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EDITORIAL

Low-molecular-weight heparin to prevent pre-eclampsia: there is no evidence and potential harm

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Pre-eclampsia is a serious complication of pregnancy that threatens both the mother and her foetus. Pre-eclampsia is characterised by early and late vascular dysfunction with many known and unknown factors interacting that ultimately lead to the classical clinical syndrome which lies in a spectrum that ranges from gestational hypertension toward HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome.[1]

At least two aspects make pre-eclampsia a disease of interest for both obstetricians and internists focused on vascular medicine. First, many case-control studies have shown an association between the occurrence of pre-eclampsia and inherited thrombophilia, although in a meta-analysis this could only be demonstrated for severe, early-onset pre-eclampsia.[2] Second, gestational hypertensive complications, such as other vascular diseases, have a tendency to recur. For instance, in a large series of Dutch women with HELLP syndrome, the recurrence rate in the subsequent pregnancy was as high as 29%.[3] Third, aspirin has been found to have a small beneficial effect on the prevention of pre-eclampsia, as well as preterm delivery and infant death, with statistically significant risk reductions of 15%, 8% and 14% respectively.[4]

It is attractive to hypothesise that anticoagulant treatment with (low-molecular-weight) heparin may have a beneficial effect on pregnancy outcome in women with a history of pre-eclampsia and a known thrombophilic defect. This has been demonstrated for women with recurrent foetal losses and antiphospholipid antibody syndrome in one of the rare randomised controlled trials that have been performed in this field.[5] However, an adequate trial has not been completed in women with hereditary thrombophilia and obstetric complications such as pre-eclampsia.[6] Only uncontrolled series have been published in which low-molecular-weight heparin suggested an improved outcome of subsequent pregnancies in women with a history of various obstetric complications.[7,8] In these series, outcome was compared with the patients' previous pregnancies, which by definition was poor, as this was a selection criterion for inclusion.

Why should we not implement anticoagulant treatment to prevent (recurrent) pre-eclampsia in women with hereditary thrombophilia? No pharmacological therapy, especially in pregnant patients, should be applied without solid evidence from appropriate clinical studies. Although the use of aspirin and/or low-molecular-weight heparin is considered safe and is being applied for prophylaxis of thromboembolic complications during pregnancy,[9,10] there is a significant burden of low-molecular-weight heparin treatment induced by the daily subcutaneous injections, as well as a high incidence of skin reactions, in particular in higher doses.[11]

In this issue of the Netherlands Journal of Medicine, Kalk and colleagues present a retrospective analysis of 58 women with a history of pre-eclampsia out of a large cohort of women who were tested for thrombophilia. They observed a risk reduction of 45% in women who were treated with both aspirin and low-molecular-weight heparin, which did not reach statistical significance. However, as the authors discuss, this study has serious limitations. These concern issues of patient selection, the small number of observations, inadequate follow-up of the original cohort of tested women, the fact that the allocation of interventions was not randomised, and the potential of inferior quality of data recording due to the retrospective character of the study.

What this study does demonstrate is the urgent need for

results from adequate, placebo-controlled trials in women with hereditary thrombophilia and pre-eclampsia, as well as other clearly defined obstetric histories.[12] In the meantime we should not implement therapies for which we have no evidence, or in other words, *in dubio, abstinae*.

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REVIEW

Diabetic nephropathy and β-cell replacement therapy

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ABSTRACT

Whole pancreas transplantation can effectively restore endogenous insulin secretion in type 1 diabetes mellitus, and prevent, retard, or reverse diabetic complications. The effect of a simultaneous pancreas and kidney transplantation (SPKT) on diabetic complications is variable. These reports must be interpreted in the light of the fact that most recipients received a pancreas in combination with a kidney graft after having already had diabetes for over two decades. Nevertheless, the potential benefits should also be balanced against the risk of peroperative morbidity and the requirement of long-term immunosuppressive medication. Transplantation of a whole pancreas is currently the only reliable option to achieve long-term normoglycaemia. The success of pancreatic islets transplantation will ultimately depend on the longevity of pancreatic islets, requiring further development of immunosuppressive regimens which are not toxic to the islets and prevent recurrent autoimmune destruction of transplanted pancreatic β-cells.

PREVENTION OF PROGRESSIVE DIABETIC NEPHROPATHY

Type 1 diabetes mellitus is an evolving disease with a rapid increase in incidence around the world and particularly in children under five years of age. According to the World Health Organisation, approximately 1.3 and 1.4 million individuals are affected with type 1 diabetes mellitus in Europe and the United States, respectively. Diabetes is already the most common single cause of end-stage renal disease (ESRD), both in the USA and Europe. About 20 to 30% of patients with type 1 or type 2 diabetes develop evidence of nephropathy. Due to the much greater prevalence of type 2 diabetes, these patients constitute over half of those diabetic patients currently starting on dialysis. In type 1 diabetes, however, a considerably larger proportion of patients progress to ESRD.

The Diabetes Control and Complications Trial (DCCT) demonstrated an approximately 50% reduction in the prevalence of eye, nerve and kidney complications with intensive treatment for hyperglycaemia.[1] This has clearly led to increased interest in reducing blood glucose concentrations to normal to delay the development and progression of diabetic complications. In native kidneys, the earliest clinical evidence of nephropathy (incipient nephropathy) is the appearance of microalbuminuria (>30 mg/day). Without specific intervention, about 80% of type 1 diabetic patients with sustained microalbuminuria progress to overt nephropathy (>300 mg/day) within 10 to 15 years and develop hypertension along the way. Approximately 50% of type 1 diabetics with overt nephropathy will progress to ESRD within 10 years and more than 80% within 20 years. Many studies have shown that in hypertensive patients with type 1 diabetes, angiotensin-converting enzyme (ACE) inhibitors can reduce the level of albuminuria and can reduce the rate of progression of renal disease.[2] It has also been shown that there is benefit in reducing the progression of albuminuria in normotensive type 1 diabetic patients.[3] As well as being the earliest manifestation of nephropathy, albuminuria is a strong predictor of greatly increased cardiovascular morbidity and mortality for patients with diabetes mellitus. Approximately 30% of diabetics with ESRD who enter renal replacement therapy have significant

coronary artery disease, which may be asymptomatic or not associated with conventional cardiovascular risk factors.[4] The excess cardiovascular morbidity is also clearly reflected in a 10% annual mortality rate while on maintenance dialysis.[5] If despite optimal glycaemic control and aggressive antihypertensive treatment (including the use of ACE inhibitors and/or angiotensin-receptor blocker therapy) progression occurs to overt nephropathy, then virtually all patients with type 1 diabetes will ultimately progress to ESRD and experience significant cardiovascular morbidity and excess mortality.[6]

DIABETES MELLITUS TYPE 1 AND PANCREAS TRANSPLANTATION

Pancreatic transplantation was first used for the treatment of diabetes in humans in 1966. The introduction of better immunosuppressive agents (calcineurin inhibitors and anti T cell antibodies), new surgical techniques, and the selection of healthier recipients has resulted in markedly improved outcomes over the past decades. As a result, the number of pancreatic transplantations has steadily increased each year. By the end of 2001, well over 16,000 pancreas transplants had been recorded in the International Pancreas Transplantation Registry. Pancreas transplantation is most commonly performed in three settings: pancreas transplantation alone in the nonuraemic diabetic patient with minimal or no evidence of diabetic nephropathy (PTA); pancreas transplantation after a successful kidney transplant (PAKT) and, in over 80% of cases, as a simultaneous pancreas and kidney transplant (SPKT) in uraemic patients.

The options for insulin-dependent patients with diabetes mellitus type 1 (IDDM) and ESRD include dialysis, a kidney transplant (deceased or living donor), or a SPKT.[7] After three decades of controversy surrounding the therapeutic validity of pancreas transplantation, a SPK transplantation has become the preferred treatment option for IDDM patients with advanced diabetic nephropathy and (or approaching) ESRD.[8] Kidney transplants accompanied by pancreas transplants from cadaver donors have similar, if not better, long-term survival rates than those of cadaver and haplo-identical living donor kidneys transplanted alone.[9,10] Proper patient selection is crucial to the success of SPKT. In general, type 1 (C-peptide deficient) insulin-dependent diabetics younger than 50 years of age are considered potential candidates and patients with significant uncorrected coronary artery disease are excluded. Recipient age and obesity appear to affect patient survival more than immunological graft loss.[11] The principal consideration in the selection of candidates, however, remains the balance between cardiovascular risk and the benefits of long-term normoglycaemia with regard to quality of life, end-organ disease, and mortality rates. Major amputations secondary to severe peripheral vascular disease or severe visual impairment are not considered absolute contraindications. These patients will benefit from reversing uraemia, but are less likely to derive improved function at the end-organ level from restitution of normoglycaemia. Studies on the efficacy of pancreas transplantation on diabetic microvascular and macrovascular disease must therefore be interpreted in the light of the fact that most recipients received a pancreas in combination with a kidney graft after having already had diabetes for over two decades. Perhaps even more important, pancreas transplantation seems to be a treatment option that can improve survival rates in type 1 diabetes with advanced, often irreversible, end-organ damage.[5] The goals of pancreas transplantation have developed beyond simply restoring normoglycaemia for a period of time and improving quality of life.[12] Pancreas transplantation, as simultaneous pancreas-kidney transplantation, is nowadays a functional and effective therapy that can reverse metabolic abnormalities and prevent or minimise many of the secondary complications of diabetes, including coronary artery disease, amputation and blindness.[13,14] We can expect that also the lesions of diabetic retinopathy will be prevented or their progression slowed if β-cell function is restored when eye disease is still at an early stage. Recent results suggest that, with the newer immunosuppressive agents, pancreas transplantation alone in nonuraemic type 1 diabetic patients may be as successful as SPKT.[15]

DIABETIC NEPHROPATHY AND EARLY PANCREAS TRANSPLANTATION

The obvious benefits of normoglycaemia would theoretically be even more profound if it becomes possible to perform pancreas transplantation or islets transplantation alone for patients without significant renal dysfunction, early in the course of diabetic nephropathy and other complications.[13,14] Single pancreas transplantation has generally been reserved for patients in whom glucose control is extremely difficult to achieve without frequent episodes of life-threatening hypoglycaemia. Nowadays, the circumstances where the risk-benefit equipoise could potentially favour pancreas transplantation may well include patients with diabetes mellitus type 1 and sustained overt diabetic nephropathy despite aggressive early intervention.[6,16] While the risks of immunosuppression are not to be underestimated, it should also be recognised that short-term morbidity and mortality after pancreas transplantation are due primarily to the chronic complications of diabetes, that rejection rates with current immunosuppressive regimen are low and that pancreas transplantation is currently the only reliable option to achieve long-term restoration of normal glucose metabolism.

IS PANCREAS TRANSPLANTATION SUPERIOR TO INTENSIVE INSULIN TREATMENT?

There are at least three reasons why pancreas transplantation is superior to intensive insulin treatment with regard to glycaemic control and the course of diabetic complications. First, the mean glycosylated haemoglobin levels in patients long term after pancreas transplantation (5.5% at five years and 5.5% at ten years) were lower than the target value of 6.0% defined in the Diabetes Control and Complication Trial (DCCT), a value that was reached at least once in only 44% of the patients in the intensive treatment group.[1] It is noteworthy that, after pancreas transplantation in nondiabetic patients, normoglycaemia was achieved despite long-term immunosuppressive treatment, which may cause insulin resistance and impaired glucose tolerance.
Secondly, in patients with intensive insulin treatment, progressive reductions in glycosylated haemoglobin values are achieved at the expense of more hypoglycaemic episodes, whereas pancreas transplantation maintains normoglycaemia without causing severe episodes of hypoglycaemia. In this context it is important to know that patients with frequent hypoglycaemic episodes were excluded from participation in the DCCT trial.[1]
Finally, whole pancreas transplantation is currently the only reliable option to achieve long-term euglycaemia and prevent (or reverse) diabetic nephropathy and other diabetic complications. Recurrent diabetic nephropathy develops in almost all diabetic patients undergoing renal transplantation. Glomerular basement thickening and mesangial expansion are seen by two years, followed by hyalinisation of the afferent and efferent arterioles by four years. Moreover, the extent of the coronary angiographic findings in candidates evaluated for transplantation had a strong predictive value for subsequent vascular events occurring within three years after a successful SPKT.[17] Intensive treatment with insulin can only delay progression of the morphological changes of early diabetic nephropathy, while approximately ten years of normoglycaemia were found to be necessary to reverse established nephropathy.[18]

PANCREAS TRANSPLANTATION, AUTOIMMUNITY AND ALLOIMMUNITY

The results reported after SPKT continue to improve. For instance, the transplant group at the North-Western University recently reported 100% patient and graft survival following SPKT in 40 consecutive recipients.[19] The incidence of rejection at one year was reported at 2.5%, which is remarkable considering this was accomplished with a steroid-free regimen. Unlike autoimmune diabetes mellitus, acute rejection of the pancreas is usually directed principally against acinar tissue, not the islets. In IDDM patients, a transplanted pancreas should be as susceptible to the autoimmune process as the native pancreas. Indeed, insulin-dependent diabetes can recur in an immunocompetent or a minimally immunosuppressed recipient of a pancreatic transplant from an identical twin or human leucocyte antigen (HLA) identical sibling. When a portion of the pancreas of a normal twin is transplanted into a diabetic twin, recurrent autoimmunity with selective β-cell destruction occurs in the recipient.[20] The donor and recipient of a pancreatic graft do not have to share HLA antigens for recurrent autoimmune destruction of the graft.[21] The recipient must therefore receive immunosuppressive therapy, not only to prevent alloimmunity (rejection of transplanted tissue from a genetically different person) but also to prevent recurrent autoimmune islet destruction. Immunotherapies, including those specifically directed against T cells, have been shown to delay disease progression in patients with IDDM of recent onset but did not prevent β-cell dysfunction.[22,23] This delay was not accompanied by changes in autoantibody levels, providing evidence of the immunological memory of islet-specific T cells.[24] It is most likely that the degree of immunosuppression required to prevent acute rejection is also sufficient to prevent recurrent autoimmune damage in the majority of recipients of a vascularised pancreas.

WHAT ARE THE DRAWBACKS FOR PANCREAS TRANSPLANTATION?

The drawbacks for whole pancreas transplantation are the necessity of major surgery, with perioperative and postoperative morbidity, as well as the lifelong need of immunosuppressive medication. It is hoped that the less invasive procedure of islets cell transplantation will convey the same benefits, with respect to survival rates and diabetic complications, as do PTA and SPKT at the present.[12,15] This approach with percutaneous, transhepatic portal vein transplantation of pancreatic islets is minimally invasive and relatively safe, but requires long-term immunosuppression as well.[25] Another limitation of human islets transplantation continues to be the variability with which viable human islets can be obtained from the human cadaver pancreas. The majority of patients who achieved insulin independence required several infusions of islets isolated from at least two donors per infusion. The increasing shortage of organs available for transplantation demands further refinement in single donor islets transplant protocols or ultimately the use of xenogeneic or stem cell sources before islets transplantation can be routinely introduced.
In contrast to most studies of transplantation of islet allografts in diabetic patients, islets autograft transplantation has been remarkably successful in nondiabetic patients

after total pancreatectomy for chronic painful pancreatitis. Many of these patients have been documented with normoglycaemia and normal HbA_{1c} values for up to 13 years after transplantation.[26] Immunosuppressive drugs, and steroids in particular, given to the allograft recipients may have an adverse effect on the function of transplanted islets.[25] Ultimately, the success of human islets transplantation will be dependent in obtaining a more reliable source of β-cells, the longevity of pancreatic islets, and further development of immunosuppressive regimens which are not toxic to islets but prevent recurrent autoimmune destruction.

PANCREAS TRANSPLANTATION AND LONG-TERM INSULIN INDEPENDENCE

The key issue in preventing progression or reverse diabetic complication is the longevity of insulin independence following transplantation. The largest series of pancreatic islets transplantation performed at the University of Alberta has reported insulin independence up to three years following islets transplantation, but most patients have required further infusions of pancreatic islets to obtain insulin independence again.[27] Whole pancreas transplantation is currently the only reliable option to achieve long-term insulin independence. Between 1986 and 2002 more than 150 simultaneous pancreas-kidney transplants were performed in the Leiden University Medical Centre. The five-year and ten-year pancreas survival in this cohort of patients, defined as freedom from exogenous insulin, was 74 and 71% respectively. In contrast to islets transplantation, these results were obtained using a single pancreatic graft.

CONCLUSION

Intensive treatment with insulin can only delay progression of the morphological changes of early diabetic nephropathy, and up to ten years of normoglycaemia were found to be necessary to reverse established nephropathy. At the present whole pancreas transplantation is the only reliable option to achieve long-term insulin independence and an SPK transplantation has become the preferred treatment option for selected IDDM patients with advanced diabetic nephropathy and (or approaching) ESRD. Another option one may consider, especially if the waiting time for a pre-emptive (i.e. before initiation of dialysis) SPKT is prolonged, is a cadaver pancreas graft after a living (un)related kidney transplantation.

The American Diabetes Association strongly endorses pancreas transplantation in diabetic patients who have received prior kidney transplants and who have life-threatening metabolic instability. As results improve, isolated pancreas transplantation will be offered with increasing frequency to diabetics with preserved renal function. Nowadays, the circumstances where the risk-benefit equipoise could potentially favour pancreas transplantation may well include patients with diabetes mellitus type 1 and sustained overt diabetic nephropathy (albuminuria >300 mg/day) despite aggressive early intervention using ACE inhibitor and/or angiotensin-receptor blocker therapy.

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REVIEW

The treatment of hepatitis C: history, presence and future

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ABSTRACT

The treatment of chronic hepatitis C has made remarkable progress over the past two decades. For interferon-α monotherapy, sustained virological response rates were between 2 and 9% in genotype 1 and between 16 and 23% in genotypes 2 and 3. By adjusting treatment duration up to 48 weeks for genotype 1 and combining regular interferon-α with ribavirin, sustained response rates could be improved to 28 to 31% in genotype 1 and around 65% in genotypes 2 and 3. Attempts to further increase efficacy included the addition of amantadine without conclusive evidence up till now. With the recent introduction of long-acting pegylated interferon-α in combination with ribavirin, sustained virological response rates of 80% can be obtained in genotypes 2 and 3. However, sustained virological response rates for patients with either genotype 1, nonresponse to prior treatment, cirrhosis or a combination of these characteristics are still less than 50%. In view of results with daily high-dose interferon-α induction in combination with prolongation of treatment duration up to 18 months, such patients might benefit from induction and prolonged PEG-IFN-α treatment and should be treated in an experimental setting.

INTRODUCTION

The Netherlands Journal of Medicine is an offspring of the Folia Medica Neerlandica (1958). The very first publication in this magazine was entitled: 'Viruses as a cause of disease', a topic which has not lost its relevance.[1]
Hepatitis C virus (HCV) is such a cause and currently leading to a global public health problem. Worldwide, 150 to 170 million people are estimated to be chronically infected with HCV of whom an estimated five million are living in Western Europe. Twenty percent of those chronically infected will eventually develop cirrhosis of the liver and its sequelae within 10 to 20 years in the absence of treatment.[2] Antiviral therapy has now been used for nearly two decades to slow down and prevent this progression. In the past years, the response rate to antiviral therapy has made remarkable progress.
Originally, the response to antiviral therapy in patients with HCV was expressed in terms of biochemical response (normalisation of serum alanine aminotransferase (ALT) levels). However, since the introduction of sensitive PCR assays for the detection of viral RNA, expression in terms of virological response is preferred. Consequently, the success of an antiviral treatment modality is expressed in terms of sustained virological response, defined as a negative result of a sensitive PCR assay for HCV-RNA after a 24-week treatment-free follow-up period. A sustained virological response can be regarded as a surrogate marker for cure of HCV, although it does not completely exclude late virological relapse.
The focus of this review is to summarise past treatments of chronic hepatitis C, to describe the present standard of care and to give recommendations how to improve therapy in the future.

TREATMENT HISTORY: INTERFERON AND RIBAVIRIN

Interferon

In 1986, three years before the identification of the hepatitis C virus by molecular cloning techniques, Hoofnagle *et al.* introduced long-term, 'low-dose' interferon-α (IFN-α) for

the treatment of chronic non-A and non-B hepatitis.[3] Based on these preliminary data, large randomised placebo-controlled trials were performed confirming the effectiveness of IFN-α.[4,5] IFN-α given as a single agent (monotherapy) at a dose of 3 million units (MU) three times a week subcutaneously for 24 weeks induced end of treatment responses (normalisation of ALT levels) in about 50% of patients. However, in about half of the responding patients a relapse was seen within six months after discontinuation of treatment. Further experience indicated that the sustained virological response was even lower; only 6 to 18%. Patients with genotypes 2 and 3 had higher sustained virological responses (16 to 23%) than patients with the predominant genotype 1 (2 to 9%, *table 1*).[6,7]
In the years following the introduction of IFN-α, strategies to increase its antiviral activity included the optimisation of dose, treatment duration and the combination with other antiviral agents. One of the first improvements was made by prolonging the treatment duration to 48 weeks. Hereby, post-treatment relapse in HCV-RNA could be reduced significantly, resulting in an increased sustained virological response rate of 7 to 11% in genotype 1 and 29 to 33% in genotype non-1 (*table 1*).[6,8] By therapy prolongation beyond 12 months, the ALT relapse rate in IFN-α monotherapy could be reduced even further.[9,10]

Ribavirin

From all the efforts to increase efficacy, the combination of IFN-α with ribavirin has been the most fruitful. Ribavirin, a nucleoside analogue in use for the treatment of respiratory syncytial virus, lowers ALT levels in many patients with chronic hepatitis C; it has however no significant effect on serum HCV-RNA levels.[11-13] When used in combination with IFN-α, it increases the end of treatment response and reduces post-treatment relapse.[7,14] Large randomised placebo-controlled trials in the USA and other countries have confirmed the enhanced efficacy of combined interferon-ribavirin therapy. Among patients with genotype 1, a sustained virological response was found in 16 to 23% of those treated for six months and in 28 to 31% of patients treated for 12 months. Results in genotype non-1 were around 65% for both six and 12 months (*table 1*).[6-8] These findings led to the recommendation that patients infected with genotype 1 require a course of 48 weeks of IFN-α plus ribavirin therapy whereas a 24-week combination therapy was sufficient for patients with genotypes 2 and 3.[2]

Amantadine

Amantadine has been used for many years to prevent infection with influenza A virus. Most randomised controlled trials were unable to demonstrate a significant beneficial effect of amantadine-IFN-α over IFN-α monotherapy, largely because of small sample sizes.[15-19] The trials are comparable in design and when the data are pooled – a total of 920 patients have been included – a modest improvement can be demonstrated (*table 2*). Health-related quality-of-life analysis showed an improvement in fatigue and vigour scores in patients receiving combined IFN-α amantadine treatment compared with those treated with IFN-α alone.[15,20] Two trials (one randomised) in IFN-α nonresponders demonstrated significant benefits from the addition of amantadine to the combination of IFN-α and ribavirin.[21,22] The mechanism with respect to this improvement in sustained response remains unclear. Currently a Dutch placebo-controlled multicentre trial on 'triple' therapy in naive patients is in progress in more than 30 hospitals (CIRA study). This study will need a large sample size to demonstrate beneficial effects of amantadine.

High-dose induction and prolonged treatment

Increasing the IFN-α dose or administrating IFN-α daily could be beneficial, because of the high viral replication rate and the short half-life of IFN-α (only hours).[23] Indeed, high-dose IFN-α daily for several weeks, i.e. induction therapy, has been used for years in Japan, resulting in high (more than 80%) initial virological response rates[24] High daily dose IFN-α therapy with or without ribavirin in Western Europe and the USA, however, had no lasting beneficial effect on sustained virological response rates.[25,26] In those early reports, a significant increase of virological

Table 1
Effect of ribavirin and treatment duration

	INTERFERON-αB[#]		INTERFERON-α2B[#] AND RIBAVIRIN[$]	
	24 WEEKS	48 WEEKS	24 WEEKS	48 WEEKS
Genotype 1	2-9[6,7]	7-11[6,8]	16-23[6-8]	28-31[6,8]
Genotype non-1*	16-23[6,7]	29-33[6,8]	50-69[6-8]	64-66[6,8]

Sustained virological response rates in percentages in genotype 1 and genotype non-1 for interferon-α2b (IFN) monotherapy and IFN plus ribavirin for 24 and 48 weeks. Between brackets the literature references from which the results are taken.
**Reflects data on genotypes 2 and 3, data on genotypes 4 to 6 are too limited for inclusion in the table. [#]Interferon-α2b subcutaneously; dosed 3 million units three times a week. [$]Ribavirin orally; dosed 1.0 to 1.2 g in two divided doses according to weight.*

Table 2
Effect of amantadine when added to interferon-α

REFERENCE	INTERFERON-α2B	INTERFERON-α2B AND AMANTADINE[$]	P*
15	13/60 (22%)	6/59 (10%)	0.087
16	17/101 (17%)	29/99 (29%)	0.036
17	15/89 (17%)	21/90 (23%)	0.280
18	15/90 (17%)	22/90 (24%)	0.197
19	17/121 (14%)	25/121 (21%)	0.175
ALL	77/461 (17%)	103/459 (22%)	0.028

Number of patients out of whole group (and percentages between brackets) with sustained virological response for interferon-α2b (IFN) monotherapy and IFN plus amantadine for 48 weeks.
*[$]Amantadine orally; dosed 200 mg in two divided doses. *Chi-square test.*

response rate (% HCV-RNA negative patients) was found during the high daily dosing period as compared with IFN-α 3 MU three times a week. However, this effect did not result in an increased sustained virological response. This failure to maintain the initial response might be explained by the premature lowering of the IFN-α dose within the first week[27] or due to a short duration of treatment which was stopped after 24 to 26 weeks (24). In a later randomised controlled trial in 373 patients,[28] two experimental induction schedules were compared with a regular schedule of 38 weeks IFN-α 5 MU every other day. In genotype 1 patients, the sustained virological response was nearly twice as high (SVR: 42% versus 27%) when treated with induction therapy (10 MU IFN-α daily for two weeks, followed by 10 MU every other day for 12 weeks, followed by 5 MU every other day for 24 weeks). Sustained virological response rates in the non-1 genotypes varied between 56 and 76% in the three treatment arms but did not differ significantly. These data suggest beneficial effects of high-dose induction and prolonged daily IFN-α dosing in genotype 1 patients in whom success is limited when treated with standard therapy.

In an effort to analyse the above-mentioned treatment strategies combining high-dose induction IFN-α and prolonged daily IFN-α plus ribavirin we performed a meta-analysis on individual treatment data of an exploratory study performed in our centre.[29] In total, 54 consecutive chronic HCV patients selected for unfavourable baseline characteristics associated with therapy resistance such as genotype 1 infection, cirrhosis, previous nonresponse to IFN-α or combinations of these, were treated intensively for 76 weeks. The first 24 patients were treated with a very intensive schedule which resulted in an overall sustained response rate of 67% (95% confidence interval 45 to 84%).[30] In the following patients, attempts were made to decrease morbidity and cost without losing efficacy. However, by shortening the induction period adverse effects decreased somewhat as did the effectiveness.[27] Thus no clear advantage was found over the original intensive treatment schedule.
The induction phase of 10 MU IFN-α daily for two to four weeks was followed by three to five MU IFN-α injections daily until week 52, and three MU daily or three times a week until week 76. Throughout the study all patients received 1000 to 1200 mg ribavirin.
The overall sustained virological response rate was 57% (95% CI 43 to 71%). Sustained virological response varied between 75 and 83% for patients with one unfavourable characteristic, between 25 and 60% for patients with two unfavourable characteristics, but was only 17% for those with three unfavourable factors. Ten patients had detectable HCV RNA at week 12, in whom treatment was discontinued (19%). Two patients experienced a virological breakthrough (4%) and one patient was HCV RNA negative at 72 weeks but relapsed in the 24 weeks of untreated follow-up (2%). Four patients were not compliant: they stopped in the first four weeks after discharge from hospital. In six patients (11%), therapy was stopped because of adverse effects (hepatic decompensation (n=2), depression (n=2), cardiac symptoms (n=1) and *Staphylococcus* sepsis (n=1)). These data indicate that patients with either genotype 1, cirrhosis or prior nonresponse can have sustained virological response rates approaching those in genotypes 2 and 3 when treated with high-dosed and prolonged IFN-α based therapy. However, in patients with combinations of these unfavourable criteria, sustained virological response rates were low.

TREATMENT TODAY: PEG-INTERFERON-α AND RIBAVIRIN

PEG-interferon-α monotherapy

The covalent attachment of polyethylene glycol (PEG) to IFN-α extends the half-life and duration of therapeutic activity of IFN-α *in-vivo*, allowing less frequent dosing.

Four randomised controlled trials have compared the efficacy and safety of PEG-IFN-α monotherapy with standard IFN-α monotherapy.[31-34] One of these studies was designed to investigate treatment efficacy and safety in patients with bridging fibrosis or cirrhosis.[32] Administration of PEG-IFN-α once weekly has an increased antiviral effect compared with IFN-α 3 MU three times a week in naive patients resulting in a reduced breakthrough rate and an increased end of treatment and sustained virological response rate. The optimal dose of PEG-IFN-α was found to be 180 μg per week for PEG-IFN-α2a and 1.5 μg/kg body weight for PEG-IFN-α2b. Sustained response rates in genotype 1 were between 12 and 31% for PEG-IFN-α and between 2 and 6% for standard IFN-α. In genotypes 2 and 3 sustained virological response rates were around 50 and 28%, respectively.

PEG-interferon-α and ribavirin

When PEG-IFN-α is combined with ribavirin the sustained response rate is further improved. Sustained virological response rates in genotype non-1 were 78% for six and 77% for 12 months PEG-IFN-α2a plus ribavirin therapy. As with the treatment with regular IFN-α plus ribavirin, there is no benefit in prolonging treatment to 48 weeks in patients with genotypes 2 and 3 (*table 3*). A reduced ribavirin dose of 800 mg daily was found to be as effective as 1000 to 1200 mg daily in patients with genotypes 2 and 3, but the standard dosage of 1000 to 1200 mg yielded better sustained response rates in patients with genotype 1 in whom sustained virological response rates were 42 to 51% (*table 4*). These outcomes are improved over standard IFN-α ribavirin therapy although still about 50% of genotype 1 patients do not respond.[35-37] During treatment, a 2 log or more decrease in viral load in the first 12 weeks is predictive for sustained virological response. Patients who fail to achieve a 2 log decrease in viral load have a limited chance of achieving sustained virological response and should stop therapy.

One of the major differences between the two PEG-IFNs is fixed dosing for PEG-IFN-α2a and dosing according to weight for PEG-IFN-α2b. Trials comparing efficacy and safety of PEG-IFN-α2a to PEG-IFN-α2b with or without ribavirin have not (yet) been conducted. However, both PEG-IFNs have been compared with standard IFN-α and the increased sustained response rates, safety profile and side effects seem similar.

Consensus guidelines

The improvement in treatment results necessitated the need for updating the available guidelines. Two consensus guidelines, both funded from the public sector to assure independence from the pharmaceutical industry, were provided in 2002.[38,39] According to the National Institutes of Health (NIH) and French consensus guidelines all

Table 3
Effect of pegylation of interferon-α

	INTERFERON- α2B[#] AND RIBAVIRIN[¥] 48 WEEKS[35-37]	P-INTERFERON-α2B/B AND RIBAVIRIN[¥] 48 WEEKS[35-37]
Genotype 1	33-36%	42[$]-46%
Genotype non-1*	61-79%	76-82[$] %

Sustained virological response rates in genotype 1 and genotype non-1 for interferon-α2b and PEG-interferon-α 2a or PEG-interferon-α2b plus ribavirin for 48 weeks.

**Reflects data on genotypes 2 and 3, data on genotype 4 to 6 are too limited for inclusion in the table. #Interferon-α2b dosed 3 million units three times a week. PEG-interferon-α2a dosed 180 μg per week. PEG-interferon-α2b dosed 1.5 μg/kg body weight per week. ¥Ribavirin orally, dosed 1.0-1.2 g in two divided doses according to weight. $Ribavirin orally. dosed 800 mg/ day in two divided doses.*

Table 4
Effect of ribavirin dose and treatment duration[36]

	PEG-INTERFERON-α2A 180 μG PER WEEK			
	RIBAVIRIN 800 MG		RIBAVIRIN 1-1.2 G	
	24 WEEKS	48 WEEKS	24 WEEKS	48 WEEKS
Genotype 1	29%	40%	41%	51%
Genotype 2-3	78%	73%	78%	77%

Sustained virological response rates in genotype 1 and genotypes 2 and 3 for PEG-interferon-α2a ribavirin for 24 and 48 weeks.

patients with chronic hepatitis C and an increased risk of developing cirrhosis are potential candidates for antiviral therapy. Patients with genotypes 2 and 3 should be treated for 24 weeks. The NIH guidelines state that sustained virological response for patients with genotypes 2 or 3 are similar to PEG-IFN-α and ribavirin or standard IFN-α and ribavirin therapy. Thus standard IFN-α and ribavirin can still be used in treating patients with genotypes 2 or 3. Since low-dosed ribavirin was found to be as effective as 1000 to 1200 mg daily, 24 weeks of treatment and an 800 mg dose of ribavirin is the new standard for patients with genotypes 2 and 3. According to the consensus statements, patients with genotype 1 should be treated with PEG-IFN-α in combination with 1 to 1.2 g ribavirin for 48 weeks.

Currently, much attention is focused on patient and virus characteristics to enable identification of patients who will or will not benefit from treatment. Major pretreatment factors influencing response rates to combination therapy are HCV genotypes and the degree of fibrosis. Viraemic level, age and gender are of less importance in pegylated IFN-α therapy.[7,31,33,35,36,40]
Since genotype 1 is the predominant genotype in many parts of the world and the improved sustained response rate with combined PEG-IFN-α and ribavirin therapy is only about 50%, more effective treatment for this large group is desirable.
Patients with cirrhosis form another group currently in need of better treatment options. In view of the fact that morbidity and mortality of chronic hepatitis C is predominantly in this category of patients it is of note that most of the large trials of the interferon-ribavirin combination as well as those assessing PEG-IFN-α with or without ribavirin contained only a minority of patients with cirrhosis. Responses in cirrhotic patients are generally less than in noncirrhotic patients although treatment with PEG-IFN-α has diminished these differences. Heathcote *et al*. treated 271 patients with bridging fibrosis or cirrhosis with IFN-α2a *versus* two schedules of PEG-IFN-α2a. Sustained response rates of 12% in genotype 1 and 51% in genotype non-1 infection were found.[32]

TREATMENT TOMORROW: FURTHER THERAPEUTIC OPTIONS FOR GENOTYPE 1 AND CIRRHOSIS

As described above, treatment with high-dose induction IFN-α and prolonged daily IFN-α plus ribavirin was successful in the majority of patients selected for treatment-resistant characteristics. Given the increased effectiveness of PEG-IFN-α, a schedule of high-dose PEG-IFN-α combined with ribavirin for a prolonged period might increase response rates. For PEG-IFN-α induction, the optimal PEG-IFN-α dosage has to be determined by measuring both the levels of IFN-α and the antiviral effects *in vivo* during therapy. Currently, a Dutch multicentre randomised trial (PIT study) comparing PEG-IFN-α induction and prolonged PEG-IFN-α and ribavirin combination treatment with standard therapy in previous nonresponders is underway. Until now, randomised studies comparing PEG-IFN-α induction to standard PEG-IFN-α therapy have not yet been published.
In naive patients, interferon-based treatment strategies can possibly be further tailored to each individual patient according to early response dynamics. By measuring the decline in viral load in each patient in the first weeks of treatment, dose and treatment duration can possibly be optimised.
Completely different forms of medications, the so-called proteinase-inhibitors, are being investigated for their (additional) anti-HCV effect. These drugs can be taken orally and appear highly effective. Phase II and III clinical trials are currently underway; results are pending. Still, it is unlikely that such new therapy will be available for routine clinical use within the next three to five years.

CONCLUSIONS AND RECOMMENDATIONS

In *figure 1* our opinion on how to treat naive patients with chronic hepatitis C is shown.
Treatment is recommended for patients with an increased risk of developing cirrhosis. Therefore patients with F0-1 (no or minor fibrosis) should only be treated when highly motivated after complete information about side effects. Genotype 2 and 3 patients without cirrhosis are optimally treated for 24 weeks with (PEG)-IFN-α in combination with a low dose (800 mg/day) of ribavirin resulting in an 80% sustained response rate. Patients with cirrhosis and genotypes 2 and 3 have a limited chance of sustained response when treated for 24 weeks and should therefore be treated with PEG-IFN-α2a/2b for 48 weeks in combination with 1000 to 1200 mg/day of ribavirin. Genotype 1 patients are preferably treated with PEG-IFN-α2a/2b in combination with 1000 to 1200 mg/day of ribavirin for 48 weeks.
'Difficult to treat patients' with either genotype 1, nonresponse to prior treatment, cirrhosis or a combination of these characteristics who, despite notable advances, still have a chance of less than 50% for sustained virological response might benefit from induction and prolonged PEG-IFN-α treatment and should preferably be treated in an experimental setting. Further research is needed to optimise treatment schedules and to investigate new antiviral drugs in clinical practice; Dutch cooperative studies have the potential to solve some of these outstanding issues.

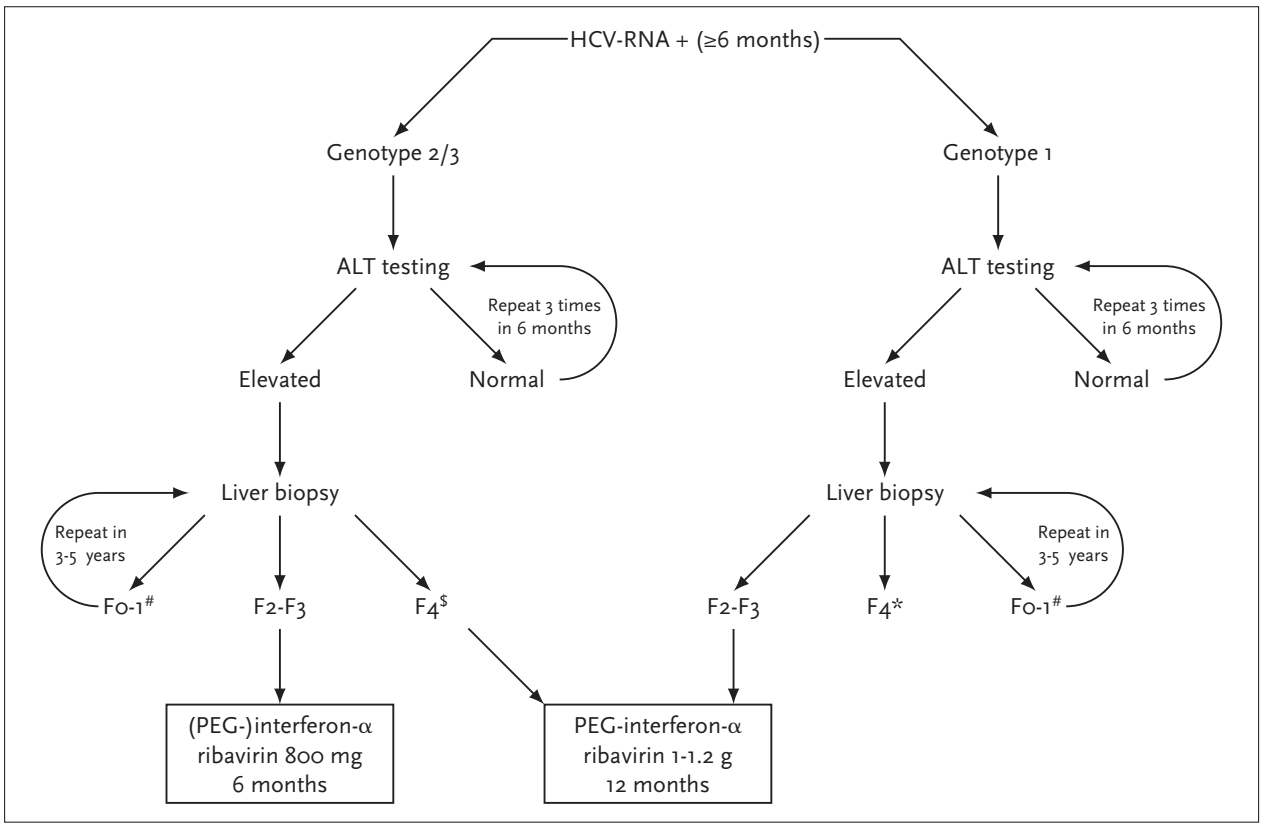

Figure 1
Individualised approach to treatment of naive patients with chronic hepatitis C according to the authors' interpretation of consensus statements[38,39]

Treatment is recommended for patients with an increased risk of developing cirrhosis, characterised by detectable HCV RNA levels, elevated alanine aminotransferase (ALT) values, a liver biopsy with portal or bridging fibrosis, and at least moderate inflammation and necrosis.
 # Patients with Fo-1 (no or minor fibrosis) have a limited risk of developing cirrhosis and should only be treated when highly motivated after complete information about side effects. Re-evaluation within three to five years is recommended. *Patients with genotype 1 and cirrhosis (F4) should in view of the limited chance of sustained virological response be treated in an experimental setting. $Patients with genotypes 2 or 3 in whom cirrhosis is likely should be treated for one year with PEG-IFN-α and standard-dosed ribavirin.

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Recurrence rate of pre-eclampsia in women with thrombophilia influenced by low-molecular-weight heparin treatment?

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ABSTRACT

Objectives: (1) To assess the recurrence rate of pre-eclampsia in women with this history before 34 weeks of pregnancy and thrombophilia. (2) To evaluate the effects of low-molecular-weight heparin (LMWH) on pregnancy outcome.

Methods: In a multicentre retrospective study subsequent pregnancies of women with a history of pre-eclampsia necessitating birth before 34 weeks and thrombophilia were analysed. Of 58 women, 26 received LMWH and aspirin (ASA) and 32 ASA (22) or no (10) medication in their subsequent pregnancies.

Results: In eight women treated with LMWH and ASA and in 16 women receiving ASA or no medication pre-eclampsia recurred in the subsequent pregnancy. (OR 0.55, 95% CI 0.15-1.31) There were no significant differences in birth weight or gestational age between both groups.

Conclusions: The recurrence rate of pre-eclampsia in women with thrombophilic disorders is high in this small retrospective study. No positive effect was found for LMWH treatment. A multicentred randomised study has been started to reach an adequate number of patients to evaluate the influence of LMWH treatment.

INTRODUCTION

Pre-eclampsia is a major problem in perinatal medicine especially in early onset pre-eclampsia before 34 weeks gestation. The exact cause of pre-eclampsia is unknown and a multifactorial origin is suggested. Maladaptation of the maternal immune system to the foetal allograft as well as genetic factors are probably involved in its aetiology.[1] More recently, several investigators confirmed the presence of thrombophilic disorders (hereditary coagulation abnormalities, anticardiolipin antibodies, hyperhomocysteinaemia) in a substantial percentage (up to 60%) of women with a history of severe early onset pre-eclampsia and small-for-gestational-age (SGA) infants.[2-4]

The recurrence rate of pre-eclampsia in women with this history necessitating delivery before 34 weeks and documented thrombophilia without treatment with low-molecular-weight heparin is still unknown. Riyazi *et al.* tested a total of 276 patients with a history of pre-eclampsia and/or foetal growth restriction for the presence of hereditary coagulation abnormalities and anticardiolipin antibodies. Ninety patients with pre-eclampsia and 15 patients with isolated foetal growth restriction had haemostatic abnormalities. In 26 patients a subsequent pregnancy occurred and they were treated with low-molecular-weight heparin (started directly after confirmation of a viable intrauterine pregnancy) and low-dose aspirin (started at 10 to 12 weeks gestational age). Pre-eclampsia recurred in 38%, and intrauterine growth restriction in 15% of pregnancies.[5]

The recurrence rate in this population with known thrombophilia is lower than two studies reporting the recurrence rate of severe pre-eclampsia or HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome in a population with unknown thrombophilic status. Sibai *et al.*[6] described a group of 125 women with a history of severe pre-eclampsia in the second trimester (range 18 to 27 weeks gestation), of which 108 women had 169 subsequent pregnancies (range 1 to 4 per woman): 59 (35%) had a normotensive pregnancy and 110 (65%) developed pre-eclampsia. Sullivan *et al.*[7] studied 481 patients with a history of HELLP syndrome. Subsequent gestations (n=195) occurred in 122 of 481 patients. Available data on 161 pregnancies showed a recurrence rate of 43%.

There is still no treatment to reduce the recurrence of pre-eclampsia in women with thrombophilia. Rai *et al.*[8] did perform a randomised study on women with pregnancies complicated by intrauterine foetal death before 28 weeks associated with anticardiolipin antibodies and unknown hereditary coagulation status. Women treated with unfractionated heparin with aspirin had better pregnancy outcome compared with women treated with aspirin only. However, in his study the entry criterion was recurrent foetal death associated with anticardiolipin antibodies and primary endpoint in this population was number of live births. Recently Kupferminc *et al.*[9] published the results of an uncontrolled study of 33 women with an earlier pregnancy complicated by severe pre-eclampsia, abruptio placentae, intrauterine growth retardation or intrauterine foetal death. These women received LMWH in their subsequent pregnancies and only 9.1% of the women developed pregnancy complications.

The study presented here concerned a retrospective study of subsequent pregnancies of women with a history of pre-eclampsia necessitating birth before 34 weeks. The aims of this study were to evaluate the recurrence rate of pre-eclampsia in women with thrombophilia and to test the hypothesis if LMWH is beneficial in reducing the recurrence of pre-eclampsia. The different treatments consisted of low-molecular-weight heparin (LMWH) in combination with aspirin or aspirin only or no medication. This retrospective study was performed in advance of a prospective randomised study to evaluate whether a study for the effects of LMWH treatment in women with thrombophilia would be beneficial.

MATERIALS AND METHODS

In a retrospective study subsequent pregnancies of women with a history of pre-eclampsia necessitating birth before 34 weeks were analysed. Inclusion criteria were women with an index pregnancy of pre-eclampsia leading to birth before 34 weeks gestation and thrombophilia. Between the period 1991 and 1998, 1146 women were tested for thrombophilic disorders in eight Dutch hospitals (*table 1*). The hereditary coagulation abnormalities included were antithrombin deficiency, protein C deficiency, activated protein C resistance with and without factor V Leiden mutation, protein S deficiency and factor II mutation.

Table 1

Results in 1146 women with a history of pre-eclampsia necessitating delivery before 34 weeks in the period between 1991 and 1998 in eight Dutch hospitals (some women had more than one thrombophilic disorder)

	TESTED	ABNORMAL	
	n	n	%
Antithrombin deficiency	1146	6	0.5
Protein C deficiency	1146	13	1
Activated protein C resistance (APCr)	1146	66	5
APCr+ factor V Leiden mutation	1146	96	8
Protein S deficiency	1146	88	8
Factor II mutation	1033	5	0.4
Anticardiolipin antibodies	990	95	9
Hyperhomocysteinaemia	990	99	10

The acquired anticardiolipin antibodies were tested as well as hereditary/acquired hyperhomocysteinaemia. In this period not all hospitals tested for all thrombophilic disorders; one hospital did not test for factor II mutation (n=113) and two hospitals did not test for anticardiolipin antibodies and hyperhomocysteinaemia (n=156). In case of coagulation abnormalities and anticardiolipin antibodies five hospitals gave aspirin or no medication and three hospitals treated with LMWH and aspirin in the subsequent pregnancy. Hyperhomocysteinaemia was treated with vitamin B6 and folic acid supplementation throughout gestation in all hospitals. For each patient, the medical records were checked to establish which treatment was applied in the subsequent pregnancy. Outcome measurement was recurrence rate of pre-eclampsia. Birth weight and gestational age in index and subsequent pregnancy were also compared between both groups.

Definitions of pre-eclampsia and eclampsia were used according to the standards of the International Society for the Study of Hypertension in Pregnancy (ISSHP).[10] Pre-eclampsia was defined as pregnancy-induced hypertension plus significant proteinuria after 20 weeks of

gestational age. Proteinuria was defined as excretion of 300 mg or more in 24 h or two readings of 2+ or higher on dipstick analysis of midstream or catheter urine specimens. HELLP syndrome was defined as the presence of (1) haemolysis, defined by increased LDH (>600 IU/l) and (2) elevated liver enzymes, defined as increased SGOT (>70 IU/l) and (3) thrombocytopenia (<100 x 10^9/l). Eclampsia was defined as the occurrence of generalised convulsions during pregnancy, during labour, or within seven days of delivery and not caused by epilepsy or other convulsive disorders.

Laboratory tests

Normal values of each centre were tested, applying the International Thrombophilia External Quality Assessment within the European Concerted Action on Thrombosis (ECAT) Foundation. The measurement procedures were standardised for each laboratory. For details of hereditary coagulation abnormalities see *table 1*. All tests were performed at least ten weeks post partum, and women were not on oral contraceptives. Anticardiolipin antibodies, immunoglobulin (Ig)G and IgM, were determined by enzyme-linked immunosorbent assay according to the Harris directives (all centres).[11]

Hyperhomocysteinaemia was diagnosed using a methionine loading test: a blood sample for determination of the fasting homocysteine concentration is drawn at 8 a.m. after an overnight fast. Subsequently, an oral dose of L-methionine (0.1g/kg body weight) is administered in orange juice. The patients had a standardised low-methionine breakfast and lunch. Patients were considered hyperhomocysteinaemic when fasting normal values and/or postloading normal values exceeded the 97.5 percentile (all centres).[12]

Statistical analysis

Analysis was carried out with SPSS for Windows (version 8.0, SPSS Inc., Chicago II) and Excel for Windows (version 5.0c, Microsoft Corporation). Odds ratios with 95% confidence intervals were calculated by logistic regression analysis. Statistical significance was defined as $p<0.05$.

RESULTS

In the total group of 1146 tested women, 407 women were found to have 468 thrombophilic disorders i.e. hereditary coagulation abnormalities (n=274) and/or anticardiolipin antibodies (n=95) and/or hyperhomocysteinemia (n=99) (*table 1*). In 48 women more than one thrombophilic disorder was found.

In this period 58 women had a subsequent pregnancy. Twenty-six patients who had a pregnancy after the index pregnancy received LMWH (nadroparin 2 dd 2850 IU anti-Xa sc a day) plus aspirin (80 mg) starting between six and 12 weeks gestational age, the other 32 patients received aspirin (n=22) or no medication (n=10). In the 26 patients who received LMWH in combination with aspirin, pre-eclampsia recurred in eight patients (30%). In the 32 patients who received aspirin or no medication, pre-eclampsia recurred in 16 patients (50%) (OR 0.55, 95% CI 0.15-1.31). The recurrence of pre-eclampsia *before* 34 weeks in the subsequent pregnancy was 2/26 (8%) *versus* 7/32 (22%) (OR 0.3, 95% CI 0.05-1.58) No difference was found in recurrence rate in women treated with aspirin (27%, 6/22) *versus* women without aspirin (40%, 4/10) (OR 0.56, 95% CI 0.11-2.72). In subsequent pregnancies the number of babies under the 10th percentile of birth weight was one of 26 in women receiving LMWH and ASA *versus* two of 12 in women receiving ASA alone and one of 10 women receiving no medication. The number of preterm deliveries before 34 weeks of gestational age was three of 26, three of 12 and two of 10, respectively.

In *table 2* the mean birth weights and mean gestational ages of the index pregnancies and subsequent pregnancies in the three groups are presented.

Table 2

Index (i) and subsequent (s) outcome of pregnancies in women receiving low-molecular-weight heparin (LMWH) and aspirin versus women receiving aspirin only or no medication (data presented as mean with standard deviation)

	LMWH + ASA N=26	ASA N=22	NO MEDICATION N=10
Mean birth weight (gram) (i)	1004 (±437)	886 (±554)	1272 (±437)
Mean birth weight (gram) (s)	2956 (±583)	2497 (±954)	2697 (±1415)
Mean gestational age (days) (i)	205 (±19)	198 (±24)	204 (±26)
Mean gestational age (days) (s)	264 (±13)	257 (±23)	260 (±38)

DISCUSSION

This study demonstrated that women with a history of early onset pre-eclampsia in their index pregnancy do have a high recurrence rate in subsequent pregnancies. This was found for women receiving LMWH, aspirin or no medication. As far as percentages can be reliably presented for the small study population, the percentages found are comparable with the study by Riyazi *et al.*[5] She reported from one hospital the recurrence rate of early onset pre-eclampsia and SGA babies in women with thrombophilia receiving LMWH and aspirin. Our study showed a low recurrence rate of pre-eclampsia in comparison with the studies by Sibai *et al.*[6] and Sullivan *et al.*[7] of women with unknown thrombophilia. Our study did not demonstrate significant benefit from LMWH in the recurrence rate. The drawn conclusion should be seen within the context of the retrospective character of the study and the limited number of subsequent pregnancies in this population. The insignificance can be merely a power problem.

In our study we report on subsequent pregnancies in women checked in the hospital in which they had their index pregnancy and thrombophilia analysis. The low percentage of found subsequent pregnancies may in part be responsible for this procedure. For practical reasons we did not contact the 407 women with thrombophilic disorders personally. From the work by Van Pampus *et al.* who did consequently contact all the patients she included in her study, we know that she found that 66% of women with a history of HELLP syndrome had subsequent pregnancies.[13] Concerning the direction of a possible bias it is plausible that we did not miss the severe early onset pre-eclampsia. This is thanks to the Dutch healthcare organisation. Preterms (<32 weeks) deliver in hospitals with neonatal intensive care units and severe pre-eclamptic women are advised to be treated in tertiary centres. All Dutch hospitals with neonatal intensive care units and tertiary centres participated in this study with the exception of one, which was not systematically examining thrombophilic factors in these patients at that time.

The distribution of thrombophilic factors of this study is in accordance with other Dutch studies.[14] Various investigators have found that the distribution of thrombophilic factors varies per population.[4,15] Factor V Leiden mutation is common in Caucasian populations, but in African and Asian countries the frequency is lower.[14]

The occurrence of pre-eclampsia in women with thrombophilia can be explained by excessive microthrombic deposition within the maternal placental circulation.[16] Therefore, thromboprophylaxis seems to be a logical preventive therapy. Recently more studies have been published of LMWH treatment in women with thrombophilia and recurrent foetal loss.[17] However, no large studies have been performed in women with a history of severe pregnancy complications such as pre-eclampsia. For years LMWH has been used as thrombophylaxis during pregnancy.[18] LMWH does not cross the placental barrier.[19] In several studies the authors concluded that the use of LMWH appears to be relatively safe and well tolerated during pregnancy, delivery and the immediate postpartum period.[19] It has a longer half-life, better bioavailability and less effect on platelets than unfractionated heparin. Furthermore, it is considered to have a better thrombophylactic effect and a lower risk on bleeding complications. As the long-term use of heparin is associated with the development of osteoporosis, bone density measurements performed by pregnant women treated with LMWH and untreated pregnant women showed similar bone density loss in both groups.[20] Furthermore, heparin-induced osteoporosis is reversible when heparin is stopped.

Despite the above-mentioned items as possible therapeutic effect and safety aspects for mother and foetus, the benefit of LMWH treatment still has to be demonstrated. For this reason an international multicentred trial has been started called FRactionated heparin in women with a history of Uteroplacental Insufficiency and Thrombophilia (FRUIT study) in which 13 Dutch centres and two Australian centres are participating. To enable an optimal inclusion of patients, all gynaecologists in the Netherlands receive information about the FRUIT study through newsletters and from the website of the Dutch Society of Obstetrics and Gynaecology.

CONCLUSION

This study demonstrates a high recurrence rate of pre-eclampsia in women with such a history and documented thrombophilia and found no effect of LMWH on pregnancy outcome. These findings support the need for an adequately sized randomised study to evaluate the effects of treatment with LMWH.

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Kalk, et al. Recurrence rate of pre-eclampsia in women with thrombophilia

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A 51-year-old man with upper abdominal pain

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CASE REPORT

A 51-year-old man presented at our Emergency Unit with severe upper abdominal pain. This pain had started some hours before, immediately after vomiting, and was least when he was lying down quietly. He had a history of alcoholism and asthma, but was not taking any medication. Last week he drank even more alcohol than usual. Physical examination revealed a patient suffering from severe pain in his upper abdomen. His blood pressure was 175/130 mmHg, with a pulse frequency of 138 beats/min and he had a temperature of 36.6 °C. The abdomen was tender and hard with a normal dull percussion of the liver and normal peristalsis. He had subcutaneous emphysema in the right supraclavicular area. Laboratory results were as follows: haemoglobin 11.3 mmol/l (8.7-10.5), leucocytes 9.8 x 10^9/l (4-12), C-reactive protein 6 mg/l (<10), alkaline phosphatase 141 U/l (50-125), γ-glutamyltransferase 1037 U/l (6-50), glutamic-pyruvic transaminase 329 U/l (5-50), glutamic-oxaloacetic transaminase 253 U/l (5-40), lactate dehydrogenase 652 U/l (200-450) and amylase 131 U/l (30-110). Chest X-ray and computed tomography of the abdomen are shown below (*figures 1* and *2*).

WHAT IS YOUR DIFFERENTIAL DIAGNOSIS?

See page 97 for the answer to this photo quiz.

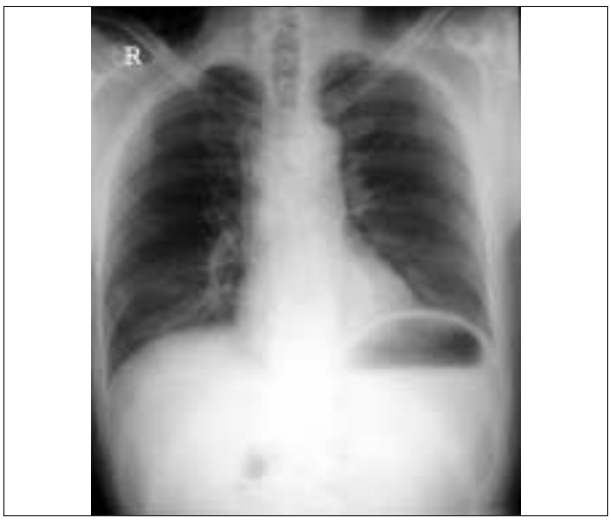

Figure 1
Chest X-ray shows discrete mediastinal and subcutaneous emphysema in the right supraclavicular area

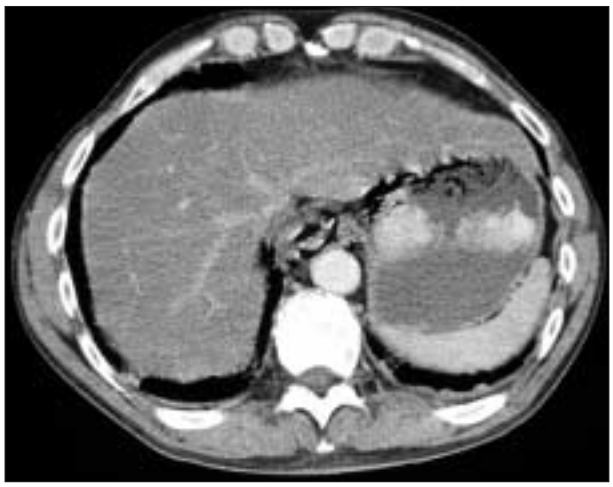

Figure 2
Computed tomography of the abdomen with intravenous and watery contrast per os shows the oesophageal rupture and emphysema between stomach and liver

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CASE REPORT

A boy with autosomal recessive hypercholesterolaemia

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ABSTRACT

We describe a 9-year-old Iranian boy with tuberous xanthomas, elevated LDL-cholesterol levels of 15.5 mmol/l, and vague complaints of chest pain while playing soccer. The consanguineous parents of the boy had normal cholesterol concentrations, which indicated an autosomal recessive disorder rather than autosomal dominant familial hypercholesterolaemia. The diagnosis of autosomal recessive hypercholesterolaemia (ARH) was confirmed by the presence of a mutation in the phosphotyrosine binding domain of a putative adaptor protein, which prevents normal internalisation of the LDL receptor (LDLR) in the liver. The clinical phenotype of ARH is similar to that of classical homozygous familial hypercholesterolaemia caused by defects in the LDLR gene, but it is more variable, generally less severe, and more responsive to lipid-lowering therapy. The patient's complaints of chest pain were not caused by ischaemia as was tested by an exercise and 24-hour electrocardiogram and by a myocardial perfusion scan. His LDL-C dropped by about 60% after being treated with a combination of 40 mg atorvastatin and 10 mg ezetimibe.

INTRODUCTION

Familial hypercholesterolaemia (FH) is an inherited autosomal dominant disorder of lipoprotein metabolism caused by a plethora of mutations in the low-density lipoprotein receptor (LDLR) gene.[1] Clinically, FH is associated with elevated levels of low-density lipoprotein cholesterol (LDL-C) that are two- to four-fold higher than in healthy individuals (*table 1*) and premature atherosclerosis. Patients develop symptoms of atherosclerotic cardiovascular disease (CVD) in the third or fourth decade of their life and xanthomas on the extensor tendons of the hands and on the Achilles tendons.[1]

In patients with two defective alleles, homozygous or compound heterozygous FH, there is little or no LDLR activity, leading to plasma LDL-C levels about six-fold higher than in healthy individuals. They develop tendon and cutaneous xanthomas early in childhood and have manifestations of premature atherosclerosis within the first two decades of life.[1]

In addition to the classical autosomal dominant form of FH, some patients have been described with the clinical expression of homozygous familial hypercholesterolaemia, but with an autosomal recessive genetic trait: autosomal recessive hypercholesterolaemia (ARH). Recently, the disorder was shown to be caused by mutations in the phosphotyrosine binding domain protein (PTB).[2-4] PTB domains are responsible for intracellular signalling and transport. The PTB domain binds the consensus sequence NPXY, a motive that is present in the cytoplasmatic domains of several cell-surface receptors, such as the LDLR.[5] The intact NPXY sequence is required for internalisation of the LDLR. Dysfunction of the binding between the PTB and the NPXY prevents internalisation of the LDLR, which results in an impaired LDLR activity. Patients with ARH have impaired hepatic LDLR function, but in contrast with homozygous FH patients, LDLR function in cultured fibroblasts *in vitro* is normal or only slightly decreased.[6] Therefore, the fibroblasts are still able to bind and

[**] **A.F.H. Stalenhoef was not involved in the handling and review process of this paper.**

Table 1
Lipid disorders characterised with xanthomas

	INHERITANCE	FREQUENCY	LDL-CHOLESTEROL	XANTHOMAS	CVD	TREATMENT	MOLECULAR DEFECT
Heterozygous familial hypercholesterolaemia	Autosomal dominant	1:400-500	2-4 fold elevated	++	3rd-4th decade	HMG CoA reductase inhibitors, cholesterol absorption inhibitors	Mutation in low-density lipoprotein receptor
Homozygous familial hypercholesterolaemia	Autosomal dominant	1:1,000,000	6-fold elevated	++++	1st-2nd decade	HMG CoA reductase inhibitors, cholesterol absorption inhibitors	Mutation in low-density lipoprotein receptor
Autosomal recessive hypercholesterolaemia	Autosomal recessive		4-fold elevated	++++	4th decade	HMG CoA reductase inhibitors, cholesterol absorption inhibitors	Mutation in phospho-tyrosine binding domain protein
Sitosterolaemia	Autosomal recessive	1:1,000,000	Normal or slightly elevated	+++++	2nd -3rd decade	Low plant sterols diet, bile acid resins	Mutation in adenosine triphosphate binding cassette
Cerebrotendinous xanthomasis	Autosomal recessive		Normal or low	+++		Chenodeoxycholic acid	Mutation in sterol 27 hydroxylase

LDL = low-density lipoprotein, CVD = cardiovascular disease, HMG-CoA = hydroxy methyl glutaryl Co enzyme A.

degrade LDL. ARH has been mapped at the short arm of chromosome 1 (1p36.1-p35).[2] Today, eight mutations have been identified in patients from Lebanon, Sardinia, Iran, Italy and the United States.[7,8]

There are several other rare conditions that are accompanied by the development of xanthomas, but they are not always accompanied by severe disturbance in plasma lipid levels per se. A similar but milder phenotype than FH is familial defective apolipoprotein B-100 (FDB). FDB is an autosomal dominant disorder associated with hypercholesterolaemia in which an amino acid substitution in apoprotein B-100 leads to low-density lipoprotein (LDL) particles which have defective binding to the LDL receptor.[9]

Sitosterolaemia, caused by accumulation of plant sterol in tissues and plasma,[10] is clinically characterised by extensive tuberous and tendon xanthomas, accelerated atherosclerosis, arthralgias and arthritis.[11,12] In contrast to patients with FH or ARH, sitosterolaemia patients usually have normal to moderately elevated total cholesterol levels but very high levels of plant sterols in their plasma, due to mutations in gene encoding for the ABCG5 and ABCG8 transporters in the gut.[13] CTX is a rare inborn disorder of bile acid synthesis in which hepatic conversion of cholesterol to cholic and chenodeoxycholic acids is impaired due to a mutation in the 27-hydroxylase gene. This disorder is clinically characterised by strongly elevated levels of cholestanol, diarrhoea in childhood, cataracts, several neurological dysfunctions, Achilles tendon xanthomas and premature atherosclerosis.[14] Another hypercholesterolaemic phenotype similar to that in heterozygous FH has also been reported in a family with homozygous mutations in the gene for 7α-hydroxylase, another enzyme in the pathway of bile acid synthesis in the liver,[15] but further families with this disorder remain to be identified.

In this report we describe a case of ARH.

CASE REPORT

A 9-year-old boy of Iranian descent was referred to our hospital. He had vague complaints of chest pain while playing soccer. Beside this problem, he had noticed strange lumps on both knees since the age of 7 years. Physical examination revealed tuberous xanthomas on both elbows, both knees and buttocks (*figure 1*). There were clear arcus cornealis lipoides. Further physical examination revealed no abnormalities, particularly no bruits or other signs of atherosclerotic disease.

Laboratory investigations revealed severely elevated levels of total serum cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C), and decreased levels of high-density lipoprotein (HDL-C) (*table 2*). Triglyceride levels were normal. The concentration of apolipoprotein B-100 was at 4.0 g/l also higher than the normal values of 0.6 to 1.4 g/l, and that of apolipoprotein A1 was with 0.69 g/l lower than the normal range of 1.1 to 1.8 g/l.

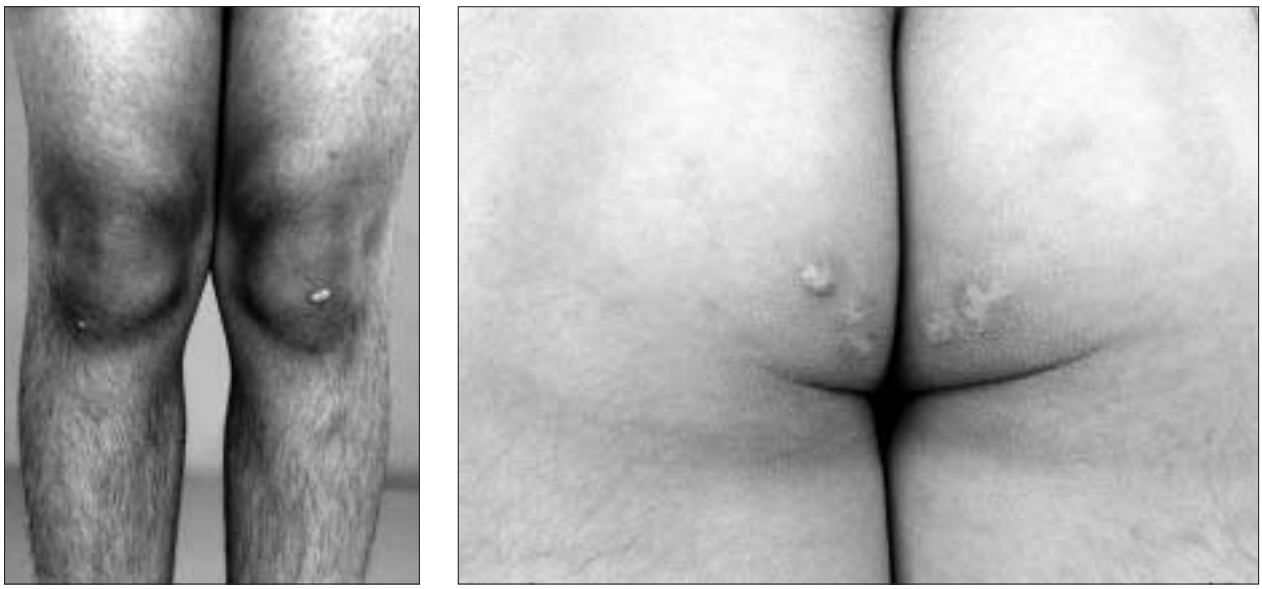

Figure 1
Tuberous xanthomasis on knees and buttocks in autosomal recessive hypercholesterolaemia

A colour version of these pictures is presented on the websit www.njmonline.nl.

Table 2
Serum cholesterol concentrations of the patient and the 5th, 50th and 95th percentiles of 5 to 9-year-old boys

	PATIENT	5TH PER-CENTILE	50TH PER-CENTILE	95TH PER-CENTILE
TC (mmol/l)	16.5	3.13	4.15	5.26
LDL-C (mmol/l)	15.5	1.74	2.41	4.91
HDL-C (mmol/l)	0.66	1.01	1.45	1.89
Triglycerides (mmol/l)	0.71	0.34	0.63	1.14

His lipoprotein (a) was 270 mg/l, which is within the normal range (<300 mg/l). No other laboratory abnormalities were found.
An exercise electrocardiogram and a 24-hour electrocardiogram were normal, in particular no ST-T segment abnormalities. A myocardial perfusion scan did not show ischaemia. Echography of the carotid arteries demonstrated thickening of the intima medial layer.
The patient's family history appeared to be positive for premature atherosclerosis. His father's mother probably died of a myocardial infarction at the age of 20 and her father died at a young age too. His mother's brother suffered from a myocardial infarction at the age of 37. The father of the boy's mother died at the age of 56 of a myocardial infarction (*figure 2*). Based on the thickening of the intima medial layer and on this family history and the diagnosis homozygous familial hypercholesterolaemia was considered. However, the boy's parents have normal cholesterol levels (mother 26 years, TC 4.5 mmol/l; father 33 years, TC 5.7 mmol/l). His 7-year-old brother also has normal cholesterol levels (TC 3.3 mmol/l). In addition, the patient's parents are blood relatives. The cholesterol levels of his parents indicate a lipid disorder of recessive origin rather than homozygous FH. This was confirmed by DNA analysis.

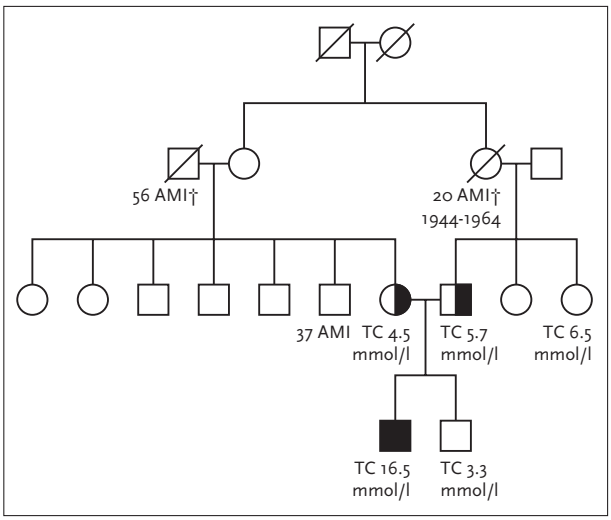

Figure 2
Family tree of the patient with ARH

Circles present females and squares present males. Open symbols indicate that no genetic defect is present or that the genetic profile is unknown, half-open symbols indicate heterozygous persons and closed symbols indicate homozygous persons. AMI = acute myocardial infarction, TC = total cholesterol. †Died.

Our patient was tested for the mutation by Professor H.H Hobbs and colleagues from the Department of Molecular Genetics, University of Texas Southwestern Medical Center, Dallas, Texas, USA, and appeared to be homozygous for the ARH5 frame shift mutation[2] that results in a premature stop codon in amino acid 33.
Treatment with an HMG-CoA reductase inhibitor was initiated. Pravastatin was started at a dosage of 40 mg upon which the LDL-C level decreased to 11.4 mmol/l. Later, the patient was treated with 40 mg of atorvastatin and his LDL-C decreased to 8.3 mmol/l. The xanthomas on his knees and buttocks became smaller, but are still present. The patient is now 14 years old; we recently added a new cholesterol absorption inhibitor, ezetimibe 10 mg, to his medication. His LDL-C decreased further to 6.6 mmol/l and his HDL-C slightly increased to 0.9 mmol/l. When asked about his condition, he still complains of shortness of breath during exercise, but a yearly exercise electrocardiogram was still negative for ischaemia.

DISCUSSION

In 1973, Khachadurian *et al.* described the first case of a patient with the clinical expression of homozygous familial hypercholesterolaemia but with an autosomal recessive genetic trait.[16] The clinical characteristics of patients with ARH resemble those of homozygous hypercholesterolaemia, but ARH patients have cholesterol levels intermediate between those of heterozygous FH and homozygous FH[6] and the onset of symptomatic CVD is somewhat later (*table 1*). In spite of the lower plasma cholesterol levels compared with homozygous FH, patients with ARH often have large and bulky xanthomas,[3,17] as was seen in the patient described here.
Patients with ARH are sensitive to a cholesterol-lowering diet and HMG-CoA reductase inhibitors. The presence of residual LDLR activity in skin fibroblasts might explain the plasma cholesterol concentrations and the response to cholesterol-lowering medication in patients with ARH.[7]
The family history suggested autosomal dominant FH initially, because some relatives probably died of a myocardial infarction at a young age. However, the boy's parents turned out to have normal cholesterol concentrations, and therefore, autosomal dominant FH could not be the disorder that caused the high cholesterol concentration in the boy. Besides, we could not establish whether the relatives died from coronary artery disease as the data were only obtained by history, and autopsy or tests for the mutation were not performed. This indicates that other (inherited) disorders might have been involved. Furthermore, if ARH was the cause of premature death of the relatives, then those individuals had to be homozygous for the disease. Thus, the only fact we were certain of is that both parents of the boy were heterozygous for ARH and that they were consanguineous. Therefore, they are the only ones who are marked as being heterozygous for ARH in *figure 2*.
The patient's complaints of chest pain were not caused by ischaemia as was tested by the exercise or 24-hour electrocardiogram and by the myocardial perfusion scan. We considered the results from these tests adequate to rule out coronary artery disease. Therefore, a coronary angiography was not indicated. Furthermore, a coronary angiography is invasive and not without risk for children at this young age.

CONCLUSION

We present a young patient with xanthomas in skin and tendons and severely elevated plasma LDL-C levels, who is homozygous for the ARH5 mutation, which confirms the clinical diagnosis of ARH.
Treatment with HMG-CoA reductase inhibitors coadministered with ezetimibe resulted in a nearly 60% reduction of LDL-C. To obtain optimal plasma cholesterol levels LDL apheresis may be indicated in these cases.

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Bijsluiter

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CASE REPORT

Ventricular fibrillation in hypercalcaemic crisis due to primary hyperparathyroidism

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ABSTRACT

We report the case of a 64-year-old man who presented with severe hypercalcaemia secondary to primary hyperparathyroidism. Soon after admission he developed ventricular fibrillation with no other cause than this severe hypercalcaemia. Although the occurrence of cardiac arrhythmias in hypercalcaemia is widely known, ventricular fibrillation has never been described before.

INTRODUCTION

Hypercalcaemic crisis, a serum calcium concentration greater than 3.50 mmol/l, is infrequent in primary hyperparathyroidism.[1,2] Nevertheless, it is a life-threatening condition requiring emergency treatment.
Although the effects of hypercalcaemia on cardiac conduction are well established, reports of severe arrhythmias caused by primary hyperparathyroidism are rare. We present a case of severe hypercalcaemia, due to primary hyperparathyroidism, complicated by ventricular fibrillation.

CASE REPORT

A 64-year-old man was admitted to the emergency department for drowsiness and dehydration. His condition used to be good, despite hypertension, pulmonary embolism and a stroke. Yet, progressive forgetfulness, polyuria and polydipsia had been present for several months, but his condition had deteriorated rapidly three days before admission.

Physical examination showed a drowsy man who was disoriented in time and place. His heart rate was 55 beats/min. Blood pressure was 110/55 mmHg despite pre-existent hypertension treated with a calcium antagonist (amlodipine). He was dehydrated.
There were no abnormalities of the neck, chest and abdomen. A 12-lead electrocardiogram (ECG) showed non-specific ST and T wave abnormality and a QTc of 425 ms (*figure 1*). A chest X-ray was normal. Laboratory evaluation showed a total serum calcium of 4.95 mmol/l (reference values: 2.2-2.6 mmol/l), a serum albumin level of 28 g/l (35-50 g/l), and substantial renal insufficiency (creatinine 312 μmol/l (75-110 μmol/l)). Potassium level was 3.3 mmol/l (3.5-5.0 mmol/l).
The patient was transferred to the ICU. Amlodipine was stopped. A combination therapy of forced saline diuresis (350 ml/h NaCl 0.9% and furosemide 7 mg/h with potassium chloride 10 g/24 h) and pamidronate 60 mg was started but the serum calcium concentration declined only slightly: within four hours from 4.95 mmol/l to 4.75 mmol/l.
Several hours after admission cardiac monitoring showed a transition from sinus rhythm to ventricular fibrillation after a very short episode of torsades des points (*figure 2*). Sinus rhythm was restored on direct current cardioversion with 360 J after two unsuccessful attempts with 200 J. Soon afterwards a new episode of ventricular fibrillation occurred (*figure 2*), which again was terminated by cardioversion. Calcium concentration was 4.92 mmol/l, potassium concentration 3.5 mmol/l and magnesium concentration 0.79 mmol/l (0.7-1.0 mmol/l).
Because of this inadequate response, we decided to start

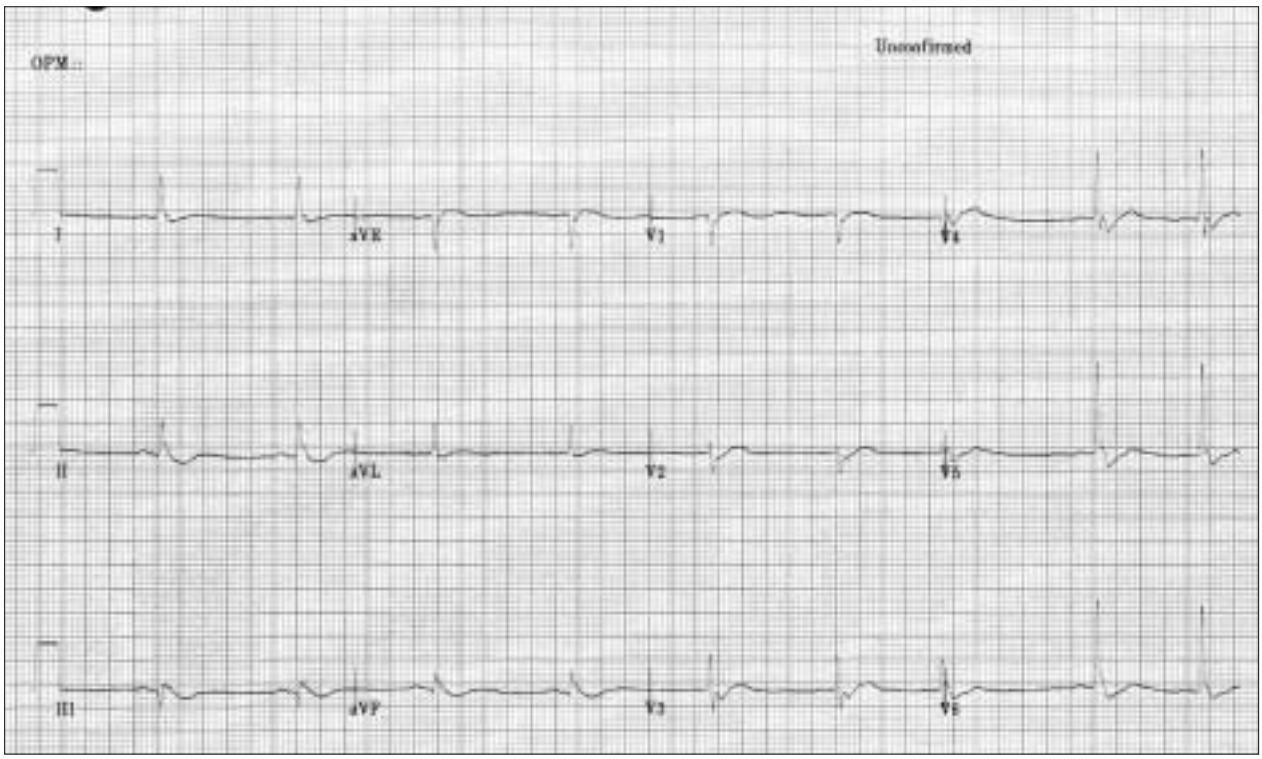

Figure 1
12-lead electrocardiogram on admission

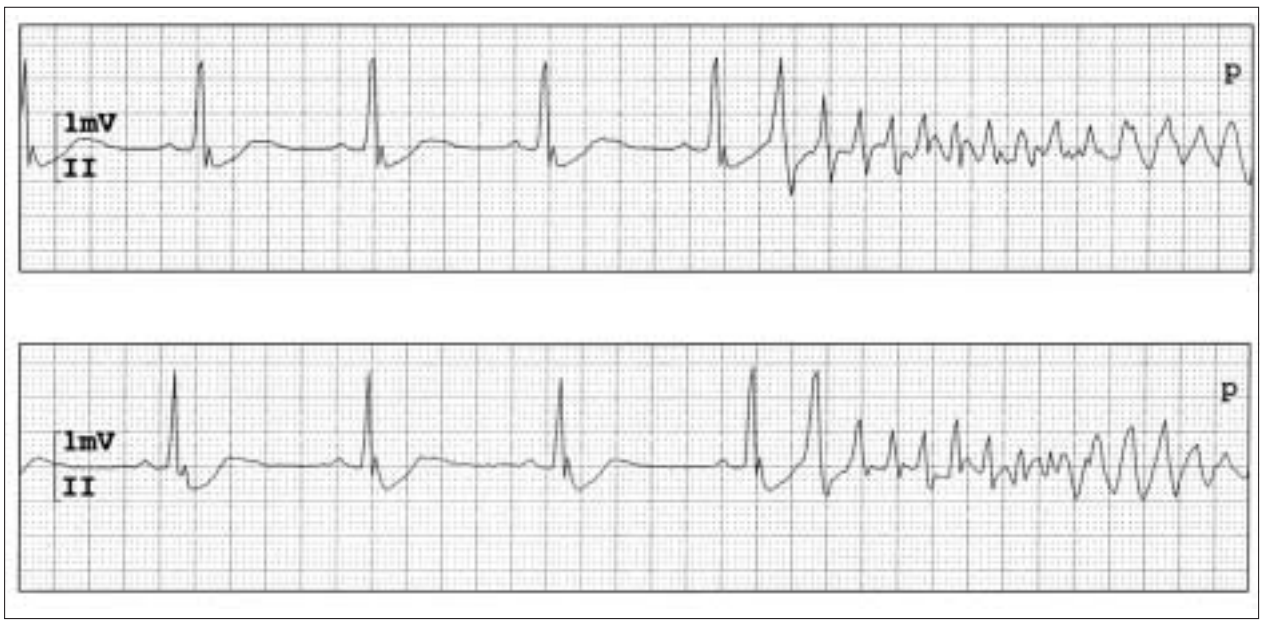

Figure 2
ECG tracing of the start of the first (upper tracing) and the second (lower tracing) episode of ventricular fibrillation

calcium free haemodialysis. After four hours the serum calcium concentration had fallen from 4.92 mmol/l to 3.56 mmol/l. However, after ending haemodialysis a rebound effect occurred with a calcium level rising to 4.11 mmol/l after five hours. This rebound phenomenon reoccurred after the next episode of haemodialysis: a serum calcium concentration decreasing from 3.90 mmol/l to 2.81 mmol/l but rising again to 3.20 mmol/l.

In the meantime, extended laboratory testing revealed a parathyroid hormone level of 172 pmol/l (<6 pmol/l). 25-OH vitamin D and FT4 levels were normal (56 nmol/l and 10 pmol/l, respectively). A neck ultrasound showed a 2.5 x 1.5 cm mass located dorsally of the right lobe of the thyroid.

Because of the two episodes of ventricular fibrillation the patient had preoperative cardiac screening including echocardiography and a dipyridamole scan. Both were normal.

After normalisation of the serum calcium level (total serum calcium 2.23 mmol/l, serum albumin 30 g/l), the patient underwent a successful parathyroidectomy and recovered fully.

DISCUSSION

Since calcium plays a major part in cardiac conduction, it is generally accepted that disorders of calcium concentration can cause arrhythmia. Hypercalcaemia decreases ventricular conduction velocity and shortens the effective refractory period. The main ECG manifestation is an alternation in the QT interval, sometimes associated with prolongation of PR interval and QRS duration.[3,4] In the second place, apart from hypercalcaemia, parathormone itself has a positive inotropic and chronotropic effect on heart cells, partly mediated by direct enhancement of calcium influx.[5] The combination of decreased ventricular conduction velocity and shortened refractory period makes the occurrence of re-entry and thereby ventricular fibrillation very likely. However, case reports on this complication of hypercalcaemia are rare.

A wide variety of rhythm disorders, such as sinus arrest, atrial fibrillation and supraventricular tachycardia in hypercalcaemia due to primary hyperparathyroidism, have been described.[6] Moreover, single case reports of sudden death have been reported.[1,7] This is generally attributed to ventricular fibrillation, despite absence of electrocardiographic monitoring.

To our knowledge, documented evidence of ventricular arrhythmias in hypercalcaemic crisis due to primary hyperparathyroidism has been reported in only four cases, namely bigeminal arrhythmia,[8] ventricular tachycardia[9] and runs of multiform ventricular tachycardia degenerating into ventricular fibrillation.[10,11]

Before attributing ventricular fibrillation in the presence of hypercalcaemia solely to this electrolyte disorder, other possible causes should be excluded. Two important other causes are serum potassium level and underlying heart disease.

Firstly, hypokalaemia and hypercalcaemia together facilitate ventricular fibrillation,[3,4] and hence it is important to know the serum potassium level in arrhythmias attributed to hypercalcaemia. In many case reports information on potassium concentration has been lacking[1,8] or described as below normal.[7,10]

Secondly, an underlying heart disease could contribute to the propensity of a patient to develop arrhythmia in hypercalcaemia, although a clear relationship remains to be established. Both myocardial scarring facilitating re-entry and vigorous treatment with forced saline diuresis might play a role. Enhanced Na^+/Ca^{2+} exchanger activity predisposes to ventricular tachyarrhythmias due to hypercalcaemia in patients with dilated cardiomyopathy.[11]

In our patient, hypokalaemia on admission was treated by intravenous administration of potassium chloride and at the moment of occurrence of ventricular fibrillation, the serum potassium concentration was within the normal range. In the second place, neither his medical history nor cardiac screening showed any underlying cardiac disease. Hence, it is very likely that in this case, ventricular fibrillation was caused by hypercalcaemia due to primary hyperparathyroidism, which makes cardiac monitoring in patients with severe hypercalcaemia absolutely necessary.

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ANSWER TO PHOTO QUIZ (ON PAGE 88)

A 51-YEAR-OLD MAN WITH UPPER ABDOMINAL PAIN

Chest X-ray showed discrete subcutaneous and mediastinal emphysema (*figure 1*). There were no signs of leaking air under the diaphragm. Computed tomography of the abdomen with intravenous and watery contrast per os revealed a rupture of the distal oesophagus and emphysema as seen in Boerhaave's syndrome (*figure 2*). The liver function tests were disturbed, probably by alcohol abuse.

The patient was transferred to a nearby university hospital for operative exploration. A longitudinal rupture of the distal oesophagus of 3 cm and a paraoesophageal food-containing collection were found which confirmed the diagnosis Boerhaave's syndrome. He was operated on successfully.

Boerhaave's syndrome, named after a famous Dutch doctor (1668-1738), consists of a rupture of the distal oesophagus by heavy vomiting, especially when the stomach is filled. This syndrome has a low incidence, but is an important entity, which should be thought of in case of an acute abdomen after vomiting. The overall mortality is 20 to 30% because of the fast development of secondary mediastinitis, bacteriaemia, a mediastinal abscess and pleuropulmonal complications.[1] In 40% of the cases of Boerhaave's syndrome heavy alcohol drinking is present (as in our patient) often leading to delay in diagnosis.[2]

DIAGNOSIS

Boerhaave's syndrome.

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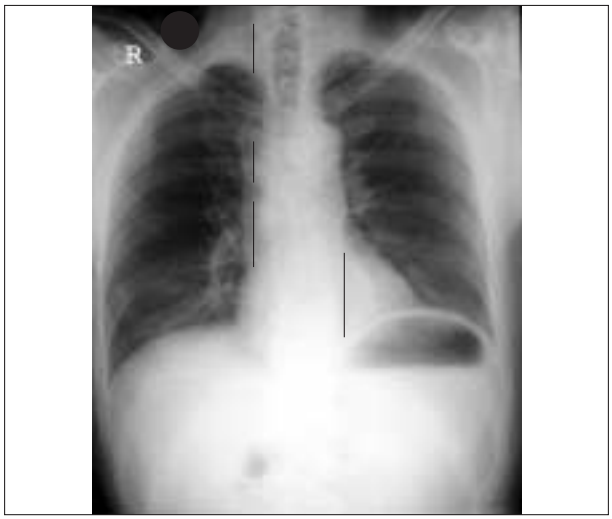

Figure 1
Chest X-ray shows discrete mediastinal and subcutaneous emphysema in the right supraclavicular area

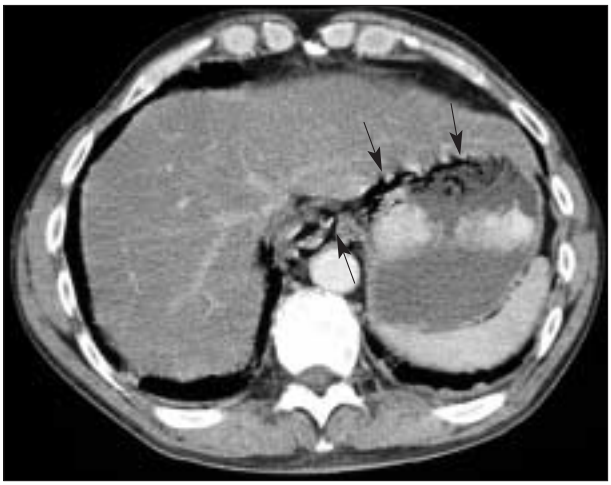

Figure 2
Computed tomography of the abdomen with intravenous and watery contrast per os shows the oesophageal rupture and emphysema between stomach and liver

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Who does become an internist?

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ABSTRACT

Internal medicine is a broad medical speciality and choosing the residency programme opens up a variety of career tracks. Despite this broad choice of subspecialities, we found that within our residency programme for internal medicine in the Nijmegen region between 1981 and 2000, 29% of the residents did not become internists but switched to other medical specialities. To further complicate the efficiency of the residency programme, about 20% of the residents who became internists did not finish within six years, but had a delay of two years due to combined internal medicine/PhD tracks (the training for internist/clinical investigator). In another 20% there is a delay of six to 12 months due to part-time training tracks as well as to (multiple) pregnancies of female residents and parental leave of both sexes.
Our data imply that nationwide data are urgently needed to re-evaluate the manpower planning for internal medicine by taking into consideration not only the number of residents starting in the residency programme but also to include the number of residents who actually do become internists.

INTRODUCTION

In the year 2000, the Netherlands Association for Internal Medicine (NIV) formulated the clinical competence requirements for the residency training programme of internists for the first time; a revision was published in 2002. In these documents internal medicine was defined as follows: 'Internal medicine is the part of medicine that is directed towards occurrence, recognition and treatment of diseases of internal organs and organ systems in adolescents and adults. Primary disorders of the central nervous system and the female reproductive organs are not considered to belong to the area of internal medicine' (Raamplan Interne Geneeskunde 2002, NIV).
It is clear from this definition that internal medicine is a broad medical speciality, and the choice of a young medical doctor to apply for the residency programme is a choice that leaves open a wide array of career tracks. Despite the broad choice of subspecialities within the field of internal medicine, it was our impression that a sizable number of residents did not become internists, or switched to another internal speciality and that – for a variety of reasons – many residents did not finish their training programme within six years.
In this short paper, we briefly review the Dutch training programme for internal medicine and present data on the numbers of residents that have become internists and of those that have not in the Nijmegen region over the last 20 years. In addition, actual data on the time needed to complete the residency training programme are provided.

STRUCTURE OF THE INTERNAL MEDICINE RESIDENCY PROGRAMME

The Dutch residency programme takes six years. Recently the structure has been revised. In short, the first 4 to 4.5 years deal with a common trunk consisting of obligatory training periods (*table 1*). Within this timeframe, elective training periods of four to six months can be done in (sub)speciality

** J.W.M. van der Meer was not involved in the handling and review process of this paper.

Table 1
The training programme for internal medicine in the Netherlands

COMMON TRUNK (4 TO 4.5 YEARS)
General internal medicine (24 months)
Intensive care (4-6 months)
Internal medicine consultation (4-6 months)
Outpatient clinic for internal medicine (8-12 months)
Electives in internal medicine (including pulmonology, cardiology)

SUBSPECIALITY TRAINING (1.5 TO 2 YEARS) IN ONE OF THE FOLOWING
General internal medicine
Endocrinology
Nephrology
Haematology
Medical oncology
Intensive care medicine
Infectious diseases
Vascular medicine
Clinical pharmacology
Blood transfusion medicine
Allergy and clinical immunology

areas. The final 1.5 to 2 years give the opportunity for the official subspeciality training programmes within internal medicine (*table 1*).
For a number of reasons, residents may not succeed in finishing within six years. First of all, pregnancies may lead to an extension of residency time; until recently one pregnancy leave of 16 weeks was accepted by the Board of the Registration Committee of Medical Specialists (MSRC), but nowadays all pregnancies have to be compensated for. Secondly, there is a growing appeal by the residents to do the training programme on a part-time basis, which is approved by the MSRC. The delay built up in this way has to be compensated for. This also holds for parental leave, which is allowed by Dutch law and the MSRC.
Finally, there is a very successful national MD/PhD track for talented residents. These residents in training for clinical investigator ('agiko') embark on an eight-year training programme (five years clinical training and three years research).
The residency programmes for internal medicine in the Netherlands are centred around the eight university medical centres (UMC), which collaborate with regional hospitals that take care of part of the training programme (two to four years). The total number of residents in the Netherlands in 2003 amounted to 781.
Furthermore, residents who have completed two years or more of the common trunk training, subsequently switch to the programme of another internal speciality instead of becoming an internist with any of the subspecialities (*table 2*). Sometimes this change occurs directly after registration as an internist.

Table 2
Internal specialities in the Netherlands

INTERNAL MEDICINE	WITH SUBSPECIALITIES (SEE TABLE 1)
Cardiology	(two years common trunk internal medicine)
Pulmonology	(two years common trunk internal medicine)
Gastroenterology	(three years common trunk internal medicine)
Rheumatology	(three years common trunk internal medicine)
Geriatrics	(two years common trunk internal medicine)

MANPOWER PLANNING FOR INTERNAL MEDICINE

Over the past decades there have been several attempts at manpower planning for internal medicine. The latest one in 1996 projected that there was a greater need for internists because of the ageing population, and the earlier retirement of internists, as well as the steadily increasing wish for part-time work. The latter was only partly due to the increasing female-male ratio among internists. Since similar trends were observed for many medical specialities, the government became concerned that the numbers of medical specialists being trained were too low to satisfy future needs.
This was the reason for installing a national committee (Capaciteitsorgaan) in 1999 to determine the capacity necessary for training enough medical specialists. Estimations are made in particular taking into account the age distribution among doctors, age of retirement, number of male and female doctors, amount of part-time work and the ageing population. The committee makes a planning of the numbers of residents starting the various training programmes, and not of the numbers that become licensed for a certain speciality. No data are available on the efficiency of the residency for internal medicine in the Netherlands, including the number of residents who do become an internist.

EFFICIENCY OF THE RESIDENCY OF INTERNAL MEDICINE

The UMC St Radboud Nijmegen, being one of the eight UMCs in the Netherlands, has the largest training programme for internal medicine: by the end of 2003, 118 residents (15% of total capacity in the Netherlands), 62% females, were in training, 60 in the UMC Nijmegen and 58 in one of the six regional hospitals. Eighteen are in

the combined internal medicine/PhD programme and nine are following a part-time (0.5 to 0.8) training programme. Between 1981 and 2000, 249 residents entered the training programme in the Nijmegen region, varying from ten a year in the 1980s to 25 in the late 1990s. *Tables 3* to 5 present some characteristics of these residents in cohorts of five years. The number of residents has increased over the years because of foreseen shortage of internists. The number of females has increased from 22 to 63% (*table 3*). Each year on average almost one resident left the programme due to making the wrong personal choice or apparent incompetence (*table 3*). Two to three residents or recently graduated internists each year switched to other internal specialities, mostly pulmonology, gastroenterology or rheumatology (*table 4*). The final efficiency of the Nijmegen internal medicine programme was therefore 61 to 75% (mean 71%) (*table 3*). The number of graduated female internists shifted from a quarter to almost two-thirds in 20 years.
For the reasons mentioned above, many residents will not finish their training within six years. About 40% of the

Table 3
Number of residents starting and completing the internal medicine training programme in Nijmegen

YEAR STARTING COHORT	STARTING RESIDENTS		RESIDENTS WHO LEFT	SWITCH TO ANOTHER INTERNAL SPECIALITY	LICENSED INTERNISTS		STARTING RESIDENTS BECOMING INTERNISTS
	N	% FEMALES			N	% FEMALES	%
1981-1985	41	22	-	13	28	25	68
1986-1990	54	46	3	18	33	42	61
1991-1995	58	41	4	11	43	47	74
1996-2000	96	63	8	16	72	63	75*

**For 1999 and 2000 predicted because of as yet uncompleted programmes.*

Table 4
Number of internal medicine residents switching to other internal specialities

YEAR STARTING COHORT	STARTING RESIDENTS	SWITCHED TO				
	N	CARDIOLOGY	PULMONOLOGY	GASTRO-ENTEROLOGY	RHEUMATOLOGY	GERIATRICS
1981-1981	41	-	3	4	6	-
1986-1990	54	-	4	7	6	1
1991-1995	58	-	1	7	3	-
1996-2000	96	1	3	6	6	-

Table 5
Number of internal medicine residents with prolongation in training due to pregnancy, parental leave and internal medicine/PhD track

YEAR STARTING COHORT	INTERNISTS WHO COMPLETED PROGRAMME		PREGNANT DURING TRAINING		PROLONGATION IN TRAINING DUE TO PREGNANCY, PARENTAL LEAVE, PART-TIME WORK	PROLONGATION IN TRAINING DUE TO INTERNAL MEDICINE/PHD TRACK
	N	N FEMALES	N	% OF FEMALES	N (% OF TOTAL)	N (% OF TOTAL)
1981-1985	28	7	*	*	*	1 (4)
1986-1990	33	14	*	*	*	6 (18)
1991-1995	43	20	8	(40)	2 (5)	7 (16)
1996-2000	72	45	20	(44)	16 (22)	15 (21)

**Not documented.*

female residents in the last ten years became pregnant during their training (*table 5*). Because of pregnancies, parental leave and part-time work up to 22% of the residents in the last five years had a delay in completing their training of six months to one year (*table 5*). Over 20 years an increasing proportion of the residents (21% in the five-year cohort) participated in scientific research (the above-mentioned MD/PhD programme), resulting in a delay of two years in completing the combined residency programme.

DISCUSSION

It is clear from the data presented here that the efficiency of the training programme for internal medicine in the Nijmegen region is only 71%. In other words, more than one out of four residents who start the training programme do not become an internist. For manpower planning at a national level these data are very important. These data do not seem to be unique for the Nijmegen region since for the Leiden region, a similar trend is seen: of the residents entering during the last ten years, 74% became internists (AE Meinders, personal communication).

It should be stressed that many of the residents who do not become internists will take positions in related specialities (such as pulmonology, gastroenterology and rheumatology). It is important to realise that these specialities have their own manpower planning, and policymakers should not confuse these with those for internal medicine. Another inefficiency in the training programme is the intermission in training due to pregnancies, part-time work, parental leave and the combined internal medicine/PhD track.
In conclusion, a considerable proportion of young doctors who enter the training programme for internal medicine do not become internists for a variety of reasons. So far, discussions about the manpower planning for internal medicine in the Netherlands have not taken into account this inefficiency of the training programme. Our data imply that nationwide data are urgently needed to adjust the manpower calculations for internal medicine by including all aspects of the inefficiency of the residency programme. Therefore, policymakers should take into consideration not only the number of residents starting in the residency programme but also include the number of residents actually becoming an internist and practising internal medicine.

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Nightmares, sleep and cardiac symptoms in the elderly

In a recent issue of this Journal (2003;61:257-61) Asplund reported that in a group of elderly men and women increased nightmares were associated with an increase in irregular heart beats and spasmodic chest pain. In the description of the study, however, no definition of nightmares was presented. The conclusion of the study was based on a questionnaire survey with questions on sleep symptoms, nightmares and cardiac symptoms. As a consequence of this kind of study no conclusions can be made on the mechanism of the reported association.

In the discussion of their findings the sleep apnoea syndromes (SAS) should be mentioned.[1] In 1999 several articles including an editorial were published in this Journal concerning the obstructive sleep apnoea syndrome.[2] In recent decades, awareness of SAS has increased both in the public mind and among medical professionals.

Obstructive SAS is the most common type, occurring in 5 to 20% of adult men, although only about 20% of these individuals need treatment. In the elderly, prevalence of SAS is much more common than in middle-aged men and women.[3,4] Obstructive SAS is characterised by recurring episodes of upper airway obstruction during sleep resulting in episodes of apnoea and/or hypopnoea. This condition is usually associated with snoring and arousals with or without anxiety, resulting in marked sleep fragmentation. Increased daytime sleepiness is also an important symptom. The recurrent hypoxaemia and hypercapnia may lead to both pulmonary and systemic hypertension, cardiac arrhythmias and decreased survival due to cardiovascular effects.[1-4]

Since no definition of nightmares was given in Asplund's study, it may well be that subjects scored arousal events with heart beating or respiratory discomfort as nightmares. It is more likely that the findings presented in his study are caused by SAS-related arousals with feelings of discomfort and SAS-related cardiovascular sequelae.

Patients suspected of sleep-disordered breathing have to be referred to a sleep clinic for evaluation. Depending on the severity of the complaints and the results of polysomnographia, patients have to be treated to relieve their symptoms and to improve their prognosis.

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1. Houwelingen KG van, Uffelen R van, Vliet ACM van. The sleep apnoea syndromes. Eur Heart J 1999;20:858-66.
2. Leeuw PW de. On sleep and death: cardiovascular risk of the obstructive sleep apnea syndrome. Neth J Med 1999;54:188-90.
3. Barthel SW, Strome M. Snoring, obstructive sleep apnea, and surgery. Med Clinics North Am 1999;83:85-96.
4. Somers V, Grassi G. The functional heterogeneity of sleep. J Hypertens 2003;21:1455-7.

REACTION FROM AUTHOR

In an informative comment on my study on nightmares and cardiac symptoms in the elderly, Dr van Vliet *et al.* point out that the sleep apnoea syndrome (SAS) is likely to explain the experience of nightmares in a proportion of the participants of the study and that persons with suspected sleep-disordered breathing (SDB) should be referred to a sleep clinic for evaluation. Some of these persons would benefit from treatment of their SDB. I agree with all that. SDB may still be an overlooked condition, although it has received considerably increased interest in recent years. Recognition of SDB is important, as treatment of the condition is often rather simple and leads to improvement in sleep, health and quality of life. Alleviation of SDB by continuous positive airway pressure (CPAP) also has a favourable influence on nightmares, as has been shown in sufferers of post-traumatic stress disorder.[1]

However, even if the incidence of heart diseases is increased in SDB sufferers, I have found no support for the idea that SDB may be present in more than a minor proportion of the total group of elderly men and women with cardiac diseases. Furthermore, the origin of nightmares is multifactorial, and only a proportion of them will be explained by SDB.

Dr van Vliet *et al.* do not mention how their comments on SAS should be interpreted when applied to a study of nightmares. Nor do their references shed any light on this issue. The report now under discussion addressed the possible relation between cardiac symptoms and nightmares. It was not restricted to an analysis of nightmares in elderly persons with *nocturnal* cardiac symptoms. Thus the opinion that a significant proportion of the increase in nightmares in elderly men and women with cardiac diseases might have been induced by SDB is neither supported nor refuted by the results of the study in question but this does not seem very likely. I still believe that the relationship between cardiac diseases and nightmares is worthy of attention and should be a subject of further study.

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REFERENCE

1. Krakow B, Melendrez D, Pedersen B, et al. Complex insomnia: insomnia and sleep-disordered breathing in a consecutive series of crime victims with nightmares and PTSD. Biol Psychiatry 2001;49:948-53.

RECTIFICATION

In the case report by F. van den Berkmortel *et al.*, in the Netherlands Journal of Medicine no. 1, a mistake was unfortunately made in the authors information on R. de Wit. Please find the correct details below:

Osteonecrosis in patients with testicular tumours treated with chemotherapy

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Beker van verlangen

Hans Vredegoor

In 1977 Hans Vredegoor (Deventer, 1953) completed his studies at the Academy of Design in Arnhem. Since 1981 he has been working as an independent expressive artist. He lives alternately in the Netherlands (Arnhem) and France (Auvergne).

Hans Vredegoor paints, makes colour etchings and uses a mixture of techniques on paper. He exhibits his work regularly in galleries all over the Netherlands and abroad. His art is represented in many company and government collections. Some of his recent exhibitions were in Galerie Witt in Dordrecht, House of Art in Meppel and Maison du Patrimoine, Châtel-Montagne in France.

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Examples:

[1.] Smilde TJ, Wissen S van, Wollersheim H, Kastelein JJP, Stalenhoef AFH. Genetic and metabolic factors predicting risk of cardiovascular disease in familial hypercholesterolemia. Neth J Med 2001;59:184-95.

[2.] Kaplan NM. Clinical Hypertension. 7th Edition. Baltimore: Williams & Wilkins; 1998.

[3.] Powell LW, Isselbacher KJ. Hemochromatosis. In: Harrison's Principles of Internal Medicine, 15th Edition, Braunwald E, Fauci AS, Kasper DL, et al. (eds). New York: McGraw-Hill; 2001. p. 2257-61.

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