data on daily sodium excretion are also in agreement with a recent survey on sodium excretion of Dutch kidney transplant recipients by Van den Berg *et al*. They showed that urinary sodium excretion was 156±62 mmol/24 hours in 660 kidney transplant recipients.[15]

Our study is the first to directly identify the prescription behaviour of the attending physicians as an opportunity for improving blood pressure control. *Figure 3* shows the optimisation possibilities of antihypertensive medications, i.e. the prescribed dosage of the class of antihypertensive drugs. According to our local protocol, a theoretical dose optimisation of the prescribed class of antihypertensive agent(s) seemed possible in 74.0% of our kidney transplant recipients with an office-based blood pressure ≥ 130/80 mmHg (*figure 3*).

The present study has some methodological limitations. First of all there is the question of setting the target blood pressure. The target of < 130/80 mmHg was derived from observational studies and therefore we should regard this threshold with caution. Especially in patients with extensive atherosclerosis, blood pressure < 130/80 mmHg may be too low. However, even if we regard measurements above 140/90 mmHg as hypertension, still about 44% of the kidney transplant recipients remain hypertensive. Secondly, the feasibility of implementing a restriction in daily sodium intake in all patients is uncertain; however, lowering sodium intake to approximately 90 mmol/day has been shown to be feasible.[16,17] Thirdly, the retrospective design and the use of single office-based blood pressure measurements may have limited the quality of the source data (as compared with for example prospective data collection including 24-hour ambulatory blood pressure measurements).[18] Fourthly, we assumed that patients using antihypertensive medications fulfilled the diagnosis 'hypertension'. However, some of these medications may have been prescribed for indications other than hypertension (e.g. renin-angiotensin system inhibition for proteinuria and beta-blockers for coronary artery disease). By these assumptions we may have overestimated the prevalence of hypertension. Furthermore, our data did not address the attending physicians' rationale for choosing a certain sub-maximal antihypertensive drug dosage e.g. due to intolerance, allergies, toxicity or comorbidities. Ultimately, the sodium excretion from 24-hour urine collections depends on the assumption that such collections have been performed adequately.

These limitations should be addressed in future prospective studies. Because adherence to antihypertensive agents may be low as compared with adherence to immunosuppressive medications future work should also address strategies to improve patients' adherence to antihypertensive therapy regimens and behavioural factors concerning medication intake.[19]

CONCLUSION

Hypertension as the foremost cardiovascular and renal risk factor in kidney transplant recipients is highly prevalent and only a minority of patients reach target blood pressures with current therapy. We have identified physicians' prescription behaviour and the patients' daily sodium intake as possible mediators to improve blood pressure control. Intensifying pharmacological therapy often seems possible and more stringent advice for lowering their daily sodium intake should be given to and followed by kidney transplant recipients.

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DISCLOSURES

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL ARTICLE

Practice, attitude and knowledge of Dutch paediatric oncologists regarding female fertility

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ABSTRACT

Background: Chemotherapy and radiotherapy for childhood cancer can result in a decreased reproductive function. It is therefore important that paediatric oncologists discuss the possible impact of treatment on female fertility and available fertility preservation options with their patients. However, it is unknown what Dutch paediatric oncologists know about of the effect of cancer treatment on female fertility, whether or not they address this issue in clinical practice, what their attitudes are towards addressing fertility after cancer treatment and fertility preservation options, and to what extent they require additional information resources.

Methods: In this nationwide quantitative cross-sectional study a survey was sent to all registered paediatric oncologists in the Netherlands (n=64).

Results: Thirty-seven paediatric oncologists participated (participation rate 58%). Fertility issues were discussed with patients and/or parents by 97%. Of the paediatric oncologists, 54-76% were aware of possibilities for fertility preservation; however only <25% reported a moderate or high confidence in their knowledge of these techniques. Paediatric oncologists stated that they had little resources to counsel their patients and 92% found educational resources not completely sufficient.

Conclusion: Paediatric oncologists are well aware of the effect that cancer treatment may have on female fertility and their responsibility to counsel their patients and/or the parents on this issue. They do not (yet) possess the knowledge to sufficiently counsel these patients and, if needed, do not frequently refer them to a fertility specialist.

KEYWORDS

Infertility, fertility preservation, paediatric oncology, late effects, cancer survivorship

INTRODUCTION

In Western countries, childhood cancer mortality rates declined by more than 50% between 1975 and 2006 as a result of more effective treatments identified and implemented during this period.[1] However, the anti-cancer treatments given to achieve these lower mortality rates may adversely affect reproductive function. In women, the pool of primordial follicles in the ovaries is fixed, and chemotherapy and radiotherapy can substantially deplete this oocyte pool. This may lead to ovarian dysfunction, infertility and premature menopause. Late effects of cancer treatment on fertility outcomes in childhood cancer survivors have been evaluated in a number of studies. Studies based on questionnaire data showed that female childhood cancer survivors had a higher risk of premature menopause[2-5] and were more likely to experience adverse pregnancy outcomes than their siblings due to the chemotherapy and radiotherapy these survivors received.[6-9] Recently, several studies have been conducted that measure ovarian reserve by means of antimullerian hormone (AMH) or ultrasound measurements[10-13], showing that the ovarian reserve is indeed depleted after certain forms of chemotherapy and pelvic radiotherapy.

A nationwide cohort study on reproductive function of female childhood survivors is currently being conducted in

the Netherlands (the DCOG LATER-VEVO study). Results of this study will provide insight into the effects of cancer treatment on the reproductive system of female childhood cancer survivors in the Netherlands and their risk of premature menopause. The effects of treatment in general will be assessed, as well as the effects of different treatment modalities, doses of drugs, radiation sites and doses, and age at time of treatment. The data gathered in this project will provide important information to girls with cancer (and their parents) about the possible adverse effects of treatment on the reproductive function. However, while conducting the nationwide study, it seemed that in Dutch paediatric oncologists knowledge about fertility issues and fertility preservation was often limited. Studies in adult oncological care indicate that knowledge about fertility issues and fertility preservation among physicians is often lacking.[14-20] In a recent study performed in Saudi Arabia, oncologists are found to have a positive attitude towards fertility preservation; however, knowledge regarding the possibilities and the success rates is poor, with up to 46% of the respondents not being familiar with any female fertility preservation options.[19] In the USA and in Canada, approximately half of the oncologists rarely referred their patients to an infertility specialist[17,20], whereas in Saudi Arabia, more than 85% did not refer[19].

Only three studies are available that have quantitatively assessed the knowledge and attitudes towards discussing female fertility issues among paediatric oncologists, two of which were performed in the USA and one in the UK.[21-23] Possibly, the lack in knowledge is due to the limited possibilities that are available in the prevention or therapy of premature menopause for female childhood cancer patients, especially when the patient is prepubertal.

Available established fertility preservation options consist of cryopreservation of embryos, vitrification of oocytes and ovarian transposition. Experimental techniques include cryopreservation of ovarian tissue, and cryopreservation of the whole ovary including vascular anastomoses. *Table 1* provides a short overview of the available techniques and their limitations in female childhood cancer patients.[24-26] To assess the current practice, the attitudes, and the knowledge of Dutch paediatric oncologists involved in oncological care regarding fertility and fertility preservation options in female childhood cancer patients, the PAK study was performed.

MATERIALS AND METHODS

The PAK study was designed as a nationwide quantitative cross-sectional study. Approval for the study was obtained and a waiver of informed consent was received from the Medical Ethics Committee of the VU University Medical Center.

Study population

The study population consisted of paediatric oncologists registered with the Dutch Childhood Oncology Group (DCOG, n=64). Paediatric oncologists were retrospectively excluded in case of retirement, or if they had treated less than five girls, aged 0-18 years, in the past year. The rationale to exclude these subjects was to ensure recent and adequate amount of experience with treating female paediatric patients.

Table 1. *Procedures and limitations of fertility preservation techniques*

Technique	Procedure	Limitations
Established techniques		
Cryopreservation of embryos	Hormonal stimulation of the ovary with exogenous FSH. Ultrasound-guided transvaginal oocyte pick-up. Fertilisation of the oocyte with the sperm in vitro. Primary freezing of the embryos. Embryo transfer after cancer treatment and follow-up is complete	• Not applicable to prepubertal girls • Male partner or sperm donor is obligate • May delay anti-cancer treatment
Vitrification of oocytes	Hormonal stimulation of the ovary with exogenous FSH. Ultrasound-guided transvaginal oocyte pick-up. Rapid freezing (vitrification) of the oocytes. Fertilisation and embryo transfer after cancer treatment and follow-up is complete	• Not applicable to prepubertal girls • May delay anti-cancer treatment
Ovarian transposition	Laparoscopic procedure to remove ovaries from the radiation field	• Effect of chemotherapy remains • Scatter radiation
Experimental techniques		
Cryopreservation of ovarian tissue	Laparoscopic or laparotomic procedure to retrieve strips of ovarian cortex. Strips are vitrified. Reimplantation of the strips (heterotopically or orthotopically) after cancer treatment and follow-up is complete	• Success rate unknown • Risk of reseeding malignancy
Transplantation of the whole ovary	Transplantation of the whole ovary with vascular anastomoses	• Success rate unknown • No pregnancies reported with this method

Data collection

Contact information of the paediatric oncologists was provided by the DCOG. The DCOG is a collaboration between paediatric oncologists and other involved experts working in the seven paediatric oncology and stem cell transplant centres in the Netherlands. Each paediatric oncologist was sent a study information package by post. This package contained a hardcopy of the survey, a cover letter and a pre-stamped and addressed return envelope, together with log-in details for filling out the online version of the survey, if preferred. In addition, the paediatric oncologists were asked to fill out a refusal form if they decided not to participate. This form included several questions regarding characteristics of the paediatric oncologist as well as a question regarding the reason for not wanting to participate in the study. After three to six weeks, paediatric oncologists who had not yet responded were sent a reminder letter by post together with another copy of the study information package. If no response was received within three months, a reminder was sent by email. This email included a hyperlink, which could directly be followed in order to fill out the survey or the refusal form online. If the paediatric oncologist also did not respond to the reminder by email, the paediatric oncologist was considered a non-responder. Participants were not reimbursed for completed surveys.

Survey development

The survey was adapted from the survey used by Duffy *et al.*[16] and was translated from English to Dutch by two independent medical translators. The two forward translations were carefully compared and a reconciled version was then back translated. The original survey was based on qualitative studies with oncologists and recommendations from a national advisory panel of experts in survivorship and reproductive technologies were incorporated.[16] It was slightly modified and some questions were deleted altogether, to account for differences in patient group (young age) and the fact that parents are often involved in decision-making regarding medical issues of their children. In general, questions regarded girls aged 0-18 years with cancer. For some questions, a discrimination was made between pre- and post-pubertal girls. The survey covered issues related to female fertility and fertility preservation in cancer treatment and included the following sections: (1) physician characteristics; (2) current practice; (3) availability and need for information or training; (4) knowledge; and (5) attitude. Five-point Likert scales were used in questions with regard to the paediatric oncologist's attitude and the confidence in their knowledge of fertility and fertility preservation in girls with cancer. We decided not to directly test knowledge. It was assumed that this might create a sense of an 'exam', which might lead to non-participation. However, in this way, it was not possible to report on the objective knowledge of paediatric oncologists as was done by Goodwin *et al.*[22]

Statistical analysis

The data were checked for normal distribution. Descriptive statistics were performed on all variables. IBM SPSS Statistics, version 20.0.0 for Windows was used for all analyses.

RESULTS

Response rate and paediatric oncologists' characteristics

In total, 64 paediatric oncologists were sent a study invitation, of whom 39 (61%) were deemed eligible.

Figure 1. *Flow chart depicting an accrual and participation rates*

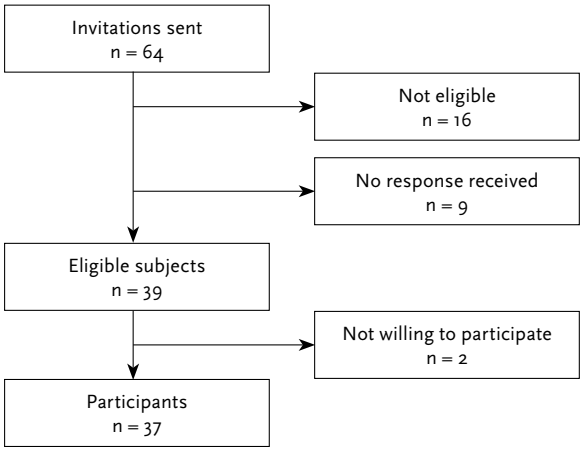

Table 2. *Characteristics of the participating paediatric oncologists (n=37)*

	Participants (n=37) N (%)
Sex	
Male	18 (48.6)
Female	19 (51.4)
Age	
30-39 years	9 (24.3)
40-49 years	18 (48.6)
50-59 years	9 (24.3)
>60 years	1 (2.7)
Years of experience	
Median	12
Range	1-30

Fourteen (22%) persons were not eligible, because they had treated less than five girls in the past year, and an additional two (4%) claimed not to be eligible but did not provide a reason for this. There were nine non-responders (14%), of whom five were female and four were male. Because of the anonymous design of the study, we were not able to evaluate whether there were differences in attitude between the participants and the non-responders. Finally, of 39 eligible subjects, 37 (58%) agreed to participate. The reasons for not participating were insufficient time (n=1) and being invited for surveys too frequently (n=1) (*figure 1*). Of the participants approximately half were male. Seventy-two per cent were between 40 and 60 years old. The median number of years in practice was 12 years (*table 2*).

Practice

Eleven paediatric oncologists (30%) treated 5-10 children aged 0-12 years annually, whereas another 30% treated 10-20 children, aged 0-12 years. Eight oncologists treated more than 20 children aged 0-12 years annually. Seven indicated that they were not sure how many children they treat. In the age group 12-18 years, 18 oncologists treated 5-10 children, seven treated 10-20 children and three treated more than 20 children annually. In this age group, nine oncologists indicated that they did not know how many children they treated. Seventy-five per cent of the paediatric oncologists reported to usually or always discuss fertility issues before the onset of treatment with prepubertal girls or their parents and 89% discussed the issue with postpubertal girls. Almost all paediatric oncologists (97%) discussed the issue with the parents if the patient was a prepubertal girl and 32% discussed it with the girl herself. In case the girl was postpubertal, 84% of the paediatric oncologists discussed the issue with the parents and 97% with the girl herself. More than three-quarters (77%) of the paediatric oncologists indicated to spend between 5-15 minutes on fertility issues, whereas 20% spent more than 15 minutes. Approximately half of the paediatric oncologists (46%) often referred their female patients to a fertility specialist, whereas 38% sometimes referred, 3% always referred and 11% never referred.

Perceived availability of fertility preservation options in own centre

All paediatric oncologists were asked which fertility preservation options were available in their own centre. As the survey was anonymous, it was not possible to substantiate the answers in the centres concerned. Therefore, when the paediatric oncologists affirmed that the requested technique was available in their centre or when they stated that it was not available, the answer was labelled 'aware of availability'. Those paediatric oncologists who responded who they did not know whether that technique was available in their centre were labelled 'unaware of availability'. Most paediatric oncologists were aware of the possibilities for cryopreservation of ovarian tissue, for ovarian transposition and for embryo cryopreservation (76%, 68%, and 65%, respectively). However, it appeared that only 54% were aware of the presence of the options for oocyte cryopreservation (*table 3*).

Table 3. *Perceived availability of fertility preservation options in own centre (n=37)*

	N (%)
Cryopreservation of ovarian tissue	
Aware of availability	28 (75.7)
Not aware of availability	8 (21.6)
Transposition of the ovaries	
Aware of availability	25 (67.6)
Not aware of availability	12 (32.4)
Cryopreservation of embryos	
Aware of availability	23 (62.2)
Not aware of availability	13 (35.1)
Cryopreservation of oocytes	
Aware of availability	19 (51.4)
Not aware of availability	17 (45.9)
Transplantation of the ovary	
Aware of availability	8 (21.6)
Not aware of availability	28 (75.7)
Percentages may not add up to 100% due to missing values.	

Information resources for female patients

It was asked which information resources for female patients were available in each centre about fertility and fertility preservation after cancer treatment. Thirty-five per cent of paediatric oncologists stated that a printed brochure was available, and 14% reported that they had a list with references to resources with regard to fertility and fertility preservation at their disposal. Forty-one per cent reported specialised nurses or social workers trained to inform female patients about fertility issues to be available. One-third of the paediatric oncologists (30%) reported to have a fertility specialist available to refer the female patient to. Sixteen per cent of the paediatric oncologists reported there were no resources at all available for female patients.

Information and education resources for paediatric oncologists

Paediatric oncologists themselves were most likely to use the scientific literature in order to stay updated on the subject of fertility preservation (68%). Other resources

used were national guidelines (35%), consult with fertility specialist (19%) or scientific meetings (5%). Three per cent of the paediatric oncologists stated that the information available on fertility preservation was not at all sufficient, while 89% found the available information to be rather or largely sufficient. Eight per cent reported the available information to be completely sufficient.

Knowledge

Overall, paediatric oncologists had a moderate or high confidence (score 4 or 5 on Likert scale) in their own knowledge of the effects of chemotherapy and radiotherapy on fertility (81% and 78% for chemotherapy and radiotherapy, respectively). However, few paediatric oncologists had a moderate or high confidence in their knowledge of ovarian transposition (24%), IVF protocols for the cryopreservation of embryos (19%) and oocytes (5%), and ovarian tissue cryopreservation (14%). Confidence in knowledge regarding health risks for the mother or foetus during pregnancy associated with various cancer treatments was rated moderate to high in 24% (mother) to 49% (foetus) of the paediatric oncologists (*table 4*).

Attitude

Respondents were asked to which extent they felt it is their responsibility to discuss fertility issues with their female patients. Ninety-seven per cent reported to find it largely to entirely their responsibility to discuss infertility with the girl or parent, whereas 75% perceived it was largely or entirely their responsibility to discuss fertility preservation. In addition, paediatric oncologists were asked whether they would accept a decrease in disease-free survival in order to increase the chance of preserving fertility. Not only their *own* opinion on this matter was questioned, but also their judgment regarding the proportion of decrease in survival that *girls and/or parents* would be willing to accept. Remarkably, many paediatric oncologists (70%) did not answer these two questions. Those paediatric oncologists

Table 4. *Proportion of paediatric oncologists reporting moderate or high confidence in knowledge of fertility issues and options for preservation (n=37)*

Item	N (%)
The risk of infertility associated with the specific chemotherapy agents that you prescribe most often	30 (81.1)
The risk of infertility associated with abdominal and pelvic irradiation	29 (78.4)
Health risks to the foetus associated with the mother having received various cancer treatments	18 (48.6)
Health risks to the mother associated with pregnancy after various cancer treatments	9 (24.3)
Surgical techniques to protect the ovary from radiation damage	9 (24.3)
Performing current protocols for IVF cycles before cancer treatment in order to freeze embryos	7 (18.9)
Cryopreserving ovarian tissue containing primordial follicles for later auto transplantation after cancer treatment	5 (13.5)
Use of GnRH agonists prior to treatment	3 (8.1)
Cryopreserving unfertilised oocytes for future fertilisation and implantation after cancer treatment	2 (5.4)
Radical trachelectomy	0

Percentages may not add up to 100% due to missing values.

Table 5. *Barriers posed to discussing fertility and fertility preservation in women with cancer (n=37)*

Item	N (%)
Patient characteristics	
Has a poor prognosis for long-term survival	9 (24.3)
Appears distressed or overwhelmed about her cancer diagnosis and/or treatment	1 (2.7)
Has aggressive disease and needs rapid initiation of cancer treatment	0
Is under age 16	0
Healthcare system barriers	
Insufficient time to discuss fertility issues with patients	33 (89.2)
Lack of knowledge about fertility preservation options	12 (32.4)
Lack of availability of fertility specialists in your geographic area	4 (10.8)
Physicians' attitude barriers	
Talking about fertility after cancer gives women false hope that they will have a normal lifespan	0
Bringing up infertility is upsetting to patients	0
Bringing up infertility could make some patients decide to forego lifesaving treatments	0
Medical considerations	
Lack of data on the effectiveness of fertility preservation options in women with cancer	8 (21.6)
Chemotherapy prior to conception could increase the risk of birth defects in offspring	7 (18.9)
Discussing options for fertility preservation could delay cancer treatment	3 (8.1)
A woman treated for cancer could have health complications during a subsequent pregnancy	2 (5.4)
The hormones used in many types of fertility preservation could stimulate the growth of cancer	2 (5.4)
A pregnancy, even after successful cancer treatment, could promote cancer recurrence	0

Reported proportions represent scores 4 or 5 on the Likert scale. Percentages may not add up to 100% due to missing values.

who did answer the question (n=11) accepted at most a 1-5% decrease in disease-free survival, and they judged that parents or patients would accept the same amount.

Perceived barriers

Paediatric oncologists were asked whether in daily clinical practice they experience certain barriers that make it less likely for them to discuss fertility or fertility preservation. The barriers reported (*table* 5) were mainly related to the healthcare system, physicians' attitude, medical considerations and patient characteristics that made it less likely to discuss fertility (preservation options). Many paediatric oncologists (89%) stated that insufficient time is an important barrier to discuss fertility issues with the patients or their parents. In addition, one-third of the paediatric oncologists found their lack of knowledge about fertility preservation options a barrier. Approximately 1 in 5 paediatric oncologists reported that the lack of scientific data on the effectiveness of fertility preservation options in women with cancer influenced their willingness to discuss fertility and fertility preservation. A poor prognosis for long-term survival was mentioned by 24% of the paediatric oncologists as a reason not to discuss fertility issues. Other factors, for example, whether the patient has an aggressive disease and needs rapid initiation of cancer treatment, whether the patient is under the age of 16, or whether the patient appears distressed or overwhelmed about her cancer diagnosis and/or treatment, did not seem to influence the paediatric oncologist's willingness to discuss fertility and fertility preservation options (*table* 5).

DISCUSSION

This is the first study assessing the practice, knowledge and attitudes towards female fertility and cancer in paediatric oncologists in the Netherlands and continental Europe. Compared with response rates from other nationwide surveys conducted among paediatric oncologists in the UK and the USA, our response rate was higher (15%[23]) or similar (68%[21]). Our high response rate might be due to the fact that there are only a limited number of paediatric oncologists in the Netherlands and since they are all acquainted, possibly, social desirability played a role in the willingness to complete the questionnaire. When interpreting the results of our study, some limitations should be considered. Although the response rate was high, self-selection bias might have been introduced. Paediatric oncologists who were more interested in the subjects of (in)fertility and fertility preservation options were possibly more likely to discuss fertility issues with their female patients and consequently might have been more likely to participate in this study. Further, within the questions regarding barriers to discuss fertility or referral options no distinction was made between pre- and post-pubertal girls. It is likely, and has been demonstrated by Kohler *et al.*, that pubertal status influences the paediatric oncologist's attitude and practice regarding fertility and fertility preservation.[23] Moreover, it is plausible that the paediatric oncologist's knowledge is less extensive in prepubertal girls, because few possibilities for fertility preservation exist in this patient group and these are mostly experimental. We decided not to directly test knowledge. It was assumed that this might create a sense of an 'exam', which might lead to non-participation. However, in this way, it was not possible to report on the objective knowledge of paediatric oncologists as was done by Goodwin *et al.*[22] When evaluating the answers given as well as the remarks made by the participants, it seemed that some questions in the survey were considered difficult to answer or could be interpreted in various ways. For some questions, this makes it difficult to draw unambiguous conclusions.

In accordance with previous literature[21,23], our results show that paediatric oncologists frequently discuss fertility issues, but referral rates remain relatively low. The reason for this might be that the options for fertility preservation (especially in prepubertal girls) are scarce. To date the procedure of ovarian tissue cryopreservation is still experimental, but it should be realised that it might take several years to decades before these young girls will request transplantation. It is likely that the techniques that are at this moment experimental will at that time be regarded as usual care and, moreover, success rates might be much higher. Although 75% of paediatric oncologists in the PAK study were aware of the possibilities for ovarian tissue cryopreservation, only 13.5% claimed that they were confident in their knowledge regarding this technique. Other studies found similar proportions of awareness.[22,23] These results indicate that there is a lack of knowledge among paediatric oncologists regarding fertility preservation options and that there is a need for additional education. Further education for paediatric oncologists should preferably be structured in protocols or guidelines, in order to standardise fertility preservation care as much as possible in the different centres. In addition, printed brochures on the effect of cancer treatment on fertility as well as fertility preservation options (established as well as experimental) should be available for all paediatric oncologists to hand out to their patients. Good counselling and if possible, adequate action to preserve fertility will add to the future quality of life of female childhood cancer survivors.

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DISCLOSURES

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ORIGINAL ARTICLE

Cost of screening strategies for kidney disease before intravenous contrast administration

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ABSTRACT

Purpose: To assess whether selective use of estimated glomerular filtration rate (eGFR) in patients with risk factors for kidney disease is more cost-effective than measuring eGFR in all patients undergoing contrast-enhanced computed tomography (CECT).

Methods: Risk factors and costs were assessed in consecutive patients. eGFR was evaluated in all patients, considering a tenability of 12 months. For the three-month tenability and the pre-selection strategy based on risk factors for kidney disease, we extrapolated data by assuming equal distribution of patient characteristics.

Results: We included 1001 patients, mean age 59.9±13.6 years.

Strategy with eGFR in all patients: eGFR measurements specifically performed for CECT in 645/1001 (in 356 patients the eGFR was already known). The total cost including costs of an extra visit to the hospital (49 patients) and absence from work (11 patients) were € 6037.20. Considering a tenability of 3 months, eGFR had to be measured in 786 patients, 60 would have paid an extra visit and 14 would have been absent from work: total cost € 7443.54. Pre-selection strategy: 807 patients had risk factors, necessitating eGFR measurement and an extra visit would be paid by 61. Fourteen patients would have been absent from work: total cost € 7585.16. Of the patients with an eGFR <60 ml/min/1.73m², 94.8% were identified including all with an eGFR <45 ml/min/1.73m².

Conclusion: Determining eGFR based on risk factors for kidney disease is not more cost-effective than eGFR testing in all patients if the eGFR is tenable for 12 months or for 3 months.

KEYWORDS

Computed tomography, contrast-induced nephropathy, cost-effective, kidney disease, prevention

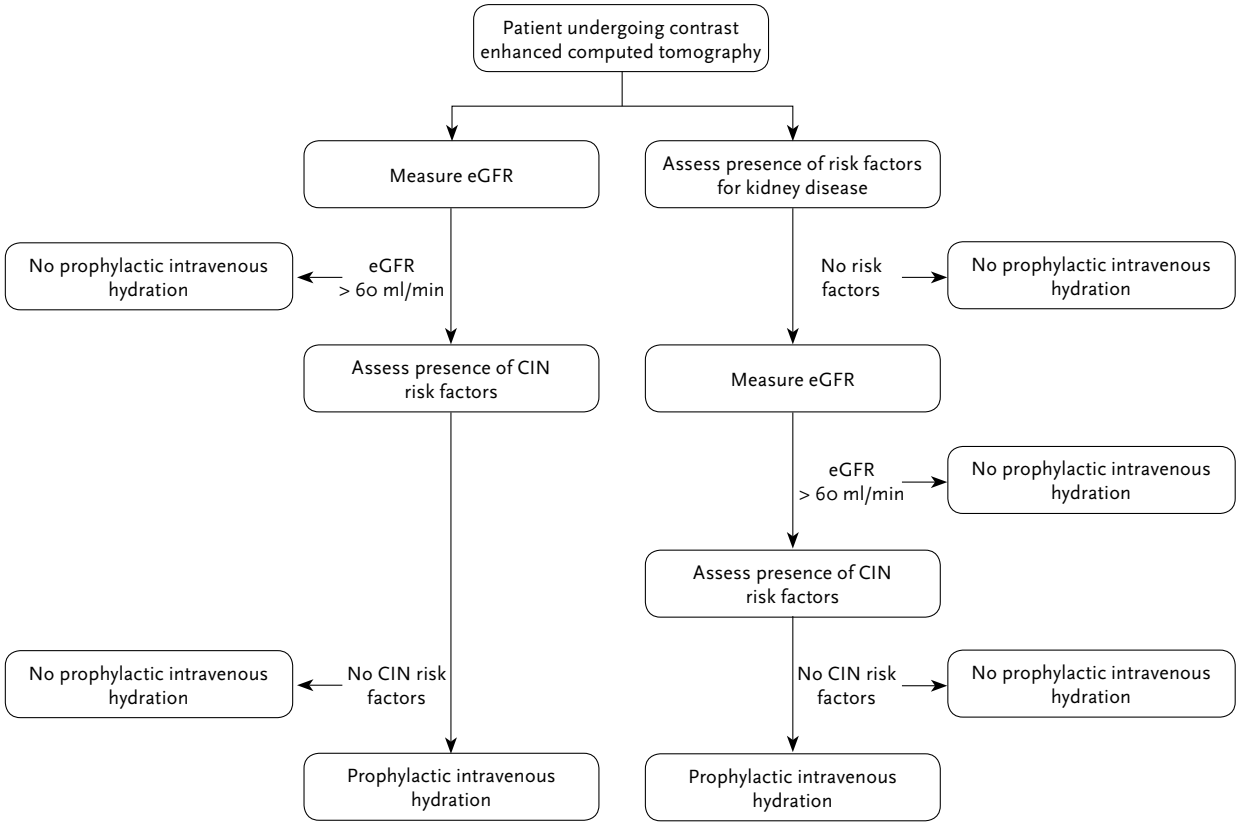
INTRODUCTION

The number of computed tomography examinations increases every year due to the improvement of availability and progress in clinical application.[1] The majority of computed tomography examinations are intravenously contrast-enhanced with iodinated contrast medium. Unfortunately the use of iodinated contrast medium can lead to acute nephropathy, also known as contrast-induced nephropathy (CIN).[2]

Worldwide several CIN prevention guidelines have been introduced.[2-8] Most guidelines describe risk profiles by which potential CIN patients can be recognised in order to determine whether CIN prevention measures are necessary.[2-8] This usually involves the recognition of patients with the most important risk factor for CIN: pre-existent (chronic) kidney disease, which is usually defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m².[2-8] Kidney disease in combination with other risk factors related to CIN, for example diabetes mellitus or cardiovascular disease, outlines the patients who need CIN prevention.[2-8] CIN prevention usually entails volume expansion through oral or intravenous hydration and discontinuation of diuretics or nephrotoxic medication.[2-8]

To screen for the presence of kidney disease, eGFR measurement is inevitable. Some CIN prevention guidelines indicate that the eGFR should be known in all patients before administration of iodinated contrast medium.[4,6,7,9] To reduce the number of eGFR measurements these guidelines usually recommend a tenability period for eGFR of 3-12 months with the exception of patients with a history of kidney disease, or a relevant medical event that might have influenced the eGFR (kidney function).[4,6,7,9] Other CIN prevention guidelines indicate that risk factors associated with kidney disease should be assessed first and if these risk factors are present, the eGFR should be measured in these patients only.[2,3,5,8] See *figure 1* for an overview of these screening strategies.

Figure 1. *Flow chart for different screening strategies*



CIN = contrast-induced nephropathy; eGFR = estimated glomerular filtration rate

The literature shows that there is a preference among radiologists to routinely measure eGFR or serum creatinine in all patients before administering iodinated contrast medium instead of measuring eGFR or serum creatinine in patients with risk factors for kidney disease.[10-12]

It is not clear which screening strategy is more cost-effective. Measuring eGFR or serum creatinine in all patients seems costly. On the other hand, if eGFR or serum creatinine is measured in a select group of patients, patients without risk factors for kidney disease but with unknown severe kidney disease (eGFR <45 ml/min/1.73m^2) would be missed. Furthermore, most CIN prevention guidelines are based on articles where iodinated contrast medium is administered intra-arterially, mostly during (emergency) cardiac intervention.[4-6,8] This patient population differs from the patient population undergoing intravenous iodinated contrast-enhanced computed tomography (CECT).[13]

We therefore wanted to compare the cost-effectiveness of the different screening strategies in patients undergoing intravenous iodinated CECT. The first screening strategy considers that eGFR is known in all patients undergoing intravenous iodinated CECT. This means that eGFR is available in all patients with a tenability of 12 months. The second strategy considers that eGFR is available in all patients with a tenability of three months. Finally, the third strategy considers a pre-selection strategy, where eGFR would have been measured after assessment of risk factors for kidney disease in patients undergoing intravenous iodinated CECT.

We will compare the costs and the number of patients with severe kidney disease (eGFR <45 ml/min/1.73m^2) who would be missed by the pre-selection strategy (effectiveness). This concerns patients without any risk factors, but with severe kidney disease.

MATERIALS AND METHODS

Design

This study was internally funded as 'Quality assessment project' in the Academic Medical Center, University of Amsterdam. The funding body was not involved in the design or the execution of this study, did not have access to the data, and was not involved in data analysis or preparation of this article.

The standard procedure at our institution is that eGFR is available in all patients prior to intravenous iodinated

CECT. A tenability of 12 months is maintained with the exception of patients with known kidney disease or a clinical event, which could affect eGFR, in these cases eGFR measurement is indicated. Estimated GFR was calculated using the four-point Modification of Diet in Renal Disease (MDRD) formula which takes into account age, sex and race and is expressed as ml/min/1.73m^2. This is in accordance with the national CIN prevention guideline that is used in our hospital.[4]

According to this guideline, in patients with pre-existent (chronic) kidney disease, defined as an eGFR <60 ml/min/1.73m^2, risk factors related to CIN should be checked.[4] This means that in patients with an eGFR >60 ml/min/1.73m^2, CIN risk factors are not checked or registered. These CIN risk factors are very similar to risk factors for kidney disease. For research purposes, we checked and registered all risk factors for CIN and kidney disease in all patients, in order to be able to simulate the screening strategy in which pre-selection by risk factor assessment for kidney disease preceding the eGFR measurement is performed.

Patient population and recruitment

Because our study did not influence standard care, participation in our study was considered a minor burden for patients (scripted interview). Informed consent was waived by the medical ethics committee of our institute.

We prospectively included consecutive patients who underwent intravenous iodinated CECT in our institute, from October 2012 until May 2013. The contrast medium used in all procedures was iopromide (Ultravist 300, Bayer, Leverkusen Germany), or iomeprol (Iomeron 400, Bracco, Milan Italy), which both have low osmolality and are nonionic.

Patients were excluded if they were <18 years of age, unresponsive due to severe illness and could not be interviewed, unwilling to participate, if they did not speak Dutch or English or if it was logistically impossible to interview the patient (e.g. if there was more than one patient at the same time, if there was no space available to interview the patient or if the patient had no time due to commitments elsewhere). Patients admitted to the intensive care or emergency department were also excluded, as most prevention guidelines are not applicable for these patients.

Data collection

Data were collected from the digital patient record as well as through scripted interviews. The data collected from the digital patient record were: age, gender, type of intravenous iodinated CECT procedure, indication for the intravenous iodinated CECT, serum creatinine and eGFR before the procedure, whether they were inpatients or outpatients and whether they were on diuretics/ nephrotoxic medication (e.g. non-steroidal anti-inflammatory drugs (NSAIDs) as well as any other medication indicated as nephrotoxic in a national database (Farmacotherapeutisch Kompas) containing information on all (human) registered drugs in the Netherlands and Europe.[14] We also assessed if multiple myeloma or Waldenström's disease was present.

To assess the presence of other risk factors we performed scripted face-to-face interviews on the day of the intravenous iodinated CECT to obtain data to supplement the findings in the digital patient record. In the interview we asked if patients suffered from diabetes mellitus, cardiovascular disease, hypertension or history of urological or nephrological disease. The interviews were conducted by four researchers (SM, RW, GN, DVV) who received interview instructions from a senior researcher (SM) to guarantee uniform data collection.

We defined the following risk factors as associated with kidney disease in patients receiving iodinated contrast medium: age >60 years, hypertension, use of nephrotoxic medication, cardiovascular disease, a history of urological or nephrological disease, diabetes mellitus, use of metformin, multiple myeloma or Waldenström's disease. These risk factors were chosen based on CIN prevention guidelines indicating that risk for kidney disease should be assessed preceding eGFR measurement.[2,3,5,8] We collected these data in all patients.

Cost-analysis

We used the costs associated with eGFR measurement to calculate direct medical costs (eGFR tests), direct non-medical costs (travel costs) and indirect non-medical costs (productivity loss) due to a visit to the hospital for eGFR measurement. We did this for all screening strategies.[15,16]

eGFR in all patients with a tenability of 12 months

To assess the costs of this screening strategy, we looked at the number of patients in whom the eGFR was measured for the sole purpose of intravenous iodinated CECT. This was done as follows.

Costs associated with eGFR measurement: As we were unable to ascertain if eGFR measurements were performed for the sole purpose of intravenous iodinated CECT in our patient population, we assumed that all eGFR measurements within one month before the intravenous iodinated CECT were for this purpose. This included the patients who stated during the interview that they paid an extra visit to the hospital for the sole purpose of eGFR measurement. For patients who stated during the interview that they paid an extra visit to the hospital for the sole purpose of eGFR measurement >1 month before intravenous iodinated CECT, costs for these eGFR measurement were added to the costs made for eGFR measurements within one month before intravenous

iodinated CECT. We considered these to be direct medical costs. For all other patients with an eGFR value >1 month before intravenous iodinated CECT, we assumed that the eGFR was already known.

Travel costs: As we had asked patients if they had to pay an extra visit to the hospital for the sole purpose of eGFR measurements in preparation for the intravenous iodinated CECT, we were able to calculate travel costs. For travel costs, we also asked them about their means of transportation to and from the hospital. All extra visits (both <1 month and after 1 month) were used for calculation of the travel costs. For the remaining patients, no travel costs were taken into account. We assumed that in these patients eGFR measurement was combined with a visit to the hospital with another purpose than eGFR measurement.

Costs associated with productivity loss: For the loss of productivity, we asked patients who had to pay an extra visit to the hospital for eGFR measurement if they had to take time off from work and if so how long.

eGFR in all patients with a tenability of three months

We also calculated costs related to an eGFR tenability of three months. We than considered that all eGFR values measured within one month were for the sole purpose of intravenous contrast-enhanced computed tomography and that eGFR should have been measured if the eGFR value was older than three months and costs associated with eGFR measurement were calculated.

To enable data extrapolation for calculation of the indirect costs (travel costs and loss of productivity), we assumed that the same percentage of patients would have paid an extra visit to the hospital and had to take time off from work, using the same means of transportation.

eGFR in patients with risk factors for kidney disease

For this screening strategy we determined the number of patients in whom eGFR would have been measured because of the presence of one or more of the above-mentioned risk factors for kidney disease. This number was used to calculate the direct costs (eGFR evaluation). We also extrapolated data for calculation of travel costs and costs associated with productivity loss.

Unit prices and costs

Costs associated with eGFR measurement: 1) Costs related to determining eGFR measurement. In our hospital these costs were € 6.03 per eGFR measurement 2) Travel costs were categorised in number of kilometres (km) using a car (€ 0.20/km + € 3.00 for parking), using public transport (€ 0.20/km) or a taxi (€ 2.00/km + € 3.50 start rate). For patients travelling by bicycle or on foot no additional costs were added. 3) Productivity related costs were calculated by the number of hours absent from work multiplied by € 32.49 for men and € 25.94 for women (this was based on information gathered by Central Bureau for Statistics the Netherlands (CBS) and represents the mean contribution value per person per hour of labour).[15] Using these costs, the total costs per strategy were calculated and also the average per patient was calculated for each strategy. This was done by dividing the total costs by the number of patients screened.

Statistical analyses

We used descriptive statistical analysis to summarise the results. We expressed the continuous data as means and standard deviation (SD) and categorical data as numbers and percentages. We organised our data using Microsoft Office Access® 2003, Microsoft Corp. Redmond, WA and analysed the data using IBM® SPSS® statistic data editor version 20 SPSS® Inc. Chicago, Il.

RESULTS

Baseline patient characteristics

Between October 2012 and May 2013 there were 1191 eligible patients. Of these patients 176 could not be included due to a language barrier, or patients did not want to participate, there was no time to interview the patient or the patients did not show up for the examination. We were finally able to interview 1015 patients. Seven patients did not receive intravenous iodinated contrast medium during their computed tomography; for another six patients the data could not be used for analysis due to incomplete data and one patient was <18 years. In total 1001 patients were included for analyses. See *figure 2*.

The mean age was 59.9 years (SD: 13.6), there were 548 males (54.7%) in the patient population and 74 patients

Figure 2. *Patient inclusion flow chart*

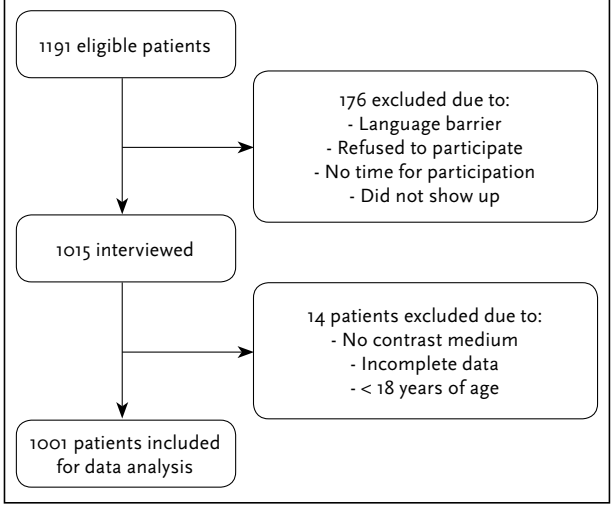


Table 1. *Baseline characteristics in patients undergoing intravenous contrast enhanced computed tomography*

Baseline characteristics	**Total study population (*n*= 1001)**	**eGFR ≥ 60 ml/ min/1.73m² (*n*=886)*****	**eGFR 45-59 ml/ min/1.73m² (*n*=82)**	**eGFR 30-44 ml/ min/1.73m² (*n*= 26)**	**eGFR 15-29 ml/ min/1.73m² (*n*= 4)**
Demographics					
Age (yrs) mean ± SD	59.9 ± 13.6	59.2 ± 13.5	65.3 ± 12.6	68.3 ± 11.9	62.8 ± 20.2
Male: female *n* (%)	548 (54.7) : 453 (45.3)	487(55.1) : 399(44.9)	41 (47.6) : 41 (52.4)	16 (61.5) :10 (38.5)	1 (25.0) : 3 (75.0)
Height (cm) mean ± SD*	172.8 ± 10.2	173.0 ± 10.3	170.9 ± 9.3	171.9 ± 8.6	172.5 ± 13.1
Weight (kg) mean ± SD	75.9 ± 16.5	75.5 ± 16.0	80.4 ± 18.3	78.0 ± 20.3	71.5 ± 7.9
BMI (kg/m²) mean ± SD*	25.4 ± 4.8	25.2 ± 4.7	27.5 ± 5.0	26.3 ± 6.3	24.1 ± 2.7
Kidney function					
Serum creatinine (µmol/l) mean ± SD**	79.0 ± 23.0	73.9 ± 15.6	105.6 ± 15.8	142.7 ± 17.9	224.5 ± 48.8
eGFR (ml/min/) mean ± SD***	-	-	53.8 ± 4.1	38.7 ± 4.0	21.5 ± 4.2
Type of CT scan					
Chest/ Abdomen *n* (%)	388 (38.8)	339 (38.3)	37 (45.1)	11 (42.3)	-
Abdomen *n* (%)	146 (14.6)	131 (14.8)	11 (13.4)	3 (11.5)	1 (25.0)
Kidney *n* (%)	107 (10.7)	89 (10.0)	12 (14.6)	5 (19.2)	1 (25.0)
Pancreas *n* (%)	95 (9.5)	90 (10.2)	4 (4.9)	1 (3.8)	-
Cardiac *n* (%)	56 (5.6)	49 (5.5)	4 (4.9)	2 (7.7)	1 (25.0)
Chest *n* (%)	53 (5.3)	51 (5.8)	2 (2.4)	-	-
Aorta *n* (%)	45 (4.5)	39 (4.4)	3 (3.7)	2 (7.7)	1 (25.0)
Liver *n* (%)	41 (4.1)	33 (3.7)	4 (4.9)	2 (7.7)	-
Cerebrum *n* (%)	12 (1.2)	12 (1.4)	-	-	-
Other *n* (%)	58 (5.8)	53 (6.0)	5 (6.1)	-	-
Indication CT scan					
Malignancy *n* (%)	451 (45.1)	393 (44.4)	43 (52.4)	12 (46.2)	-
Suspected malignancy *n* (%)	260 (26.0)	233 (26.3)	20 (24.4)	7 (26.9)	-
Vascular deformation *n* (%)	79 (7.9)	70 (7.9)	6 (7.3)	2 (7.7)	1 (25.0)
Nephrological disease *n* (%)	34 (3.4)	29 (3.3)	3 (3.7)	2 (7.7)	-
Infection *n* (%)	51 (5.1)	51 (5.8)	-	-	-
Kidney donation *n* (%)	15 (1.5)	15 (1.7)	-	-	-
Family history of cardiac disease	13 (1.3)	12 (1.4)	1 (1.2)	-	-
Pulmonary embolism	7 (0.7)	5 (0.6)	2 (2.4)	-	-
Macroscopic haematuria	6 (0.6)	3 (0.3)	1 (1.2)	1 (3.8)	1 (25.0)
Cysts (liver, kidney, pancreas)	7 (0.7)	7 (0.8)	-	-	-
Angina pectoris	9 (0.9)	8 (0.9)	1 (1.2)	-	-
Other *n* (%)	69 (6.9)	60 (6.8)	5 (6.2)	2 (7.7)	2 (50.0)
Patient status					
Inpatient *n* (%)	74 (7.4)	55 (6.2)	9 (11.0)	8 (30.8)	1 (25.0)
Outpatient *n* (%)	927 (92.6)	831 (93.8)	73 (89.0)	18 (69.2)	3 (75.0)

***One patient did not know their height; **serum creatinine values were missing in 25 patients; ***eGFR was missing in 3 patients: these patients could not be categorised; other information was available.**

(7.4%) were inpatients, 5.7% of the patient population were Afro-European (n=57).
Most patients underwent intravenous iodinated CECT because of a malignancy (n=451, 45.1%) or because a malignancy was suspected (n=260, 26.0%). CECT of the chest and abdominal region was the most common examination (n=388, 38.8%).
The mean serum creatinine at baseline was 79.0 μmol/l (SD: 23.0). The eGFR was ≥60 ml/min/1.73m² in 882 (88.1%) patients, 82 (8.2%) patients had an eGFR between 45-59 ml/min/1.73m², 26 (2.6%) between 30-44 ml/min/1.73m² and 4 (0.4%) patients had an eGFR <30 ml/min/1.73m². In three patients eGFR was unknown but we had complete information on risk factors and indirect cost. We therefore included these patients in our analysis. See *table 1* for detailed information.

Risk factors for kidney disease

In total 576 (57.5%) of the patients were aged >60 years at the time of the examination. Hypertension was present in 370 (37.0%) patients, 301 (30.1%) used nephrotoxic medication, 295 (29.5%) suffered from cardiovascular disease, 232 (23.2%) patients had a history of urological or kidney disease, 137 (13.7%) patients suffered from diabetes mellitus and 89 (8.9%) patients used metformin at the time of the intravenous iodinated CECT. Of the 1001 patients, 807 (80.6%) had ≥1 risk factor for chronic kidney disease.
Of the 886 patients with an eGFR ≥60 ml/min/1.73m², 694 (78.3%) patients had ≥1 risk factors for kidney disease. There were 78 patients (95.1%) with an eGFR between 45-59 ml/min/1.73m², 26 (100%) with an eGFR between 30-44 ml/min/1.73m² and 4 (100%) with an eGFR <30 ml/min/1.73m² who had ≥1 risk factors for kidney disease. All three patients with an unknown eGFR had ≥1 risk factors for kidney disease. In total 112 patients had an eGFR <60 ml/min/1.73m² and 108 (98.4%) had risk factors for kidney disease. Two patients had no risk factors and would not be identified by risk factor assessment. Of the 30 patients with an eGFR <45 ml/min/1.73m², all were identified through risk factor assessment. No patients who would be classified as being at risk for CIN were missed by either strategy because these patients with an eGFR <60 ml/min/1.73m² had no risk factors. See *table 2* for more details on risk factors for kidney disease.

Direct medical costs

eGFR in all patients with a tenability of 12 months

In 631 (63.0%) patients the eGFR was measured within one month of the intravenous iodinated CECT and we considered these eGFR measurements to be related to the intravenous iodinated CECT.
When we asked patients if they had paid an extra visit to the hospital for the eGFR measurement only, 49 (4.9%) patients answered affirmatively. Of these 49 patients, 35 reported that eGFR measurement took place within one month of the intravenous iodinated CECT, 11 patients reported that they had to pay an extra visit for the sole purpose of eGFR measurement between 1-3 months and 3 (0.3%) between 3-12 months before the intravenous iodinated CECT. In total 645 (631+11+3) eGFR measurements were performed for intravenous iodinated CECT. To calculate direct medical costs we multiplied this by the cost of the eGFR

Table 2. *Risk factors for kidney disease*

Risk factors for kidney disease *n* (%)	**Total study population (*n*= 1001)***	**eGFR ≥ 60 ml/min/1.73m² (*n*= 886)**	**eGFR 45-59 ml/min/1.73m² (*n*=82)**	**eGFR 30-44 ml/min/1.73m² (*n*= 26)**	**eGFR 15-29 ml/min/1.73m² (*n*= 4)**
Age >60 years	576 (57.5)	492 (55.1)	60 (73.2)	20 (76.9)	2 (50.0)
Hypertension	370 (37.0)	302 (34.0)	51 (62.2)	15 (46.2)	2 (50.0)
Use of nephrotoxic medication	301 (30.1)	254 (28.7)	33 (40.2)	12 (46.2)	2 (50.0)
Cardiovascular disease	295 (29.5)	252 (28.4)	29 (35.4)	13 (50.0)	1 (25.0)
Urological/ nephrological history	232 (23.2)	167 (18.8)	39 (47.6)	22 (84.6)	3 (75.0)
Diabetes mellitus	137 (13.7)	112 (12.6)	15 (18.3)	10 (38.5)	-
Use of metformin	89 (8.9)	76 (8.6)	7 (8.5)	6 (23.1)	-
Multiple myeloma/ Waldenström's disease	3 (0.3)	2 (0.2)	1 (1.2)	-	-
Total number of patients with risk factor(s) *n* (%)	807 (80.6)	694 (78.3)	78 (95.1)	26 (100)	4 (100)

***eGFR was missing in 3 patients: these patients could not be categorised; other information was available.**

measurement (€ 6.03); the costs for eGFR measurement were € 3889.35. See *tables 3* and *4* for more details.

eGFR in all patients with a tenability of three months
As mentioned above, in 631 (63.0%) patients the eGFR was measured within one month of the intravenous iodinated CECT. Another 11 patients had to pay an extra visit for the sole purpose of eGFR measurement between 1-3 months. In 144 patients the eGFR was measured >3 months before the intravenous iodinated CECT. With a tenability of three months eGFR would have been measured in another 144 patients.
For this strategy eGFR would have been measured in 786 (78.5%, 631+144+11) patients, multiplied by € 6.03, the cost for eGFR testing would have been: € 4739.58. See *tables 3* and *4* for details.

eGFR in patients with risk factors for kidney disease
When risk factors for kidney disease were assessed, 807 (80.6%) patients had ≥1 risk factors indicating eGFR measurement, multiplied by € 6.03, the costs for eGFR measurement would have been € 4866.21. See *tables 3* and *4*.

Indirect medical costs (travel costs)
eGFR in all patients with a tenability of 12 months
Forty-nine patients (7.6%) paid an extra visit to the hospital for the sole purpose of measuring the eGFR. Thirty-two patients travelled by car over a total distance of 1172.9 km (one way), multiplied by € 0.20, making the cost of the trip € 469.16 (to and from hospital); with the addition of € 3.00 parking costs per visit, the travelling costs were € 565.16. Seven patients used public transportation covering a total distance of 390.1 km (one way), multiplied by € 0.20, costing € 156.04 (to and from hospital). One patient used a taxi over a distance of 13.9 km (one way), multiplied by € 2.00, making the costs (to and from hospital) € 55.60; with the addition of twice € 3.50 starting rate (to and from hospital), the taxi costs were € 62.60. The other ten patients travelled by bicycle or foot (59.9 km one way). The total travelling costs for eGFR measurement were: € 783.80. See *table 5* for more details.

eGFR in all patients with a tenability of three months
If we had maintained a tenability of three months, 60 patients (7.6% of 786) would have travelled to have eGFR measured. At an average of € 783.80/49 per patient (see previous paragraph) this would cost € 959.76. See *table 5* for more details.

eGFR in patients with risk factors for kidney disease
When we extrapolated data for the 807 patients with risk factors for kidney disease (hence an indication for eGFR measurement) we found that 61 (7.6% of 807) patients would have travelled for eGFR testing. At an average of € 783.80/49, multiplied by 61, this would cost € 975.75. See *table 5* for more details.

Table 3. *eGFR measurement*

eGFR available for all patients tenability 12 months		**eGFR available for all patients tenability 3 months***		**eGFR determination after risk assessment****	
eGFR within one month of examination *n* (%)	631 (62.1)*	**eGFR within one month of examination *n* (%)**	631 (62.1)	**Patients with pre-selection risk factors *n* (%)**	807 (80.6)*
eGFR > 1 month *n* (%)	370 (36.9)	**eGFR > 3 month *n* (%)**	144 (14.4)	***NA***	-
Extra visit *n* (after one month)	14*	**Extra visit *n* (%) (between 1-3 months)**	11* (1.1)	***NA***	-
Total eGFR for CT n (%)*	645 (64.4)	***Total eGFR for CT n* (%)***	786 (78.5)	***Total eGFR for CT n* (%)***	807 (80.6%)
Total extra visits n (%)**	49 (7.6% of 645)	***Total extra visits n* (%)****	60 (±7.6% of 786)***	***Total extra visits n* (%)****	61 (±7.6% of 807)***

*** Used for calculation of total eGFR for CT direct costs; ** Used for calculation of indirect costs (see table 4); *** Extrapolated (same percentage as in the first model)**

Table 4. *Direct costs associated with eGFR determination*

eGFR available for all patients tenability 12 months		**eGFR available for all patients tenability 3 months***		**eGFR determination after risk assessment****	
Total eGFR for CT *n* (%)*	645	**Total eGFR for CT *n* (%)**	786	**Total eGFR for CT *n* (%)**	807
Costs €	3,889.35	**Costs €**	4,739.58	**Costs €**	4,866.21

*** Within 1 months and extra visit in > 1 months; ** These numbers were extrapolated from the total patient population**

Table 5. *Travel costs associated with eGFR measurement*

eGFR available for all patients tenability 12 months ***n*** **= 49**			**eGFR available for all patients tenability 3 months*** ***n*** **= 60**	**eGFR test after risk assessment*** ***n*** **= 61**
Means of transportation	**Distance** Km**	**Costs €**	**Costs €**	**Costs €**
Car (*n*=32)	1172.9	565.16	Average travel cost per patient €15.99 *(783.80/49)*	Average travel cost per patient €15.99 *(783.80/49)*
Public transportation (*n*=7)	390.1	156.04		
Taxi (*n*=1)	13.9	62.60		
Bicycle/ by foot (*n*=9)	59.9	0		
Total	1636.8	783.80	959.76	975.75

*** These numbers were extrapolated from the total patient population; **distance was given for one way.**

Indirect non-medical costs (productivity loss)

eGFR in all patients with a tenability of 12 months

We also calculated loss of productivity. Of the 49 patients who had to pay an extra visit to the hospital for the sole purpose of the eGFR measurement 11 (22.4%) patients had to take a leave of absence from work. Eight men were absent for 31 hours in total and 3 women for 14 hours in total. Costs: 31 multiplied by € 32.49 plus 14 multiplied by € 25.49 resulted in a total of € 1364.05. See *table 5*.

eGFR in all patients with a tenability of three months

If we had maintained a tenability of 3 months, we would find that 14 (22.4% of 60) patients would have taken leave of absence. Of these 14 patients there would have been 10 men and 4 women (based on same distribution). This would result in 38 hours and 45 minutes of absence from work for the men and 18 hours and 40 minutes for the women. This would lead to a productivity loss of € 1258.99 for the men and € 482.48 for the women, in total € 1743.20. See *table 6*.

eGFR in patients with risk factors for kidney disease

Extrapolation for the group of patients with risk factors for kidney disease also resulted in 14 patients (22.4% of 61 patients) who would have taken leave of absence, resulting in the same amount of € 1743.20. See *table 6*.

Total costs per strategy

We added all the costs for the population of 1001 patients in whom eGFR was made available either in all patients with tenability of eGFR of 12 months, 3 months or in all patients with risk factors for kidney disease. Total costs if eGFR had been known in all patients with a tenability of 12 months were: € 6037.20 (average € 6.03/patient). If tenability had been three months, the total cost would be € 7442.54 (average of € 7.43/patient).

For the strategy of patient population with risk factors for kidney disease, the total costs were: € 7585.16 (average of € 7.58/patient).

DISCUSSION

Our results suggest that measuring eGFR based on risk factors for kidney disease (pre-selection strategy) is not more cost-effective than eGFR measurement in all patients if the eGFR is tenable for 12 months. Because the patients with an eGFR <60 ml/min/1.73m^2 who were missed by the pre-selection strategy had no risk factors, the risk for CIN can be considered to be comparable with patients with an eGFR ≥60 ml/min/1.73m^2.[2-8] If tenability of eGFR is set at three months, the costs are comparable with the pre-selection strategy.

Arguments for the strategy in which eGFR is available to all patients prior to intravenous iodinated CECT are that it is safer and implementation is fairly easy.[4] However tenability for eGFR of 12 months is rather long and a tenability of three months does not seem as cost-effective. Our results also suggest that when risk factors for kidney disease are assessed preceding eGFR measurement almost all patients with kidney disease (eGFR <60 ml/min/1.73m^2) including all patients with rather severe kidney disease (eGFR <45 ml/min/1.73m^2) are identified, thus this strategy seems equally safe/effective. On the other hand, with an incidence of kidney disease of 11.2% (eGFR <60 ml/min/1.73m^2) and eGFR measurement in 63%, 78% and 80% of the patients, respectively, none of the strategies seem cost-effective. There again, the difference in screening costs per patient of 1-2 euros seems relatively small, but with the increasing number of iodinated CECT examinations annually the cost reduction achieved by more cost-effective screening strategies could be substantial.[1]

Table 6. *Productivity loss associated with eGFR measurement*

eGFR available for all patients tenability 12 months		**eGFR available for all patients tenability 3 months***		**eGFR test after risk assessment***	
Absence from work (m : f = 8 : 3)	***n* =11 (22.4% of 49)**	**Absence from work (m : f = 10 : 4)**	***n* =14 (± 22.4% of 60)**	**Absence from work (m : f = 10 : 4)**	***n* =14 (± 22.4% of 61)**
Men hours	31	Men hours	38.75	Men hours	38.75
Women hours	14	Women hours	18.66	Women hours	18.66
Costs productivity loss		Costs productivity loss		Costs productivity loss	
Men €	1007.19	Men €	1258.99	Men €	1258.99
Women €	356,86	Women €	484.21	Women €	484.21
***Total* €**	1364.05	***Total* €**	1743.20	***Total* €**	1743.20
***These numbers were extrapolated from the total patient population; **distance was given for one way.**					

Since the risk factors mentioned in most guidelines were based on expert opinion or studies describing the relationship with risk factors and serum creatinine instead of eGFR a way to improve cost-effectiveness could be to reduce the number of risk factors in screening for kidney disease in CIN prevention guidelines. This will reduce the number of eGFR measurements and costs. Recent literature suggests that other risk factors are related to kidney disease in patients undergoing intravenous iodinated CECT.[17-19] Utsunomia *et al.* showed that risk factors associated with kidney disease were cardiovascular disease, advanced age (>70 years) and diabetes mellitus in patients undergoing intravenous iodinated CECT without oncological disease.[17] A recent meta-analysis suggests that kidney disease, advanced age (>65 years), use of NSAIDs, malignancy and diabetes are associated with CIN in patients undergoing intravenous iodinated CECT.[18] This could mean that a combination of these risk factors could provide a more specific and thus cost-effective screening tool for patients at risk for CIN and could reduce the number of eGFR measurements.

LIMITATIONS

Our study has some limitations. One limitation was that we had to extrapolate data to enable cost analyses. Hence we do not know in all patients with risk factors for kidney disease if eGFR was measured for the sole purpose of intravenous iodinated CECT.

Another limitation was that we did not know the actual number of patients in whom eGFR was measured for the sole purpose of intravenous iodinated CECT in the strategy in which eGFR should be available in all patients. Because our time frame was rather wide (within one month) it is possible that eGFR was measured for other purposes. The time gap between the interview and eGFR measurement could have introduced a recollection bias, leading to underestimation of the number of extra visits for eGFR measurement.

Our study was performed in an academic medical centre in the Netherlands and costs cannot be directly translated to other (peripheral) hospitals and other countries.

Furthermore we were not able to take into account the labour intensity of the screening strategies. Nonetheless, we do feel that our results give an indication of the potential proportional difference in cost-effectiveness between strategies.

Besides the additional costs of strategy in which eGFR is measured based on risk factors, patients also had to travel more often to the hospital for eGFR measurement. Patients could experience physical and emotional inconvenience. On the other hand, patients could interpret the eGFR measurement as a safety measure and therefore feel safer, this could translate into more convenience. Unfortunately we could not quantify the potential (in)convenience suffered by patients undergoing iodinated CECT, as we used data of one strategy (used in our institute), to extrapolate data for the other two strategies. The (in) convenience would therefore be directly related to the number of visits instead of potential difference in patient population between strategies. We do think that in daily practice clinicians try to take this into account by trying to combine the eGFR measurement with other visits to the hospital.

CONCLUSION

Measuring eGFR in a selected group of patients based on assessment of risk factors for kidney disease seems to cost more but is equally effective/safe compared with a strategy in which eGFR is available for all patients when undergoing intravenous iodinated CECT.

To reduce the cost of either strategy, a more tailored model for patients undergoing intravenous iodinated CECT is needed in order to simplify prevention strategies, thereby reducing the number of eGFR measurements. The recent insights gained with respect to CIN risk factors for intravenous contrast medium for CECT can be instrumental. Perhaps a combination of reducing the number of risk factors in the screening for kidney disease and a tenability period for the eGFR value would achieve a more cost-effective CIN prevention strategy.

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Bilateral dacryoadenitis as a presenting symptom of an extra-ocular disease

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CASE REPORT

A 49-year-old woman, with no medical history, presented with bilateral swollen eyelids, progressive conjunctivitis and proptosis for the last month *(figure 1)*. She was referred by the ophthalmologist because an underlying disease was suspected. Magnetic resonance imaging of the orbitae showed bilateral enlargement of the lacrimal glands *(figure 2)*. Treatment by the ophthalmologist with antihistamines, topical corticosteroids and antibiotics had no effect.

She had no other complaints. Physical examination showed evident swelling of both eyes without nasal or oral inflammation. Laboratory investigations showed: C-reactive protein 109 mg/l (0-10), haemoglobin 6.6 mmol/l (7.5-10.0), with a normal cellular volume, leucocytes 10.0 x 10^9/l (4.0-10.0), and a normal serum creatinine; IgG4 levels were within normal limits. Urinalysis showed erythrocytes (3+), leucocytes (2+) and protein (1+).

Figure 1. *Patient with bilateral swollen eyelids*

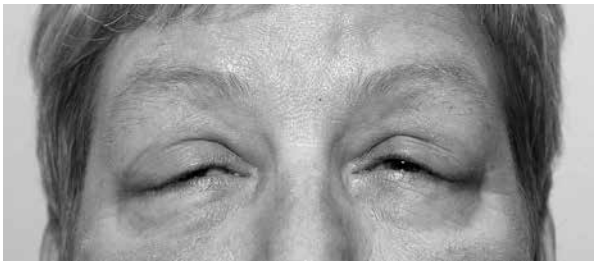
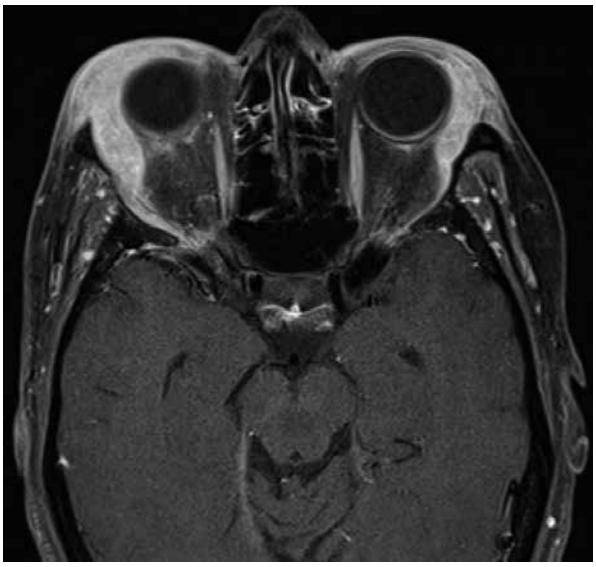


Figure 2. *Magnetic resonance imaging after gadolinium administration showing bilateral swelling of the lacrimal glands*



WHAT IS YOUR DIAGNOSIS?

See page 285 for the answer to this photo quiz.

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PHOTO QUIZ

Acute abdominal pain, painful left shoulder and near collapse

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CASE REPORT

A 28-year-old patient presented to the emergency department with acute pain in the left upper abdominal quadrant and left shoulder, and a near collapse. He had an unremarkable medical history, used no medication and had not experienced any recent trauma. During the previous two weeks he had been ill with flu-like symptoms. Physical examination showed blood pressure 120/65 mmHg, heart rate 85/minute, temperature 36.2 °C, supraclavicular lymphadenopathy and pain in the left upper abdominal quadrant without signs of peritonitis. Examination of the left shoulder was normal. Laboratory results showed a haemoglobin level of 8.8 mmol/l, leukocytosis 12.1 x 10^9/l, lymphocytosis 7.13 x 10^9/l and elevated liver screen (aspartate aminotransferase 231 U/l, alanine aminotransferase 424 U/l, alkaline phosphatase 468 U/l, gGT gamma glutamyl transpeptidase 387 U/l, and bilirubin 32 mmol/l). Chest X-ray was normal.

He was admitted to the general ward for observation. During the following hours his condition worsened with progressive abdominal pain and decreasing haemoglobin level from 8.8-6.3 mmol/l. An abdominal ultrasound was performed (*figure 1*).

WHAT IS YOUR DIAGNOSIS?

See page 286 for the answer to this photo quiz.

Figure 1. *Abdominal ultrasound. Panel A shows an enlarged spleen with a cranial-caudal length of 17 cm, and cranial and lateral fluid collections with alternating ultrasound density. Panel B shows a fluid collection between the liver and the right kidney*

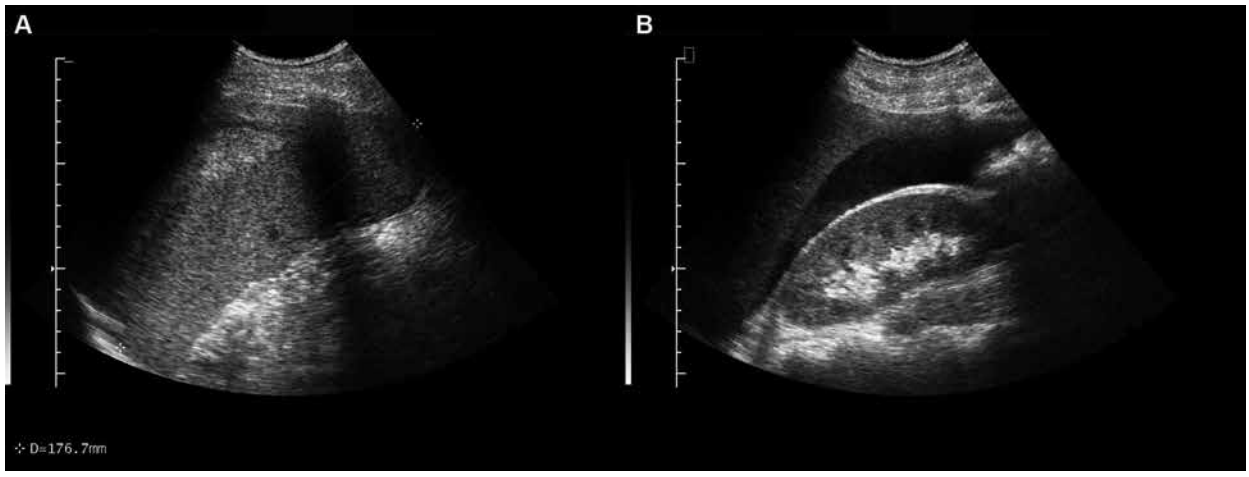

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PHOTO QUIZ

A woman with abdominal pain and swelling

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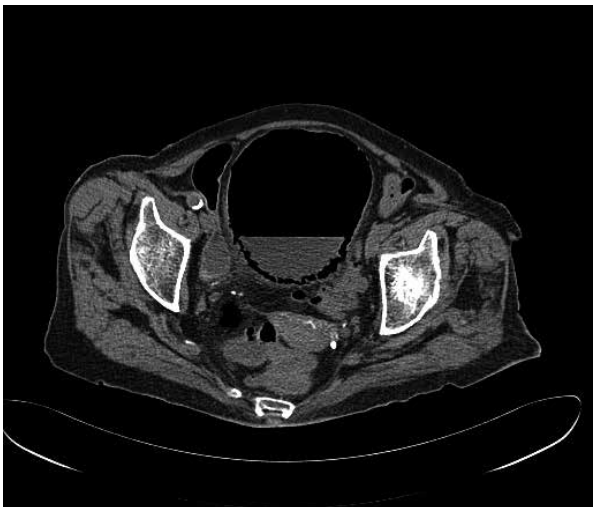
CASE REPORT

An 87-year-old woman presented with acute and progressive suprapubic pain and swelling (*figure 1A*). The patient had a history of recurrent lower urinary tract infections with haematuria. She had hypertension and chronic kidney injury and had undergone coronary artery bypass graft surgery. She had had multiple myeloma for 12 years, for which she only received supportive treatment with routine blood transfusions. She did not complain of nausea or vomiting, but did have intermittent diarrhoea. In the past years, she was treated several times with different antibiotics for relapsing urinary tract infections.

Figure 1A. *Abdominal swelling*

Figure 1B. *Computed tomography of the abdomen*



Percussion of the lesion was hypertympanic. Laboratory tests showed acute on chronic renal insufficiency, complicated by metabolic acidosis with hyperkalaemia. An ultrasound was inconclusive. The image of the computed tomography scan is shown in *figure 1B*.

WHAT IS YOUR DIAGNOSIS?

See page 287 for the answer to this photo quiz.

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PHOTO QUIZ

A woman with asymmetrical facial swelling

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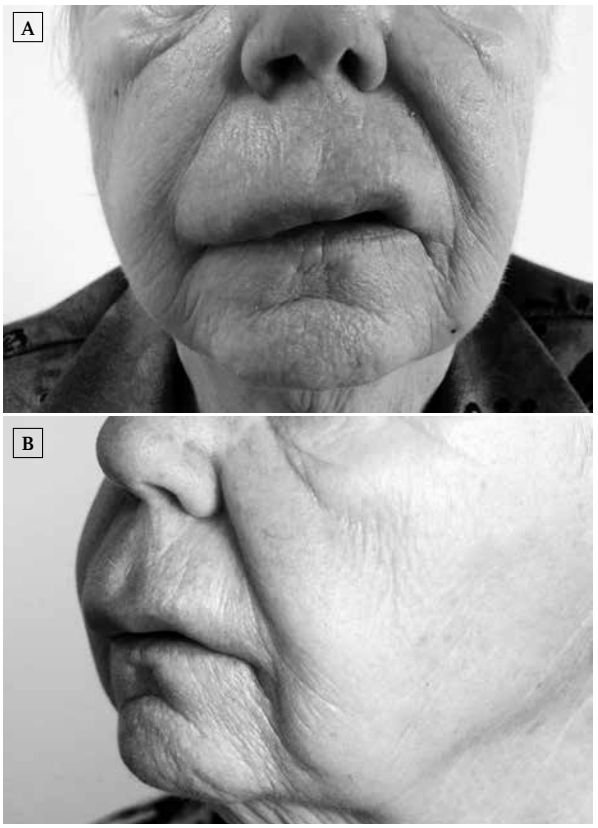
CASE REPORT

A 69-year-old woman visited the Department of Dermatology because of a six-month history of persistent subcutaneous asymptomatic swelling of the upper lip and cheeks. The swelling did not seem to have a particular pattern of occurrence, particularly not after ingestion of food. There was no dyspnoea, rhinoconjunctivitis, fever or other symptoms. Her medical history included COPD and diabetes mellitus type II. Patient had already visited the Department of Otorhinolaryngology and Oral and Maxillofacial Surgery with the same complaint but unfortunately that did not lead to a diagnosis or therapy.
Although initially denied, and only after persistent questioning, the patient later admitted she had had a cosmetic treatment nine years ago using silicone oil, a permanent filler. She was injected with 2.5 cc polydimethylsiloxane in the cheeks and upper lip. On physical examination, an asymmetrical swelling of the upper lip and a diffuse swelling of the cheeks was observed (*figure 1*). At these locations two firm nodules of 2-3 cm could be palpated. Photographs were taken with permission of the patient.

Figure 1. *Pictures of the patient showing an asymmetrical swelling of the upper lip and swelling of the cheeks: frontal (A) and lateral (B) view. Photographs were taken and published with permission of the patient*



WHAT IS YOUR DIAGNOSIS?

See page 288 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 281)

BILATERAL DACRYOADENITIS AS A PRESENTING SYMPTOM OF AN EXTRA-OCULAR DISEASE

Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis with renal involvement was suspected. Autoimmune investigation showed positive ANCA immunofluorescence for myeloperoxidase of 47 kU/l (<10). Microscopic examination of the urine showed >40 % dysmorphic red cells without casts. A chest X-ray, computed tomography (CT) of the thorax and sonography of the kidneys, showed no abnormalities.

Renal biopsy revealed a segmental necrotising crescentic glomerulonephritis, without immune deposits (pauci-immune) on immunofluorescence. Because granulomatosis was absent, the diagnosis of 'microscopic polyangiitis' (MPA) was made, although granulomatosis with polyangiitis (GPA) could not be entirely excluded.[1,2]

MPA is an ANCA-associated autoimmune vasculitis affecting the medium and small arteries and veins. Typically the upper airways and kidneys are involved. Ophthalmological involvement occurs in approximately 5 to 30% of cases and may be, as in our patient, the presenting symptom. Conjunctivitis is present in 30% of the patients with ocular complications; severe episcleritis and uveitis are rare.[3] We did not find any literature relating dacryoadenitis to MPA.

The patient was treated with oral cyclophosphamide in a dose of 2 mg/kg/day and oral prednisone 60 mg once daily. Her complaints subsided quickly and she was discharged in a good condition.

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ANSWER TO PHOTO QUIZ (PAGE 282)

ACUTE ABDOMINAL PAIN, PAINFUL LEFT SHOULDER AND NEAR COLLAPSE

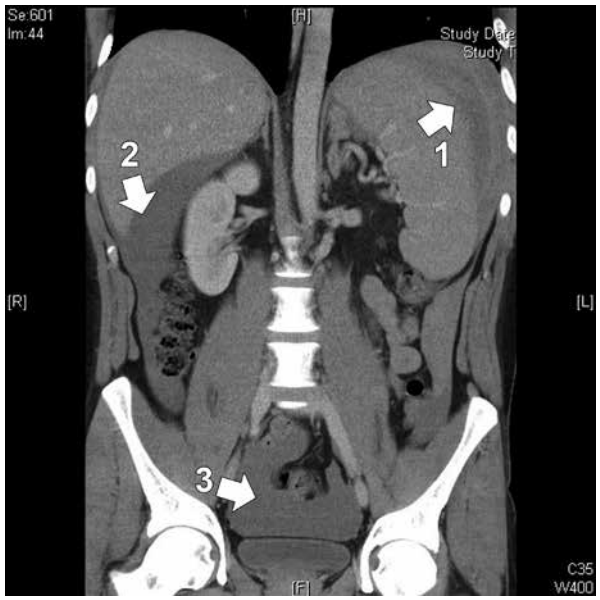
DIAGNOSIS

Abdominal ultrasound showed an enlarged spleen and fluid collections suspicious for haematoma (*figure 1*). CT scan showed a subcapsular haematoma of the spleen and abdominal fluid collections suspicious for haematoma (*figure 2*). He was admitted to the intensive care unit for primary stabilisation. Exploratory laparotomy revealed a total rupture of the spleen capsule and a large abdominal haematoma. Due to ongoing haemorrhage a total splenectomy was performed.

Eventually serological results showed an acute Epstein-Barr virus infection. We diagnosed spontaneous splenic rupture due to infectious mononucleosis. He was vaccinated (Pneumovax® and Meningovax®), received a prescription for amoxicillin-clavulanate 'on demand' and was informed about annual flu vaccination and travelling to malaria endemic areas.

Spontaneous splenic rupture, the most severe complication of infectious mononucleosis, is rare.[1-5]

Figure 2. *AP reconstruction of CT scan, showing an enlarged spleen with a subcapsular haematoma (arrow 1), a fluid collection between the liver and the right kidney extending in the paracolic area (arrow 2) and a fluid collection in the pelvic cavity (arrow 3), both suspicious for blood*



The reported incidence of clinically confirmed splenomegaly in patients with infectious mononucleosis differs from 10-50%.[1,6] On ultrasound, 100% of patients show splenomegaly, with maximum enlargement in the second to third week of illness.[1] Splenomegaly develops due to infiltration of lymphoid cells into the red pulp, trabeculae, capsule and blood vessels. This leads to oedema, softening and weakening of the spleen parenchyma and capsule, with increased risk of rupture as result. Mild trauma or Valsalva manoeuvre can cause rupture.

The presentation of spontaneous splenic rupture is often aspecific and the diagnosis can be easily missed, as our case demonstrates.[3] General symptoms are (sub)acute abdominal pain in the upper left quadrant and signs of shock. Pain in the left shoulder, the classical Kehr's sign, can be present and helpful for the diagnosis. This referred pain is the result of irritation of the diaphragm due to the presence of blood in the peritoneal cavity.[2-4]

Diagnostic tools are abdominal ultrasound and CT scan. First choice therapy has been splenectomy for years. The downside is the loss of immunological function and risk of post-splenectomy sepsis.[1-6] Therefore, some authors advocate conservative therapy in strictly selected cases without haemodynamic instability.[1,2,5]

This case demonstrates the difficult and treacherous aspects of the atypical presentation of spontaneous splenic rupture, complicating infectious mononucleosis.

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ANSWER TO PHOTO QUIZ (PAGE 283)

A WOMAN WITH ABDOMINAL PAIN AND SWELLING

DIAGNOSIS

The abdominal swelling and hypertympanic percussion in the suprapubic region are consistent with air in the bladder. Therefore, the ultrasound was inconclusive. The computed tomography scan shows an image consistent with emphysematous cystitis, with air in the bladder and bladder wall. Emphysematous cystitis is an uncommon condition in which gas-forming (fermenting) pathogens create pockets of gas in the bladder, as well as in and around the bladder wall. Patients affected by this disease often have chronic urinary tract infections, a neurogenic bladder, or diabetes mellitus.[1] The most common pathogen causing emphysematous cystitis is *E. coli*, but other pathogens are reported as well, such as *Enterobacter* species, *Klebsiella pneumonia*, *Streptococcus* species, *Clostridium perfringens*, and *Candida albicans*.[2]

Soon after admission, the volume of urine output declined. The patient had acute on chronic renal failure, complicated by metabolic acidosis and hyperkalaemia. Cystography showed inflammation of nearly all visible tissue. Urine cultures of the past year and the current admission showed group B *Streptococcus*, *E. coli*, and *Enterobacter* cloacae, and some were polymicrobial. A urinary catheter was inserted and the patient was intravenously treated with ceftriaxone for ten days, followed by co-trimoxazole orally for seven days. The patient recovered fully to her previous condition.

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ANSWER TO PHOTO QUIZ (PAGE 284)

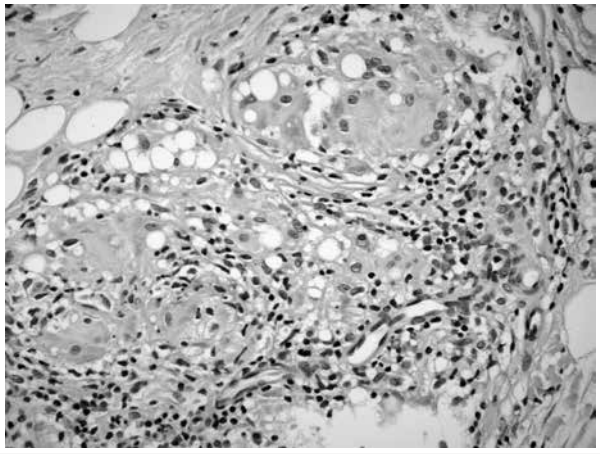
A WOMAN WITH ASYMMETRICAL FACIAL SWELLING

DIAGNOSIS

We suspected a granulomatous reaction caused by the silicone oil injected nine years earlier. A punch biopsy of the upper lip nodule was performed, and histopathological evaluation confirmed the diagnosis. It showed formation of granulomas and histiocytic giant cells with vacuoles, surrounded by a lymphohistiocytic infiltrate (*figure 2*).

Injectable fillers are increasingly used for cosmetic purposes. Over 150 injectable fillers are available worldwide. Fillers can be categorised as temporary, semi-permanent, or permanent, depending on the amount of time the substance remains in the injected area.[1] Although soft tissue fillers in general are considered safe, numerous studies have been published describing late adverse events. One of these rare late complications is the formation of foreign body granulomas, encapsulating the injected material. Incidence rates vary from 0.02-1%.[2] Many patients, however, are unable to recall which particular type of filler material was used.

Figure 2. *Histopathological findings included formation of granulomas and histiocytic giant cells with vacuoles, surrounded by a lymphohistiocytic infiltrate (haematoxylin-eosin, X200)*



Foreign body granulomas usually appear 6-24 months after injection, although periods of up to ten years have been reported.[3] It often presents as a sudden onset of painless, firm nodules with local redness at the site of injection. The diagnosis is based on the clinical presentation and histological examination. The differential diagnosis should include angio-oedema, Melkersson-Rosenthal syndrome, cellulitis, allergic contact dermatitis, sarcoidosis and tuberculosis.

The exact pathogenesis of these foreign body granulomas, also described as silicone granulomas or siliconomas, is still unknown. The volume of the injected filler, the impurities of a filler substance or the injection technique have been suggested as causative factors. Trauma, drugs or infection may be possible triggers for this late complication.

Intralesional or systemic corticosteroids are usually the treatment of choice although often with only a temporary result. Minocycline has also been reported as a successful treatment. Surgical removal is often not feasible because complete removal of widely spread filler material will lead to unacceptable scarring.

Conclusion: filler-induced granulomatous reactions should be included in the differential diagnosis of facial swelling.

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SPECIAL REPORT

Divergent paradigm shifts in national, European and American cardiovascular prevention guidelines

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KEYWORDS

Cardiovascular, prevention, guidelines, drug therapy, blood pressure, cholesterol

INTRODUCTION

In the last two years, both European and American guidelines for cardiovascular risk management have been updated. In both continents, but particularly in the US, these updates were more than trivial. In addition, continental separation in which evidence is considered admissible, and how epidemiological evidence is translated into guidelines, is becoming apparent. This separation is important and requires reflection on both sides of the Atlantic to judge whether we are on the right track to sensible and optimal cardiovascular risk management. Also, the updates cause discussion between medical professionals, which is already occurring in the Netherlands between cardiologists and other professionals caring for cardiovascular patients. These discussions may not always benefit patients.

In this commentary, we will summarise and discuss recent developments in cardiovascular prevention paradigms, and how these translate into guidelines. The focus will be on drug therapy for lipid and blood pressure management. We will place these developments in perspective with regards to the national Dutch guidelines. Finally, we will ask ourselves whether we are to choose the 'European' or the 'American' style of cardiovascular prevention.

DEVELOPMENTS IN EUROPE

In 2012, The European Society of Cardiology (ESC) presented its updated guidelines on cardiovascular disease (CVD) prevention.[1] The writing task force liberally allowed all types of epidemiological evidence, extrapolations from such evidence, and expert opinion, and consistently reported classes for recommendation and levels for evidence.

The prevention approach in the ESC guidelines is based on generic risk categories, which include the following:

- *Very high risk*: patients with previous cardiovascular events, signs of atherosclerosis (detected by, for example, stress testing or carotid ultrasonography), diabetes mellitus (DM) with at least one additional risk factor or target organ damage (e.g. microalbuminuria), severe renal insufficiency and, finally, individuals with a calculated ten-year mortality risk of 10% or more;
- *High risk*: patients with a markedly elevated single risk factor, DM without additional risk factors, moderate renal insufficiency, or a ten-year mortality risk of 5-10%;
- *Moderate risk*: patients with a ten-year mortality risk of 1-5%;
- *Low risk*.

This use of explicit generic risk categories differs from the previous 2007 ESC guidelines, where separate, less explicit considerations regarding risk were given for patients with hypertension and dyslipidaemia.[2] The 2007 version also did not qualify those with pre-clinical signs of atherosclerosis to automatically be at 'very high risk', which may have a huge impact, depending on how liberally physicians and patients decide to perform/undergo for example carotid intima-media-thickness (IMT) measurements or coronary calcium assessments. The 2012 version suggests 'consideration' of carotid ultrasonography and coronary calcium testing in those at *moderate risk*, although it fails to explain how exactly information from these tests should be incorporated in treatment decisions.

For hypertension management, the 2012 guideline recommends immediate treatment in all patients at 'high' or 'very high' risk, with a universal target of 140/90 mmHg. Importantly, the guideline also recommends treatment in all other patients at 'moderate' risk (e.g. ten-year CVD mortality risk >1%) if lifestyle measures fail to normalise blood pressure after a few months' time. In both the 2007 and the 2012 guidelines, treatment of 'high-normal' blood pressure (systolic 130-140 mmHg) is implicitly suggested for all patients with DM and microalbuminuria, as well as those with CVD.

For lipid-lowering drugs, the 2007 guideline recommended statins for all patients with previous CVD, DM with signs of target organ damage, 'marked hyperlipidaemia', and those at >5% mortality risk, with a generic low-density lipoprotein (LDL) target of 2.5 mmol/l, and an optional target of <2.0 mmol/l 'if feasible'. The 2007 guideline was not very clear about non-statin antihyperlipidaemic drugs. In the 2012 version, lipid management recommendations became significantly more aggressive. Treatment is suggested, for example, even in healthy low-risk (<1% ten-year risk) subjects with an LDL of >4.9 mmol/l, as well as in moderate (1-5%) risk individuals with an LDL >2.5 mmol/l. It also calls for 'immediate drug intervention' in all individuals at 'very high risk' who have an LDL of >1.8 mmol/l, even if they are asymptomatic. In daily practice, this implies, for example, immediate statin therapy in all patients with an increased carotid IMT. Treatment targets are the same as threshold LDL levels. Finally, the 2012 guideline implicitly recommends the liberal use of non-statin drugs if lipid targets are not reached with maximum tolerated statin doses.

Taken together, the ESC has maintained its traditional strategy of allowing the full range of types of epidemiological evidence, extrapolations from such evidence, and expert opinion to nurture the guideline recommendations. Risk thresholds for drug treatment have become very low (e.g.: >1% mortality risk per ten years, signs of pre-clinical atherosclerotic disease). In terms of treatment targets, the central hypotheses are simple: lower is better, both for blood pressure and, in particular, for cholesterol. For the latter, all means of lowering LDL cholesterol to its lowest possible level seem justified. The ESC 2012 guideline is beyond doubt the most aggressive to date.

DEVELOPMENTS IN THE UNITED STATES

The US has separate guidelines for lipid management and for hypertension. Both have been recently updated, and shared remarkable similarities in a novel general approach to admission of only high-grade epidemiological evidence.

Cholesterol guidelines

In November 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) updated the 2001 Adult Treatment Panel (ATP) guideline on the treatment of cholesterol.[3] The previous version largely followed the traditional cholesterol hypothesis, and interpreted the clinical trial evidence solely in this context: higher LDL means higher risk, and the more LDL is lowered, the more effective risk reduction will be.[4] Hence, LDL lowering to specific targets was central in the recommendations, and the choice for the type of statin was determined mainly by its LDL-lowering potential.

Work on the new guideline started in 2008 and more strictly and uniquely focused on evidence from large randomised clinical trials (RCTs) to address two main questions: (1) does evidence from RCTs support a specific treatment goal for LDL or HDL cholesterol? and (2) what are the risk-benefit profiles of specific cholesterol-lowering drug regimens?

For the first question, the task force concludes there is insufficient evidence from robust RCTs to support either LDL or HDL treatment targets. For the second question, the new guideline identifies four patient categories for which RCT evidence supports benefit from statins:

- Patients with established clinical cardiovascular disease;
- Patients aged 40-75 years with DM and an LDL between 1.8 and 4.9 mmol/l;
- Adults with an LDL of 4.9 mmol/l and higher;
- Adults 40-75 years with an LDL ≥1.8 mmol/ and a calculated ten-year CVD event risk of 7.5% or higher.

These four groups were chosen because they are congruent with eligibility criteria of statin trials with clinical endpoints, and the specific treatment strategies used in these trials now prevail over LDL targets obtained from meta-regression analyses of on-treatment LDL levels versus event risk. The recommendations thus focus not on LDL cholesterol, but on specific first-line treatment strategies in patient groups that showed benefit in clinical trials. Further, the guideline explicitly encourages a 'risk discussion' between the physician and the patient, resulting in a shared decision to start or defer statin therapy.

What follows is a recommendation to consider high-intensity statins (atorvastatin 40-80 mg, rosuvastatin 20-40 mg) in Category 1 patients up to 75 years old, in Category 3 patients and (optional) in Category 4 patients. Moderate-intensity statin therapy (simvastatin or pravastatin 20-40 mg, low-dose atorvastatin or rosuvastatin, or 40 mg of fluvastatin or lovastatin) is advocated for Category 1 patients older than 75 years, for Category 2 patients, and (optional) for Category 4 patients.

Moderate-intensity statins are considered 'reasonable' for those with a 5.0 to 7.4% ten-year event risk. Statins are explicitly discouraged for patients on haemodialysis or in class II-IV heart failure, as clinical trial evidence does not support a net benefit in these patients. Monitoring LDL levels is only recommended to assess adherence, not to guide treatment to any particular LDL goal. Of note, this approach effectively rules out non-statin lipid-lowering drugs from the recommendation, simply because evidence with clinical endpoints is lacking. This contrasts with the 2001 guideline, which recommended statins, bile acid sequestrants or nicotinic acid for lipid lowering.[4]

Blood pressure guidelines

In January 2014, the longest ever awaited cardiovascular prevention guideline was finally released: the 8th Joint National Committee hypertension guidelines (JNC8).[5] Like the American cholesterol guidelines, the methodology focus shifted from non-systematic literature review of all types of epidemiological studies, to systematic review of randomised clinical trials and adoption of a strict protocol to translate this evidence to recommendations. Another similarity was that the JNC8 committee, as did the ACC/AHA committee, phrased critical questions that guided the recommendations:

- Does antihypertensive therapy at specific blood pressure thresholds improve health outcomes?
- Do randomised clinical trials support blood pressure treatment targets?
- Do various antihypertensive drug (classes) differ in benefit or harm?

The JNC8 guideline no longer addressed hypertension definitions, but strictly focused on evidence-based treatment thresholds and treatment targets. Also, the choice of drugs was more directly based on trial evidence, rather than on generic considerations of drug class properties, which previously resulted in the recommendation to use thiazide-type diuretics as first-line treatment in most patients.[6] Finally, JNC8 no longer uses risk categories, which is in line with the strategy to focus more exclusively on RCTs to guide recommendations: no RCT has ever used absolute baseline risk as an inclusion criterion.

The most widely discussed recommendation of the JNC8 guideline is to increase the systolic blood pressure threshold and treatment target for antihypertensive treatment from 140 to 150 mmHg in all patients above 60 years of age. For patients with DM or chronic kidney disease, the committee also concluded that the former more strict target of 130/80 mmHg was insufficiently supported by clinical trial evidence, and so this target was also raised to 140/90 mmHg in the 2014 update. Finally, the updated guideline explicitly discourages the combination of an ACE inhibitor and an angiotensin-receptor blocker.

SYNTHESIS AND DISCUSSION

Table 1 summarises critical differences between the most recent European and US cardiovascular prevention guidelines. In addition, a third column is added to highlight the position of the multidisciplinary Dutch Cardiovascular Risk Management (CVRM) guideline, which was issued in 2011, and included representatives of all major clinical disciplines (family medicine, internal medicine, cardiology, neurology, etc.) in its writing committee.[7]

Taken together, both the European and the US guidelines employ more complex criteria for primary prevention than the Dutch guidelines, which mainly look at calculated ten-year event risk and whether LDL cholesterol and systolic blood pressure (SBP) are above a threshold level above which treatment efficacy is believed to be proven beyond reasonable doubt.

Not only are the European and US guidelines more complex than the Dutch guidelines, they are also significantly more aggressive, albeit in different ways. The ESC guidelines are aggressive in that even patients at very low ten-year mortality risk of ≥1% (corresponding to event risks of approximately 2 to 4% [7]) are considered eligible for antihyperlipidaemic treatment if their LDL exceeds 2.5 mmol/l. The LDL treatment threshold is even lower at 1.8 mmol/l for patients with an estimated risk of ≥5%. With regard to hypertension, if we assume an average relative risk reduction of 30% for antihypertensive treatment for healthy individuals with a 3% ten-year event risk, the corresponding ten-year number needed-to-treat (NNT) to prevent a single event is approximately 100 (1000 per year!).

In terms of eligibility criteria for primary preventive treatment, the US Guidelines are even more aggressive than those from Europe. All patients with an LDL ≥1.8 mmol/l and an estimated ten-year *event* risk of ≥7.5% 'should be treated', and statins are considered 'reasonable' for those with a 5 to 7.5% event risk. Although the *event* risk thresholds are thus generally higher than the corresponding *mortality* risk thresholds from the US guidelines, the LDL threshold is considerably lower for a large number of individuals. For hypertension, no absolute risk threshold is advocated, and a non-smoking 40-year-old female with a favourable lipid profile, but a blood pressure of for example 150/90 mmHg, would qualify for treatment, even though the ten-year event risk is substantially lower than 1%. For this category of not-too-rare patients, the maximum NNT raises to extreme heights, as shown in *table 1*. In comparison, implementation of the Dutch CVRM guidelines is generally associated with ten-year NNTs of <20.

This remarkable difference in NNTs between the Dutch and the recent international guidelines is not primarily based on differences in interpretation of the cardiovascular

Table 1. *Comparison of updated European, US, and Dutch National guidelines for cardiovascular risk management*

	European ESC Guidelines	**US Guidelines (ACC/AHA and JNC8)**	**Dutch CVRM Guidelines**
Main criteria for treatment	Established CVD, pre-clinical CVD, DM, 10-year *mortality* (†) risk	Established CVD, DM, LDL-cholesterol, 10-year CVD *event* risk	Established CVD, 10-year CVD *event* risk
Cholesterol			
Risk threshold for patients without CVD	- All patients with LDL ≥4.9 mmol/l; - LDL≥2.5 mmol/l and 10-y † risk >1% - LDL≥1.8 mmol/l, and 10-y † risk >5% or complicated DM or (preclinical) CVD	- All patients with LDL ≥4.9 mmol/l; - DM and LDL ≥1.8 mmol/l; - LDL ≥1.8 mmol/l and 10-y event, risk ≥7.5% ('reasonable' for >5%)	10-y event risk ≥20% and LDL >2.5 mmol/l (DM is considered a separate category with risk estimation based on adding 15 years to age)
Treatment target	LDL 1.8-2.5 mmol/l	None	LDL 2.5 mmol/l
Recommended drugs	Statin or any other lipid lowering drug	Statins only; high vs low intensity	Statins, others discouraged
Blood pressure			
Risk threshold for patients without CVD	10-y † risk ≥1% and BP ≥140/90 mmHg (130/90 for CVD and complicated DM)	- Adults ≥60-y and BP ≥150/90 mmHg - Adults <60-y and BP ≥140/90 mmHg	10-y event risk ≥20% and SBP >140 mmHg
Treatment target	130-140 mmHg	140 mmHg (150 if age ≥60-y)	140 mmHg
Recommended drugs	All major drug classes	All major drug classes	Thiazide-type, calcium blockers, ACE inhibitor.
Estimated maximum 10-year NNT for hypertension treatment	100	>200	20

ESC = European Society of Cardiology; US = United States; ACC = American College of Cardiology; AHA = American Heart Association; JNC8 = Eight Joint National Committee; CVRM = cardiovascular risk management; CVD = cardiovascular disease; DM = diabetes mellitus; LDL = low-density lipoprotein cholesterol; NNT = number needed to treat.

prevention literature. In fact, little doubt was expressed by the working committee of the Dutch guidelines that antihypertensives and statins would be effective in patients at substantially lower risks than the 20% event-risk threshold. Rather, the CVRM guideline is based on a maximum NNT that was generally considered acceptable from both an individual and a societal perspective. Also, the Dutch guideline committee was hesitant to conclude that very long-term treatment was proven safe in young low-risk patients. Here, thus, the Dutch and the international guidelines seem to part. International guidelines increasingly focus on what is effective, Dutch guidelines maintain a traditional focus on what is effective and reasonable in terms of anticipated absolute benefit. Why the international guidelines move towards more aggressive approaches is unclear. The focus on absolute benefit has lost none of its virtues, at least in our opinion.

What has been the response to the international guidelines? Somewhat surprisingly, the updated ESC guidelines received very few comments in the literature. The response to the US updates has been significantly more intense. The ACC/AHA cholesterol guideline has been criticised for holding on to a too strict definition of 'evidence' by only including epidemiological evidence coming from randomised clinical trials.[8] Concerns have also been raised that the risk prediction tool used in the ACC/AHA guideline is inaccurate.[9] It has further received major criticism for lowering the threshold for statin treatment.[10,11] Patients with an LDL as low as 1.9 mmol/l would be considered for statin treatment if their ten-year event risk exceeds only 5%, even if this risk is mainly defined by age, smoking and blood pressure. In the US only, over 45 million middle-aged Americans would qualify for statin treatment, which corresponds to one in every three American adults.[9] Worldwide, over a billion (1000 million) non-diseased individuals would qualify for statins if the ACC/AHA cholesterol guidelines were fully implemented.[11] Popular media, such as the New York Times, called upon people in good cardiovascular heath to ignore the cholesterol guidelines for this same reason of excessive NNTs.[www.nytimes.com/2013/11/19/opinion)

The updated JNC hypertension guidelines were only a few weeks old when we wrote this manuscript, but fierce responses have already been published. Only days after JNC8 was officially released, a minority from the JNC panel published a comment stating that they disagreed with raising the SBP target from 140 to 150 mmHg in patients older than 60 years.[12]

Within the Netherlands, there is less concern over updates in European or US cardiovascular guidelines. The Dutch Society of Cardiology (NVVC), however, has made a noticeable move to endorse the National CVRM guidelines in 2011, but also the ESC guideline, even though the recommendations have very different implications for patients and healthy individuals qualifying for primary prevention. To date, it is unclear whether Dutch cardiologists indeed feel we should collectively move towards the much more aggressive prevention strategies propagated by the ESC guidelines.

Our personal view is that both the US and the European guidelines contain positive elements that are noteworthy, but both are problematic in other respects.

The ESC guideline correctly maintains a focus on absolute risk thresholds for initiating preventive drug treatment, but the threshold has become extremely low, exposing many patients to treatments that provide only very small absolute risk reductions. Also, the lack of focus on clinical trial evidence has allowed a very liberal strategy towards for example non-statin antihyperlipidaemic treatment, which we feel is problematic.

The US guidelines shift the weight of attention to randomised clinical trial evidence. Although randomised clinical trials are arguably more objective, they are affected by significant selection bias, and trial data availability is largely determined by the pharmaceutical industry. The rational and far more common approach is sensibly weighing different types of evidence, giving credits to the objectivity of RCT, but also acknowledging the added value of observational studies and meta-regression analyses. Disqualifying this approach has had profound effects. For example, the fact that no clinical trial selected patients based on absolute risk calculation precluded the use of baseline risk in the JNC8 guidelines. By not allowing absolute baseline risk estimation to the selection process for antihypertensive treatment, the JNC8 guideline effectively recommends antihypertensive treatment for a large proportion of the adult population. Another example that follows from admitting only trial evidence is that although the 150 mmHg treatment goal for patients over 60 years may make sense for this group at large, compelling evidence from observational and meta-regression analyses strongly calls for extra caution in the oldest old, particularly those who are frail.[13]

In conclusion, international cardiovascular prevention guidelines are becoming more and more aggressive, but methods for weighing the evidence have become increasingly dissimilar. Guideline paradigms are shifting, but not all in a similar direction.

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A skin lesion that catches the eye

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ABSTRACT

Primary cutaneous gamma-delta T-cell lymphoma (PCGD-TCL) is rare and only represents 1% of all cutaneous T-cell lymphomas. To our knowledge, only 40 cases have been described. It often presents with generalised skin lesions, preferentially affecting the extremities. There is a well-documented association with haemophagocytic syndrome. Treatment is difficult since PCGD-TCL is often resistant to chemotherapy and radiotherapy. Most case reports describe an aggressive clinical course with an estimated mean survival of 15 months.

We present a 72-year-old female patient with stage IV primary cutaneous gamma-delta T-cell lymphoma. Our patient presented with fever, night sweats and multiple skin lesions (*figure 1*). Computed axial tomography of chest and abdomen revealed multiple solid nodular lesions in both kidneys. During admission a subconjunctival lesion appeared and progressed rapidly (*figure 2*).

Histopathological examination of skin biopsy revealed infiltration of atypical lymphocytes with hyperchromatic irregular nuclei. Immunophenotyping pattern of skin biopsy was compatible with PCGD-TLC. Clonal gamma-delta T-cells were also detected by immunohistochemical analysis of peripheral blood and bone marrow. Polymerase chain reaction amplification revealed clonal rearrangement of the T-cell receptor gamma chain gene. These findings together were consistent with stage IV primary cutaneous gamma-delta T-cell lymphoma. The rapid progression of the subconjunctival extra-nodal manifestation is characteristic for the aggressive course of this lymphoma. Our patient was treated with two cycles of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone). However, her clinical condition deteriorated rapidly. She declined further therapy and died within three months of initial presentation.

KEYWORDS

Haemophagocytic syndrome, primary cutaneous gamma-delta T-cell lymphoma, subconjunctival lesion

CASE REPORT

A 72-year-old female patient presented with fever, night sweats and multiple skin lesions. Her history included paroxysmal atrial fibrillation, hypertension and a stroke. At physical examination there were no enlarged lymph nodes. Multiple erythematous cutaneous nodules were present on the upper extremities and abdomen (*figure 1*). A skin biopsy was performed.

Laboratory results showed: haemoglobin 7.2 mmol/l, leucocytes 1.3 x 10^9/l with a lymphocytopenia of 0.4 x 10^9/l, thrombocytes 99 x 10^9/l, lactate dehydrogenase 857 IU/l and haptoglobin <0.1 g/l.

Viral serology was negative for human immunodeficiency virus, Epstein-Barr virus, Cytomegalovirus, and hepatitis A, B and C. Autoimmune serology was also negative. Computed axial tomography of the chest and abdomen revealed multiple solid nodular lesions in both kidneys. During her admission a subconjunctival lesion appeared and progressed rapidly within three days (*figure 2*).

DIAGNOSIS

Histopathological examination of the skin biopsy revealed an infiltration of atypical lymphocytes with hyperchromatic irregular nuclei. Immunophenotyping by immunohistochemical analysis characterised the infiltrate as CD2+, CD3+, CD4-, CD5-, CD7-, CD8-, CD20-, CD30- and CD56-. Polymerase chain reaction amplification revealed clonal rearrangement of the T-cell receptor gamma chain gene. Clonal gamma-delta T-cells were also detected by

immunohistochemical analysis of peripheral blood and bone marrow. These findings together were consistent with stage IV primary cutaneous gamma-delta T-cell lymphoma (PCGD-TCL) accompanied by multiple extra nodal manifestations.

Figure 1. *Multiple erythematous cutaneous nodules on the upper extremities*

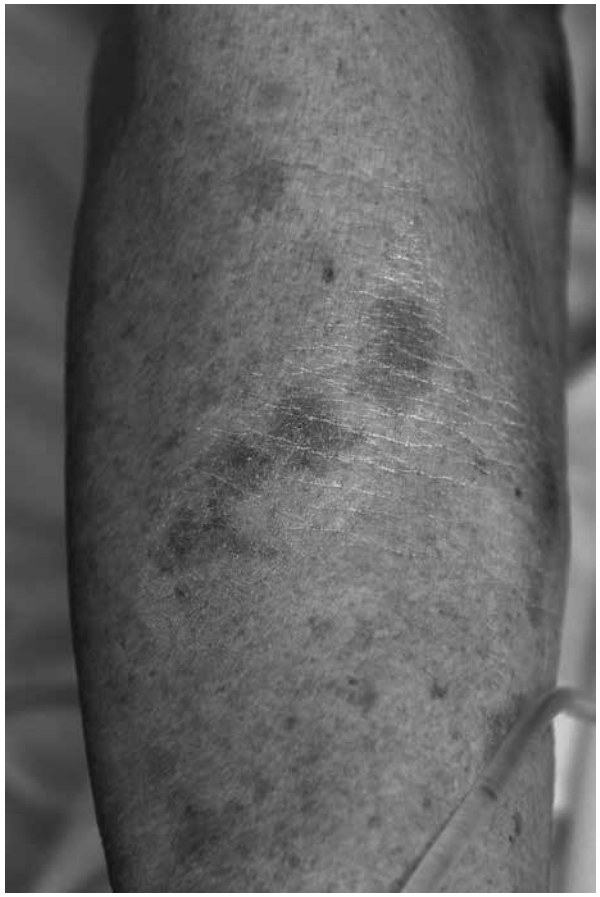
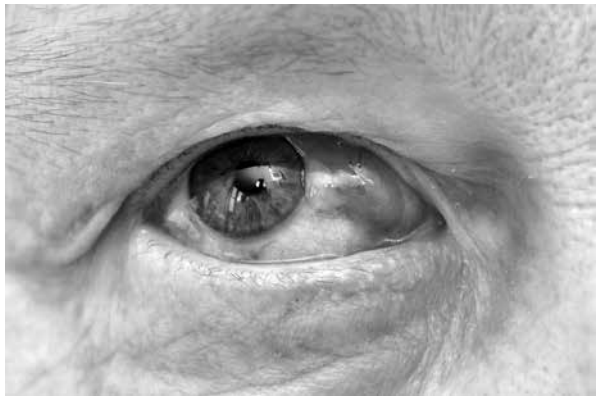


Figure 2. *Subconjunctival lesion*



T-cell lymphomas represent less than 15% of all non-Hodgkin lymphomas. PCGD-TCL has been included in the WHO classification of myeloid and lymphoid neoplasms since 2008 and has been estimated to represent 1% of all cutaneous T- cell lymphomas. To our knowledge, only 40 cases have been described.[1]

PCGD-TCL is composed of a clonal proliferation of mature, activated gamma-delta T-cells with a cytotoxic phenotype. It often presents with generalised skin lesions, preferentially affecting the extremities. Dissemination to mucosa and other extra-nodal sites is frequently observed, but involvement of lymph nodes, spleen or bone marrow is uncommon. There is a well-documented association with haemophagocytic syndrome, also known as haemophagocytic lymphohistiocytosis.[2]

The diagnosis in our patient was compatible with the characteristic immunophenotype of PCGD-TLC, although CD56 was negative.[3] There was clonal rearrangement of the T-cell receptor gamma chain gene. This is seen in approximately 70% of all cases.[4] Treatment is difficult, as PCGD-TCL is often resistant to chemotherapy and radiotherapy. There are no clinical trials targeting PCGD-TCL. Systemic multiagent chemotherapy CHOP has previously been used. In young patients allogeneic haematopoietic stem cell transplantation should be considered.[1] Most case reports describe an aggressive clinical course with an estimated mean survival of 15 months.[1,2,4]

Our patient was treated with two cycles of CHOP and experienced multiple septic episodes. Although the subconjunctival and skin lesions improved, her clinical condition deteriorated rapidly. She declined further therapy and died within three months of initial presentation.

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